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Aims and scope

Journal of Yeungnam Medical Science (J Yeungnam Med Sci, JYMS, eISSN 2799-8010, https://e-jyms.org), the official publication of the Yeungnam University College of Medicine and Yeungnam University Institute Medical Science, is a peer-reviewed and open access journal in the medical field. Its regional focus is mainly Korea, but it welcomes submissions from researchers all over the world.

JYMS aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, and communications. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all fields of medicine.

The first volume was published in December 1984 in Korean. YUJM is being published in English since 2018 and Journal title changed from YUJM to JYMS in January 2022. JYMS is published in English, four times a year (January 31, April 30, July 31, and October 31).

JYMS is indexed/tracked/covered by PubMed Central, PubMed, CAS, DOAJ, KoreaMed, Korea Citation Index, KoMCI, WPRIM, DOI/CrossRef, and Google Scholar.

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JYMS
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Journal title changes from *Yeungnam University Journal of Medicine* to *Journal of Yeungnam Medical Science*

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Happy New Year!

On behalf of the editorial board, I am pleased to announce that *Yeungnam University Journal of Medicine* (YUJM, eISSN 2384-0293) has changed its title to *Journal of Yeungnam Medical Science* (JYMS, eISSN 2799-8010), starting January 2022. Under its new name, JYMS will further increase its international visibility and recognition.

YUJM was first published as the official journal of the Yeungnam University College of Medicine in December 1984, in Korean. The journal's mission was to facilitate scientific communication between medical personnel in Korea. Since its inception, YUJM has changed its cover on many occasions (Fig. 1) and made tremendous progress. YUJM has been publishing in English since 2018 and has been indexed in the Korea Citation Index (KCI candidate, December 2016; KCI, October 2018), Directory of Open Access Journals (DOAJ, June 2019), PubMed/PubMed Central (PMC, October 2019), and Chemical Abstracts Service (CAS, October 2020).

Currently, JYMS is an international, peer-reviewed, and open-access journal, dedicated to the development of medicine through the propagation of medical knowledge by publishing high-quality reviews, original articles, case reports, image vignettes, and communications. JYMS will continue with the vision and volume number of the YUJM.

To promote JYMS to Scopus- and SCIE-indexed journals, editorial board members will continue to make efforts to maintain the high scientific standards of the journal. Moreover, there is a need to increase the international recognition of JYMS to broaden its international readership. JYMS has invited internationally recognized experts as editorial board members as part of the effort. Now renowned researchers from seven countries comprise the editorial board. JYMS will continue to recruit more international editorial board members. JYMS supports its editorial board members to improve the journal's quality.

Finally, I would like to express my sincere thanks to the former editor-in-chief, members of the editorial board, reviewers, manuscript editors, and publishers for their utmost devotion to the success of JYMS. In particular, I sincerely appreciate all authors of the articles for their support and contribution. I hope that researchers can actively share their valuable knowledge in medicine through JYMS.

Editor-in-Chief of
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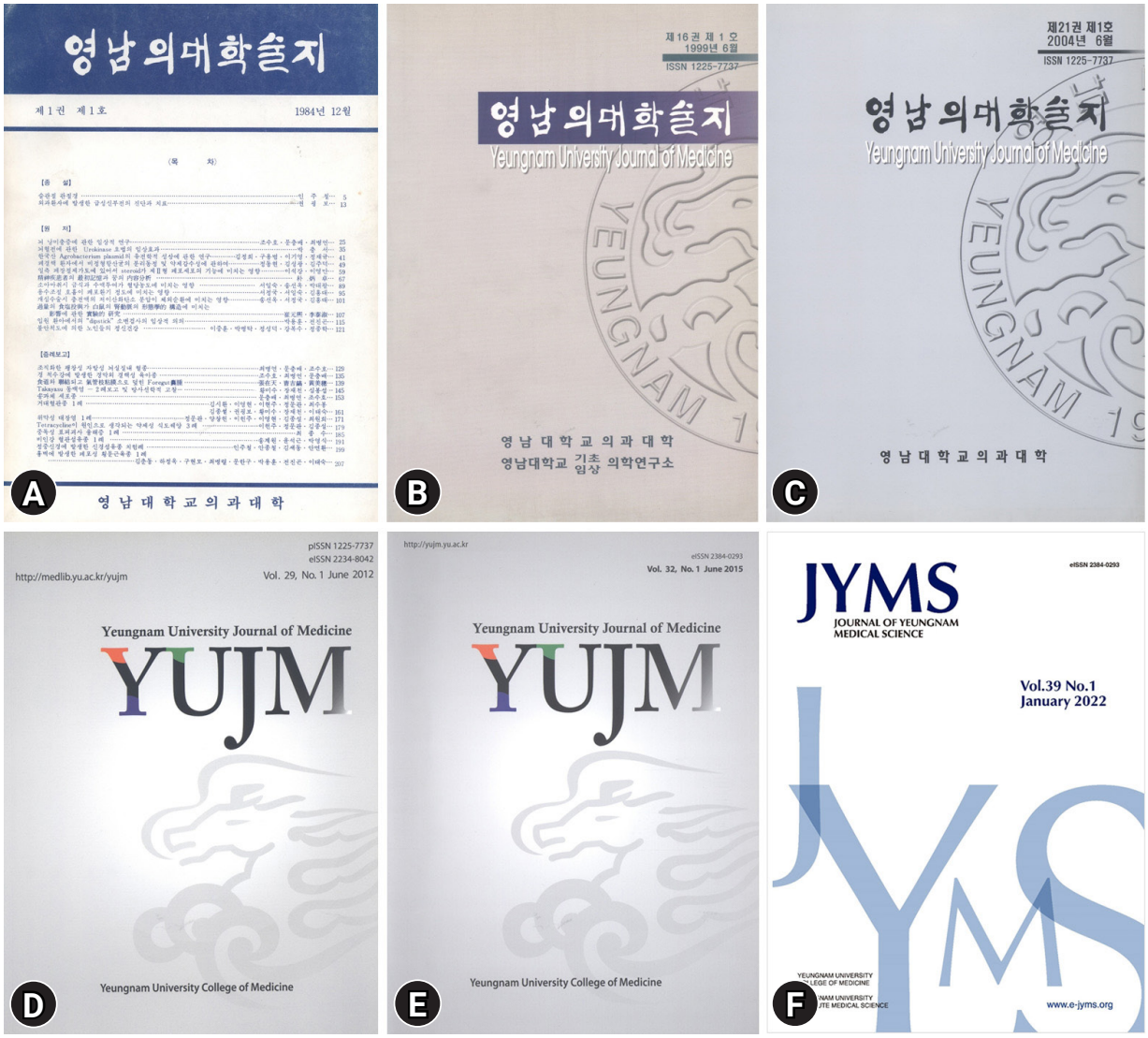

Fig. 1. Cover changes in *Journal of Yeungnam Medical Science*. (A) The first issue in 1984. (B) Between Volume 16 (1999) and 20 (2003). (C) Between Volume 21 (2004) and 28 (2011). (D) Between Volume 29 (2012) and 31 (2014). (E) Between Volume 32 (2015) and 38 (2021). (F) New cover from Volume 39 in 2022.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Review article

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Ocular adnexal mucosa-associated lymphoid tissue lymphoma: a narrative review

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Lymphoma is the most common primary tumor of the orbit, accounting for 55% of all orbital malignancies. When divided into histopathological subtypes, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) comprises the largest proportion. Clinical manifestations are unspecific, but in patients with slow-growing painless orbital mass, or red conjunctival lesion suggestive of 'salmon patch', ocular adnexa lymphoma (OAL) should be suspected. Although the pathogenetic mechanism of ocular adnexal MALT lymphoma (OAML) is not yet fully understood, the relationship between OAML and *Chlamydia psittaci* has been hypothesized recently, similar to that between gastric MALT lymphoma and *Helicobacter pylori*. This suggests a new treatment option for OAML; bacterial eradication therapy with systemic antibiotics. Several other treatment methods for OAML have been introduced, but no treatment guidelines have been established yet. In this article, we summarize the current knowledge on the clinical features, pathogenesis, diagnostic methods, therapeutic strategies, and prognosis of OAML.

Keywords: *Chlamydia psittaci*; Etiology; Marginal zone B-cell lymphoma; Ocular adnexal lymphoma; Orbital neoplasms

Introduction

Lymphoma is a type of blood malignancy that begins in lymphocytes which include B-lymphocytes, T-lymphocytes, and natural killer (NK) cells. There are two main categories of lymphoma: those presenting with a specific type of cellular abnormality dubbed a Reed-Sternberg cell, called classic Hodgkin lymphomas (HLs), and the others called non-Hodgkin lymphomas (NHLs) [1]. HL accounts for approximately 10% of all lymphomas, while the remaining 90% are NHL [2]. NHL is also divided into B-cell and T-cell lymphomas. B-cell lymphoma accounts for more than 85% of all lymphoid neoplasms [1]. Although orbital lymphoma is rare, accounting for only 1% of all NHL cases, it is the most common primary orbital cancer in adults, accounting for 55% of all malignancies in the orbit [3-5]. The majority of NHL of the orbit and ocular adnexa are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [6]. This review article summarizes the previously published literature on ocular adnexal MALT lymphoma (OAML), with an overview of its clinical features, treatment options, and prognostic outcome.

Clinical features

Ocular adnexal lymphoma (OAL), which mainly involves the conjunctiva, lacrimal gland, orbital fat, lacrimal sac, and eyelid, has various clinical presentations depending on the lesion. In addition, it cannot be easily differentiated from other orbital diseases because it has no pathognomonic signs or symptoms.

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Conjunctival involvement is observed in 26% of OALs, which shows a characteristic red, swollen, painless lesion called 'salmon patch,' making it easier to detect the disease [7]. However, a high index of suspicion is required because it may mimic chronic conjunctivitis in rare cases [8].

Intraorbital lymphoma usually presents with a variety of symptoms, including proptosis, palpable mass, swelling, ptosis, limited eye motility, displacement of the eye, and diplopia [7,9-12]. In particular, computed tomography (CT) or magnetic resonance imaging (MRI) should be considered in patients with proptosis, especially unilateral proptosis, since it is the most common symptom of orbital B-cell lymphoma [11,13].

Pathogenesis

The histopathological features of OAML are similar to those of other MALT lymphomas. Under physiological conditions, the connective tissues of the orbit are devoid of lymphoid tissue and lymphatic drainage [14]. Hence, for lymphoma to develop in the orbit, organized lymphoid tissue must be acquired first, as observed in gastric MALT lymphoma [15]. Several conditions, including chronic inflammation and autoimmune disorders, are associated with the pathogenesis of OAML.

1. Chronic antigenic stimulation

Over the last few years, the relationship between lymphoma and chronic antigenic stimulation has garnered increasing attention. As a paradigmatic example, *Helicobacter pylori* infection triggers chronic antigenic stimulation and plays a key role in the development of gastric MALT lymphoma [15]. Likewise, the detection of *Chlamydia psittaci* DNA in 80% of patients with OAML suggests that *C. psittaci* infection is related to the development of OAML [16]. *C. psittaci* is the known causative bacterium of psittacosis, which is caused by contact with infected animals, and half of the OAL patients have reported close contact with household animals [16,17]. Potential pathogenesis of OAML related to chlamydial infection is similar to that of gastric MALT lymphoma caused by *H. pylori*. This pathogenesis model is also observed in cutaneous B-cell lymphoma caused by *Borrelia burgdorferi* and small intestinal MALT lymphoma caused by *Campylobacter jejuni*. The chronic inflammation induced by *C. psittaci* facilitates the development of MALT in the orbit. Then, clonal expansion and proliferation of B-cell in the marginal zone of lymphoid follicles could occur in a state of persistent chlamydial infection. These clonal B-cells (antigen-dependent lymphoma clones) invade the germinal center of lymphoid follicles, causing chromosomal aberrations, resulting in an environment in which clonal expansion can continue without antigenic stimulation (antigen-independent lymphoma clones) [18]. Several studies have confirmed an association between *C. psittaci* and OAL, while others did not, which indicates the possibility of geographical variation [7,13,19-26]. Interestingly, tumor regression was observed in 38% of *C. psittaci* DNA-negative OAL after bacterial eradication therapy with doxycycline, suggesting that other microbial agents, such as doxycycline-sensitive bacteria, may be involved in the development of OAL [27]. Epstein-Barr virus (EBV), human T-cell leukemia virus type 1 (HTLV-1), hepatitis C virus (HCV), and human herpes simplex virus-8 are known to be associated with malignant lymphoma, and one study reported HCV seropositivity in 13% of OAL patients [28,29].

2. Immune disorders

Lymphoma is the most common cancer and the most common cause of cancer-deaths in human immunodeficiency virus (HIV) -infected patients [30,31]. Although the mechanism of lymphoma development in HIV patients is not clearly known, one study found that virologic suppression with highly active antiretroviral therapy reduces the risk of lymphoma [31]. Hence, advanced immunosuppression, higher levels of circulating viremia, and a high prevalence of oncogenic viruses (especially EBV) may be associated with an increased risk of lymphoma in HIV patients [31-34].

In addition, it has been reported that there is an increased risk of NHL in patients with autoimmune disorders such as Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis, immune thrombocytopenic purpura, and autoimmune hemolytic anemia [35,36].

3. Genetic abnormality

Similar to other malignancies, several chromosomal abnormalities are observed in the OAL. In the case of MALT lymphoma, different chromosomal alterations are detected depending on the site of origin [20]. In particular, trisomy 3 and 18, 5q (ODZ2) and 9p (JMJD2C), t(11;18)(q21;q21), t(14;18)(q32;q21), t(3;14)(p14.1;q32), and A20 inactivation (6q23 deletion) are associated with OAML [20,37]. One study reported a higher incidence of trisomy 3 in orbital MALT lymphoma than in conjunctival MALT lymphoma, while another reported that trisomy 18 was more common in young women with conjunctival involvement, which shows a high recurrence rate [38,39]. However, there is not much data yet on the genetic aspect of OAL, so further investigation is needed to fully understand it.

Diagnosis

The definitive diagnostic method of OAL is histopathologic verifi-

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cation. However, neuroimaging techniques, including CT or MRI, are also necessary to measure the size of the lesion or to differentiate it from other orbital diseases. In a two-phase contrast enhancement CT scan, orbital lymphoma shows a decrease in density in the delayed phase, which is in contrast to the orbital inflammatory pseudotumor showing increased density on delayed imaging [40]. An MRI scan shows a mass with isointensity on the T1 image and an iso-hyperintense signal on T2. Furthermore, quantified tumor blood flow (TBF) values measured by arterial spin labeling and apparent diffusion coefficient (ADC) on diffusion-weighted imaging could be helpful in differentiating lymphoma from other expansive orbital diseases. In particular, lymphoma represents high TBF and low ADC values compared to idiopathic orbital inflammatory pseudotumors, which may be difficult to differentiate clinically [41,42]. After determining the size and location of the lesion, a histopathological examination should be performed through an open biopsy [1]. Histopathologic examination of OAML may not always be conclusive since it mainly consists of small lymphoma cells that lack cellular atypia, and have a similar appearance to small lymphocytes [43,44]. Thus, it is often challenging to differentiate lymphoma from reactive lymphoid hyperplasia [44]. In this case, determining the clonal B-cell population by polymerase chain reaction (PCR) analysis of immunoglobulin heavy chain gene rearrangement can help in the differential diagnosis [45]. Further immunohistochemical examination shows CD20+, CD79a+, IgM+ with light-chain restriction, PAX5+, bcl-2+, TCL1+, CD11c+/–, CD43+/–, CD21+/–, CD35+/–, IgD–, CD3–, CD5–, CD10–, CD23–, cyclin D1–, bcl–6–, and MUM1– cells as classical immunophenotype [38,46-51]. In addition, systemic evaluation, such as full-body positron emission tomography-CT and bone marrow biopsy should also be performed [52,53].

Staging

The Ann Arbor staging system, commonly used in the staging of NHL, is a system for the staging of HL [54-56]. This staging system divides the disease into four stages: (I) single localized disease, (II) two or more lesions on one side of the diaphragm, or (III) both sides of the diaphragm, and (IV) metastatic disease. The involvement of the localized extranodal site is recognized by the subscript E (i.e., stage I_E) [57]. However, the Ann Arbor system is not suitable for the staging of OAML because it does not consider anatomic location, multicentricity, bilaterality, or extent of primary tumor infiltration; thus, two-thirds of OAML cases are classified as stage I_E [56,58,59]. To overcome this limitation of the Ann Arbor system, the American Joint Committee on Cancer proposed a new staging system for OAL [60]. This TNM staging system determines the stage of OAL based on the size and extent of the primary tumor (T), involvement of local lymph nodes (N), and the presence or absence of tumor metastasis (M) [56,59]. Although several studies have demonstrated the usefulness of TNM staging for OAL, new treatment protocols based on this staging system remain to be investigated [58,59].

Treatment

Although many treatment options for OAL have been reported, no definite guidelines have yet been universally accepted. When a therapeutic decision for OAL is made, the location and extension of the tumor, the presence or absence of metastasis, prognostic factors of the patients, and treatment-related toxicity or adverse effects should be considered.

1. Surgical resection

Surgical resection is listed first, not only because it is the most conventional treatment option for tumors but also because it is necessary for the diagnosis of OAL. Some MALT lymphomas of the conjunctiva or lacrimal glands can be completely resected; however, excessive efforts to completely resect lymphoma are not recommended, as they could be associated with a high risk of complications. Furthermore, a study reported that complete resection of OAML did not affect overall survival rates [61]. Surgery can be used in combination with other treatment options, such as chemotherapy and radiation therapy, to reduce the tumor size. For localized low-grade MALT lymphoma in older patients who do not want invasive treatment, the watch-and-wait strategy could be an option after surgical resection or biopsy [61,62].

2. Radiation therapy

Radiation therapy is frequently used in the treatment of OAL and has been the mainstay of treatment for many years. It may be used to eradicate tumors and is also used to reduce the size of the tumor before surgery or as a combination therapy with chemotherapy or immunotherapy. Although there is no gold standard for the dose of radiation, 28–36 Gy is commonly prescribed for low-grade lymphomas such as MALT lymphoma or follicular lymphoma, and 30–40 Gy for high-grade lymphomas such as diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL) [62]. In low-grade lymphoma, the 5-year local control rate was 86% for < 30 Gy and 100% for ≥ 30 Gy. In the case of MALT lymphoma alone, the overall local control rate was 96% at 5 years and 86% at 10 years (range, 23.1–45 Gy; median D1.8, 31.8 Gy) [63]. As noted in many studies, radiation therapy shows a good local control rate, but it can cause some adverse effects, including cutaneous re-

actions, cataracts, dry eyes, macular degeneration, retinopathy, and corneal ulceration, particularly at doses of 30 Gy or higher [64-67]. Therefore, some authors prefer ultra-low-dose radiation therapy, which uses only 4–8 Gy in total, and the minimal incidence of adverse effects has been reported [68,69]. However, this remains controversial, as some authors reported a high recurrence rate in low-dose treatment, especially below 30 Gy [12,24,63]. Likewise, a lens shielding technique using a lead contact lens or cylindrical shield to prevent the development of cataract is worth considering, although there are some reports of high recurrence rates [11,12,50,64,65].

3. Chemotherapy

Chemotherapy is often used in OAL with systemic involvement or high-grade lymphomas such as DLBCL. The combination regimen of cyclophosphamide, doxorubicin (hydroxydaunorubicin/adriamycin), vincristine (Oncovin; Eli Lilly and Company, Indianapolis, IN, USA), and prednisone (CHOP) is the most commonly used. Other common combination regimens include hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine) and CVP (cyclophosphamide, vincristine, and prednisone). As a monotherapy, chlorambucil is frequently used for treating indolent lymphomas, showing a 79% complete response and 21% partial response (PR) rate with good tolerability in orbital MALT lymphoma [70]. Oxaliplatin and purine analogs, including fludarabine and cladribine, have also been used recently [50,71-73].

4. Systemic antibiotics

More than 90% of gastric MALT lymphomas are related to *H. pylori* infection, and after this was proven, bacterial eradication therapy with systemic antibiotics became an important part of treatment [74-76]. A similar relationship between *C. psittaci* and OAL has been proposed. Several authors have reported high rates of *C. psittaci* infection in patients with OAML, 80% in Italy [16] and 78% in South Korea [77]. However, no such association has been found in Japan [21,78], the Netherlands [22], France [79], Cuba [80], and the United States [7,23,38,81], suggesting geographical variation. A multicenter prospective phase II trial conducted in four countries (Chile, Italy, Spain, and Switzerland) showed a good response rate to first-line eradication therapy with doxycycline for OAML; complete remission (CR) in 18%, PR in 47%, and overall response rate (ORR) of 65% [26]. In South Korea, a study on 90 patients with OAML found a 34% ORR with first-line doxycycline treatment. In addition, this study reported that the ORR of second-line treatment with radiotherapy for patients who progressed after doxycycline treatment was 100% [82]. Furthermore, considering that doxycycline treatment was effective even in 38% of *C. psittaci* DNA-negative patients according to one study, it seems that it could be used in most OAML patients [27]. On the other hand, one author reported that doxycycline treatment in patients who had not been tested for chlamydia infection showed no effect on OAML [83]. In summary, the effectiveness of bacterial eradication therapy with doxycycline for OAML remains controversial, but it is worth considering as it is a safe and cost-effective treatment option.

5. Immunotherapy

Rituximab is a chimeric human/mouse monoclonal antibody against CD20 and B-lymphocyte surface antigens [84]. The function of CD20 is not fully known, and it is thought to be involved in the activation and regulation of B-cells [85]. Although rituximab is a mainstay in the treatment of B-cell NHL, it is not commonly used as monotherapy in OAML patients, and only a few authors have reported the efficacy of this monoclonal antibody [86,87]. Except in the case of relapsed OAML, rituximab shows a good response, but its efficacy is lower than that reported in gastric MALT lymphomas due to its high recurrence rate [87]. Rituximab is also widely used as part of a combination regimen with chemotherapy. For example, the combination of rituximab and chlorambucil showed great success in OAL patients with EMZL and follicular lymphoma as first-line treatment (CR in 89%, PR in 11%, ORR in 100%) [88]. In addition, combination therapy with CHOP (R-CHOP) has improved treatment outcomes in patients with DLBCL and MCL [89,90]. Several authors have reported successful results from intralesional interferon-α injection in conjunctival MALT lymphoma with minimal side effects [91-93], although further research through large clinical trials is needed.

Prognosis

Based on the available scientific literature, the histological subtype may act as the most important predictor of mortality in OAL. One study found that the 5-year lymphoma-related mortality rate was as follows: 12% for EMZL, 19% for diffuse lymphoplasmacytic lymphoma, 22% for follicle center lymphoma, 48% for DLBCL, and 53% for other lymphoma variants (i.e., MCL, chronic lymphocytic lymphoma, etc.) [94]. Another study reported lymphoma-related mortality as 2% for EMZL, 33% for follicular lymphoma, 38% for DLBCL, 100% for MCL, and 100% for peripheral T-cell lymphoma and NK cell lymphoma [95]. Other prognostic factors include the stage at presentation, primary or secondary status, and whether the disease is unilateral or bilateral [95-97]. According to a study, the rates of extraorbital spread and lympho-

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ma-related death are the lowest in conjunctival lymphoma, followed by deep orbital lymphoma and lacrimal gland lymphoma, and the highest in eyelid lymphoma [97].

Conclusion

As the most common cancer that occurs in the orbit, the characteristics of OAL should be noted. Furthermore, the incidence of OAL has been reported to increase steadily over the past few decades [5,25,98]. In South Korea, OAML accounts for a particularly higher proportion of OAL compared to that in Western countries [99,100]. The size and location of the tumor should be measured using radiology imaging techniques such as CT and MRI, and an open biopsy should be performed to make a histopathological diagnosis. OAL has different prognostic outcomes depending on its histological subtype, and MALT-type lymphoma has a good ORR if treated properly. Although the TNM staging of OAL is not yet widely used and no large-scale clinical trial has been conducted, further research should be conducted in the future to establish a first-line treatment protocol based on it.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Formal analysis, Project administration, Supervision: JHS; Data curation: HUC; Writing-original draft: HUC; Writing-review & editing: JHS.

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Anatomical endoscopic enucleation of the prostate for bladder outlet obstruction: a narrative review

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Anatomical endoscopic enucleation of the prostate (AEEP) differs from other endoscopic modalities for bladder outlet obstruction (BOO) because it extracts the whole benign prostatic hyperplasia component. AEEP has been launched for almost 40 years as a first-line treatment method for BOO regardless of prostate size according to several guidelines. However, it remains underperformed worldwide. In this review article, we elaborate on the advantages and disadvantages of AEEP compared to other surgical modalities for BOO to investigate its efficacy and safety as a gold standard surgical management option for males with BOO.

Keywords: Endoscopy; Health care outcome assessment; Prostatic hyperplasia

Introduction

Benign prostatic hyperplasia (BPH) is the most common benign disease in men, which influence more than 50% of male over the age of 60 years. About 30% of patients with lower urinary tract symptoms (LUTS) due to BPH require management, and about 20% are refractory to clinical management and therefore perform operative management [1]. Recent technological advancements purpose to sustain excellent functional results while diminishing the complications related to the surgical management of BPH. Anatomical endoscopic enucleation of the prostate (AEEP) was initially introduced by Hiraoka [2] and has been determined to be an excellent approach for the surgical management of LUTS due to BPH.

AEEP differs from other endoscopic modalities for bladder outlet obstruction (BOO) as it extracts the whole BPH component of the prostate. Multiple energy sources can be employed to do AEEP such as high-power (100 W or more), low-power holmium (70 W or less), diode, greenlight, and thulium lasers, and monopolar and bipolar diathermy (Table 1). AEEP apparently exhibits the same safety profile as the excellent endoscopic non-enucleating procedure (ENE) and the same long-term functional results as simple prostatectomy (SP). It can also be safely done in patients using anticoagulants [3,4]. AEEP has been performed for almost 40 years as a first-line treatment modality for BOO regardless of prostate size according to both the American Urological Association and the European Association of Urology guidelines [5,6]. In this review article, we elaborate on the advantages and disadvantages of AEEP compared to other surgical procedures for BOO to investigate its efficacy and safety as a gold standard surgical management modality for males with BOO.

Advantages of anatomical endoscopic enucleation of the prostate

Endoscopic surgery is usually more favorable than SP for BPH

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Table 1. A variety of energy sources for anatomical endoscopic enucleation of the prostate

Energy source	Abbreviation
Holmium laser enucleation of the prostate	HoLEP
Thulium laser enucleation of the prostate	ThuLEP
Diode laser enucleation of the prostate	DiLEP
Greenlight laser enucleation of the prostate	GreenLEP
Plasmakinetic enucleation of the prostate	PKEP
Plasma kinetic enucleo-resection of the prostate	PKERP
Photovaporization and enucleation of the prostate	PVEP
Bipolar transurethral enucleation of the prostate	BTUEP
Monopolar transurethral enucleo-resection of the prostate	MTUERP

with a prostate volume of > 80 mL due to its minimally invasive nature [6]. In the last two decades, AEEP for BPH has been advanced and has steadily become a popular modality as an alternative to SP [7]. Holmium laser enucleation (HoLEP) was the first laser method used in BPH endoscopic surgery [8]. After the launch of the holmium laser, diode and thulium lasers were also developed to be used for AEEP [9,10]. Subsequently, AEEP with bipolar energy has arisen as an alternative surgical procedure that can reduce medical costs compared to those incurred for laser AEEP [11]. Both laser and bipolar AEEP are expected to enhance safety outcomes due to better coagulation and fewer transurethral resection syndrome complications.

Functional outcomes

1. Detrusor pressure at maximum flow rate (PdetQmax): better relief of bladder outlet obstruction

In the first randomized clinical trial (RCT) of HoLEP vs. transurethral resection of the prostate (TURP), greater release of BOO was observed after HoLEP compared to after TURP with mean PdetQmax improving from 76.2 to 20.8 cmH_2O vs. 70 to 40.7 cmH_2O, respectively. This is particularly relevant for patients with impaired detrusor function and those with refractory urinary retention [12].

2. International prostate symptom score, maximum urinary flow rate, post-void residual volume and quality of life: at least equivalent, if not better improvements

Level 1a demonstration recommends that AEEP furnishes at least equivalent, but possibly greater enhancements, in international prostate symptom score (IPSS), maximum urinary flow rates (Qmax), and post-void residual volumes (PVR) compared to those provided by vaporization and resection procedures [13].

A meta-analysis of data from several RCTs described that of the following techniques: bipolar TURP, HoLEP, and greenlight laser photoselective vaporization of the prostate (PVP), only HoLEP provides a greater level of enhancements in IPSS, Qmax, and PVR when compared to that provided by monopolar TURP [14]. Another meta-analysis comparing AEEP to ENE presents significant precedence for AEEP in terms of IPSS, Qmax, and PVR; however, the clinical significance of these findings remains questionable as they are limited: IPSS superiority of 0.29 to 1.44 points, Qmax superiority of 0.26 to 1.87 mL/sec, and PVR superiority of –3.69 to –14.98 mL. There were no clinically significant differences between ENE and AEEP in terms of advancement in quality of life (QoL) scores [3].

Perioperative outcomes

1. Less bleeding, shorter catheter time, and hospital stay

While TURP procedure meets blood vessels with every swipe, AEEP merely meets blood vessels on the inner aspect of the peripheral zone (PZ), and perforates between transitional zone and PZ. RCTs and meta-analyses constantly present less bleeding, shorter catheter times and consequently shorter hospital stays for AEEP when compared to those for TURP [13]. A recent meta-analysis presented a lesser reduction in serum hemoglobin (–0.54 mg/dL, $p < 0.005$), fewer blood transfusions (odds ratio, 0.83; $p < 0.005$), shorter catheter times (–0.58 days, $p < 0.05$), and shorter hospital stays (–0.91 days, $p < 0.005$) after AEEP compared to those after resection procedures [3].

2. Superior catheter-free rates for males with urinary retention and high effectiveness in males with impaired detrusor contractility

One of the most outstanding dominance of AEEP is its particularly high catheter-free rate in patient with urinary retention even in the condition of decreased or absent detrusor contractility. Elzayat et al. [15] showed that 98.3% of males with non-neurogenic repeated urinary retention became catheter-free state after HoLEP. A retrospective comparison of 72 patients who underwent HoLEP vs. 31 patients who underwent PVP for refractory urinary retention was presented. The catheter-free rates at a median follow-up period of 6 months were 74% for PVP patients and 99% for HoLEP patients despite 41.9% of PVP patients and 37.5% of HoLEP patients showing proof of decreased detrusor contractility [16].

In a prospective study, Mitchell et al. [17] performed HoLEP to males with nonneurogenic bladder hypocontractility or acontractility. About 35.7% of those with hypocontractility had cathe-

ter-dependent urinary retention as did all those with acontractility. At a median follow-up period of 24.7 months, all patients who had preoperative urinary retention and hypocontractility were catheter-free, and 94.7% of patients who had urinary retention and acontractility were voiding without the requirement for a catheter. Interestingly, 78.9% of patients with acontractile bladders showed significant improvement of detrusor contractility postoperatively [17]. In a retrospective study comparing results of HoLEP to those of TURP in patients with detrusor underactivity, 57% of TURP patients needed α-blocker medications and 28% required anticholinergics postoperatively. These demands were lower for HoLEP at 12% and 17%, respectively [18].

3. Highly safe and effective for males with large prostates and independent of prostate volume

One of the most widely approved advantages of AEEP is its efficacy and safety in patients with large prostates [13]. A meta-analysis of three RCTs comparing HoLEP and SP reported similar enhancements in IPSS, QoL, Qmax, and PVR at both 12 and 24 months. HoLEP was related to less blood loss, fewer blood transfusions, shorter catheter time, and shorter hospital stay. The influence on potency and continence were similar in both groups, but postoperative complications were less often after HoLEP. No reoperations were needed for the regrowth of BPH in both groups [19,20].

Kuntz et al. [21] showed that about four hundred patients performing HoLEP were stratified into three groups according to preoperative prostate volume (< 40, 40–79, and ≥ 80 mL). The association between the reduction in serum hemoglobin level and prostate volume was very puny (r = 0.229). There were no clinically significant differences seen in terms of blood loss or blood transfusions among the groups. The median catheter time and hospital stay were similar among the groups. At the 1-month follow-up period, there were no clinically significant differences seen in Qmax or PVR scores. In a Korean retrospective study, a total of 502 HoLEP patients were stratified into three groups based on the preoperative prostate volume; group A (< 100 mL), group B (100–200 mL), and group C (> 200 mL). Catheter time and hospital stay were longer, and transient postoperative urinary incontinence was more common in group C. However, there were no clinically significant differences observed in terms of blood transfusion rate, urinary tract infection, recurrence, reoperation, clot retention, de novo urethral stricture, and bladder neck contracture. And IPSS with QoL, Qmax, and PVR scores were not significantly different at the 6-month follow-up [22].

Other advantages of anatomical endoscopic enucleation of the prostate

1. High durability of anatomical endoscopic enucleation of the prostate

AEEP is the most durable surgical procedure for BOO. The longest follow-up period currently obtainable in peer-reviewed literature is over 10 years after HoLEP. Mean IPSS and QoL scores were 3.6 and 0.7, respectively, with mean Qmax at 26.9 mL/sec. Additionally, the reoperation rate due to regrowth of prostate was 0.7%. In another RCT comparing HoLEP and TURP with a mean follow-up period of 7.6 years, none of the patients in the HoLEP group needed reoperation compared to 18% in the TURP group [23,24].

2. Efficacy and safety in elderly patients

Piao et al. [25] divided HoLEP patients into four groups according to age at operation (group A, 50–59 years; group B, 60–69 years; group C, 70–79 years; and group D, ≥ 80 years). Despite patients aged ≥ 80 years taking significantly higher American Society of Anesthesiologists grades and rates of anticoagulation usage, greater enucleation weights, longer surgery times, and the incidence of adverse events were similar among the groups. The duration of hospital stay was longer for patients in group D compared to the other groups. There were no clinically significant differences observed across groups for IPSS, Qmax, and PVR scores at 6 months.

Limitations of anatomical endoscopic enucleation of the prostate

Why has AEEP not yet been accepted as the gold standard surgical modality of BPH despite having the aforementioned advantages and being introduced for almost 40 years [26]? A gold standard procedure must be safe, efficient, reproducible, and cost-effective compared to the current best choice of management. AEEP has not attained this status due to several issues, and therefore, it still remains seriously underused [27].

1. Multiple energy sources and technique

AEEP can be performed using various equipment and energies. Some of them apply retrograde blunt dissection during the operation along the prostate capsule plane whereas others apply the energy source to dissect. Specimen removal can also be performed in multiple methods, with the mushroom technique or with various morcellators [26]. The absence of superiority in these options over another and the lack of standardization makes it difficult to launch an enucleation program and choose among the multiple surgical

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techniques and energy sources. Each has a unique technical aspect and needs specific surgical techniques that may not inevitable be transposable.

2. High costs

Most hospitals have typical bipolar TURP system that would be sufficient for the treatment of BPH. The requirement for laser fibers, high-power laser generators, and morcellators is a hurdle to the widespread achievement of AEEP [28]. It has been demonstrated that HoLEP is related with a 9.6%–24.5% hospital net cost savings as compared to SP due to the shorter hospital stay related with it [26,29]. However, the initial investment for procuring its equipment can be a significant obstacle mainly because the cost of initial hospitalization is at most comparable between TURP and HoLEP [29].

3. Steep learning curve

A perception of the learning curve (LC) is crucial for deciding the extent to which surgical experience is needed to offer reproducible results. In AEEP, the LC tends to be sheer and 50 to 60 cases are needed to efficiently do enucleation with effective morcellation [30]. The other limiting factor for the execution of AEEP is the requirement for a mentor during the LC. Under the guidance of a mentor, the LC can be decreased to < 25 cases [31]. The lack of easily reachable mentorship is the other limiting factor in AEEP execution, although some surgeons have overcome AEEP in a self-taught manner. Another limitation for the widespread performance of AEEP is that most residents complete their training period without grasping this surgical technique. Thus, urologists who purpose to start AEEP must experience a fellowship or at least devote money and time in observerships and hands-on courses [26].

4. Postoperative outcomes and complications

1) Outcomes

TURP and PVP fulfill adequate and durable symptom release in most cases, but they do not always complete the removal of whole adenoma, frequently without reaching the true prostate capsule. This may lead the patient to symptom relapse and adenoma regrowth. In a recent meta-analysis, AEEP showed significantly better IPSS and Qmax enhancements than ENE. Nevertheless, these differences are questionable because the Qmax enhancement between groups was 1.0 mL/sec in the short term and 1.77 mL/sec in the long term, respectively. Furthermore, the IPSS score was only 0.86 points lower in the endoscopic enucleation of the prostate group and was merely noted in the mid-term follow-up analysis. There was no clinically significant difference observed in other functional results and QoL scores regardless of the follow-up duration. While comparing perioperative data between ENE and AEEP, there were clinically significant differences observed that favor AEEP in terms of catheterization time and duration of hospital stay, but with longer operation time [3,26].

2) Complications

The complication profile of AEEP differs from that expected with ENE. AEEP is related to less bleeding and lower blood transfusion rate, but a higher incidence of bladder injury [3]. Elevated incontinence rates during the early AEEP LC period can also be assumed [32]. Moreover, transient stress urinary incontinence (SUI) is an adverse event caused by sphincteric stretching due to wider intraurethral movements done to remove adenoma. The incidence of transient SUI has been reported to be as high as 26% at 3 months after AEEP [26]. Urethral stenosis is another complication that may happen due to longer surgical procedures that also often require larger scopes, especially for morcellation. The incidence of this status in AEEP ranges from 1.4% to 3.0% [33,34].

Conclusion

AEEP is considered an alternative surgical treatment of BPH since it provides the capacity to manage many patients safely and effectively than any other BPH modality. It offers at least equivalent enhancements in Qmax, PVR, and IPSS scores when compared to those in TURP in patients with prostate volumes of < 100 mL and is more likely to make patients catheter-free even in the condition of impaired detrusor function. However, it is still underperformed globally. The most commonly reported cause is its steep LC. To overcome this problem, a well-structured and focused mentorship program that is more practicable now than ever before because of the increasing accessibility of experienced mentors is suggested. More long-term RCTs may offer an answer to whether AEEP could substitute ENE as the gold standard for surgical management of BPH in the future.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: THK, PHS; Formal analysis, Supervision: THK; Writing-original draft: THK, PHS; Writing-review & editing: PHS.

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Puncture needle with a hard plastic sheath and plastic wings minimizes repuncture attempts in ultrasound-guided paracentesis: a retrospective case-control study

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Background: This study was performed to evaluate periprocedural factors, complications, and repuncture rate of the newly developed puncture needle and compare it with the routinely used puncture needle for ultrasound (US)-guided paracentesis.

Methods: We retrospectively identified 137 patients who underwent US-guided paracentesis between July 2018 and March 2019. Among them, 82 patients underwent US-guided paracentesis with a newly developed puncture needle. The other 55 patients underwent US-guided paracentesis with a routinely used puncture needle. The periprocedural factors, complications, and repuncture rate were compared between the two groups using the Mann-Whitney U test and Fisher exact test. The repuncture-associated factors were assessed using logistic regression analysis.

Results: There were no major or minor complications in either group. The rate of repuncture was significantly lower in the group using the newly developed puncture needle compared with the group using the routinely used puncture needle ($p=0.01$). The duration of the procedure was significantly shorter with the newly developed puncture needle compared with the routinely used puncture needle ($p=0.01$). In univariate analysis, the thickness of the abdominal wall ($p=0.04$) and the use of the newly developed puncture needle ($p=0.01$) were significantly associated with the rate of repuncture. In multivariate analysis, only the use of the newly developed puncture needle was significantly associated with the rate of repuncture.

Conclusion: Using this novel puncture needle with a hard plastic sheath and plastic wings, the rate of repuncture and the duration of the procedure were decreased without complications of US-guided paracentesis.

Keywords: Ascites; Paracentesis; Puncture; Ultrasonography

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Introduction

Ascites is the presence of abnormal fluid in the abdominopelvic cavity. Approximately 75% of patients with ascites have liver cirrhosis [1]. Ascites is a common complication in patients hospitalized with liver cirrhosis [2,3]. Non-cirrhotic causes of ascites include malignancy, tuberculosis, and pancreatic ascites [4]. In such cases, ascites drainage is important for diagnosing the cause.

Paracentesis is classified as diagnostic or therapeutic based on its purpose. In most cases, diagnostic paracentesis is performed to assess portal hypertension and infected fluid collection [5]. For the differential diagnosis of ascites, tests for the gross appearance of fluid, cell count correction, white blood cell count, and serum ascites albumin gradient are performed [6-10].

Therapeutic paracentesis is performed to relieve abdominal distension and pain in patients with massive ascites. Generally, over 5 L of fluid is drained for therapeutic paracentesis [11]. Albumin is used for plasma expansion to prevent hypovolemia [12]. Despite the risk of hypovolemia, therapeutic paracentesis should be performed in patients with refractory ascites.

Recently, the frequency of ultrasound (US)-guided paracentesis is higher than that of landmark-guided paracentesis. Based on the complication and success rates, US-guided paracentesis has been recommended [13], regardless of the purpose (diagnostic or therapeutic paracentesis).

At our institute, many punctures are performed under US guidance, several of which require repuncture due to the lack of continuous drainage. Recently, a newly developed puncture needle was introduced with a hard plastic sheath and plastic wings, unlike the previously used puncture needle. The plastic wings were thought to be close to the skin, making it easier to fix the sheath after the puncture.

In this retrospective study, we evaluated the periprocedural factors, complications, and repuncture rate of the newly developed puncture needle in US-guided paracentesis. In addition, we compared it to the routinely used puncture needle for US-guided paracentesis.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Pusan National University (IRB No: PNUH 1907-012-080), and all patients included in this study provided written informed consent to undergo the use of all puncture needles in ultrasound-guided paracentesis.

1. Study patients

We searched the institutional database from July 2018 to March 2019 for patients who had undergone US-guided paracentesis with available records in a case form (discussed later). Among the 234 eligible patients, 97 were excluded because of minimum-to-mild ascites (depth of peritoneal fluid less than 3 cm on US). Finally, 137 patients (95 men, 42 women; median age, 62 years; range, 31–84 years) were included. Among them, 82 patients, classified as group A (57 men, 25 women; median age, 62 years) underwent US-guided paracentesis with a newly developed puncture needle, and other 55 patients, classified as group B (38 men, 17 women; median age, 60 years) underwent US-guided paracentesis with a routinely used puncture needle, with a general sheath, and without plastic wings. The puncture needle type was randomly selected.

2. Clinical and periprocedural data collection

We retrospectively analyzed reporting templates for US-guided therapeutic paracentesis. At our institution, the clinical and periprocedural data for all patients who underwent US-guided paracentesis were recorded. The reporting template contained the following items: sex, age, platelet count, prothrombin time (PT), PT-international normalized ratio (INR), type of puncture needle (newly developed vs. routinely used), amount of ascites, the thickness of the abdominal wall, duration of the procedure from puncture to fixation, degree of pain, puncture site, and presence of repuncture. For the amount of ascites and thickness of the abdominal wall, the depth of peritoneal fluid and the distance between the skin and ascites were measured in cm on US before puncture. The degree of pain was assessed on the Likert scale (1–10; 1, no pain; 10, intolerable pain) using a questionnaire following paracentesis. The puncture site was selected based on the location of ascites, depending on the operator's comfort. If the drainage was not smooth after the puncture, repuncture was performed immediately using the same puncture needle. We also reviewed the medical records for complications associated with US-guided paracentesis and classified them as major and minor based on the Society of Interventional Radiology guidelines [14].

3. Device application

Compared to the routinely used puncture needle (BD Angiocath Plus; Becton Dickinson Medical, Franklin Lakes, NJ, USA), the newly developed puncture needle (3S-A.D.Cath-16 gauge; Dukwoo Medical, Hwaseong, Korea) was longer (50 mm vs. 45 mm). The newly developed puncture needle had a hard plastic sheath and plastic wings. Both puncture needles had the same diameter (16 gauge) and the same method of application (Fig. 1).

All patients underwent US-guided therapeutic paracentesis in the supine position, performed by a single radiologist (SBH, 7 years of clinical experience). Punctures were made at the right lower quadrant and left lower quadrant of the abdomen, and the location targeting the Morrison's pouch. Subsequently, the fluid was drained, and the metallic introducer needle was removed. Drainage of ascites was performed by fixing the remnant plastic sheath. When using the routinely used puncture needle, gauze packing was performed around the remnant plastic sheath. In the other case, plastic wings were attached to the skin by taping.

4. Statistical analysis

For periprocedural factors, categorical and continuous variables were expressed as counts (percentage) and median (range), respectively. We compared the periprocedural factors between the two groups using the Mann-Whitney U test and Fisher exact test and assessed the repuncture-associated factors using logistic regression analysis. For all tests, statistical significance was set at $p < 0.05$. All statistical analyses were performed using the IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

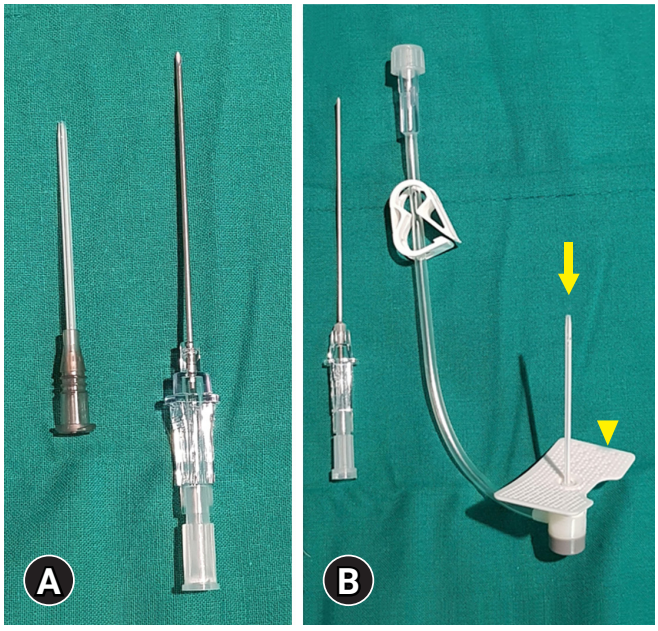

Fig. 1. Puncture needles for paracentesis. (A) Routinely used puncture needle. (B) Newly developed puncture needle. The newly developed puncture needle has a hard plastic sheath (arrow) and plastic wings (arrowhead).

Results

1. Characteristics and periprocedural factors of the study population

Among the 137 patients, group A underwent US-guided paracentesis with the newly developed puncture needle, and group B underwent US-guided paracentesis with the routinely used puncture needle. The clinical causes of ascites were not significantly different between the two groups (Table 1). The rate of repuncture was significantly lower in group A (6.1%; 95% confidence interval [CI], 2.3–13.8) than in group B (21.8%; 95% CI, 12.8–34.5) ($p = 0.01$). The duration of the procedure was significantly shorter in group A (median duration of 1 minute) than in group B (median duration of 2 minutes) ($p = 0.03$) (Table 2). Other characteristics and periprocedural factors were not significantly different between the two groups.

2. Complications and factors associated with the repuncture

There were no major or minor complications in either group. The thickness of the abdominal wall ($p = 0.04$) and use of the newly developed puncture needle ($p = 0.01$) were significantly associated with the rate of repuncture in the univariate analysis. In the multivariate analysis, only the use of the newly developed puncture needle was significantly associated with the rate of repuncture ($p = 0.02$) (Table 3).

In the five cases of repuncture where US-guided paracentesis was done with the newly developed puncture needle, all repunctures were performed in patients with carcinomatosis peritonei. Among the 12 cases of repuncture with the routinely used punc-

Table 1. The clinical cause of ascites in two groups

Clinical cause of ascites	All patients (n = 137)	Group A[a] (n = 82)	Group B[b] (n = 55)	*p*-value
Liver cirrhosis	105	62 (75.6)	43 (78.2)	0.84
Malignancy	29	18 (22.0)[c]	11 (20.0)[d]	0.83
Tuberculosis	3	2 (2.4)	1 (1.8)	> 0.99

Values are presented as number only or number (%).
[a]Group A: group with the newly developed puncture needle. [b]Group B: group with the routinely used puncture needle. [c]Ascites due to carcinomatosis peritonei (five patients with stomach cancer, five patients with cholangiocarcinoma, four patients with pancreatic cancer, and four patients with ovarian cancer). [d]Ascites due to carcinomatosis peritonei (three patients with pancreatic cancer, three patients with cholangiocarcinoma, three patients with stomach cancer, and two patients with ovarian cancer).

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Table 2. The characteristics and periprocedural factors of the two groups

Characteristic and periprocedural factor	Group A[a]	Group B[b]	*p*-value
No. of cases	82	55	NA
Age (yr)	62 (39–84)	60 (31–84)	0.19
No. of women	25 (30.5)	17 (30.9)	>0.99
Platelet count before procedure	127,500 (24,000–380,000)	146,000 (45,000–367,100)	0.32
PT-INR	1.21 (0.9–16.3)	1.16 (0.91–16.3)	0.22
Amount of ascites (cm)	8.0 (3.0–12.0)	7.0 (3.0–15.3)	0.82
Thickness of abdomen (cm)	2.0 (0.9–3.7)	2.0 (0.7–3.6)	0.42
Duration of procedure (min)	1.0 (1.0–4.0)	2.0 (1.0–6.0)	0.03
Degree of pain	3 (1–7)	3 (1–4)	0.87
Presence of repuncture	5 (6.1)	12 (21.8)	0.01
Puncture site			0.47
Right lower quadrant	63 (76.8)	47 (85.5)	
Left lower quadrant	8 (9.8)	4 (7.3)	
Morrison's pouch	11 (13.4)	4 (7.3)	

Values are presented as number only, median (range), or number (%).
[a]Group A: group with the newly developed puncture needle. [b]Group B: group with the routinely used puncture needle.
NA, not available; PT, prothrombin time; INR, international normalized ratio.

Table 3. Clinical and periprocedural factors associated with repuncture

Clinical and periprocedural factor	Univariate analysis		Multivariate analysis	
	Odds ratio	*p*-value	Odds ratio	*p*-value
Age	0.97	0.24		
Sex	1.70	0.32		
Amount of ascites	0.85	0.85		
Thickness of abdomen	2.30	0.04	2.10	0.06
Device				
Routine	1[a]		1[a]	
Hard plastic sheath	0.23	0.01	0.23	0.02
Puncture site				
Right lower quadrant	1[a]			
Left lower quadrant	0.62	0.66		
Morrison's pouch	1.06	0.95		
Cause of ascites				
Liver cirrhosis	1[a]			
Malignancy	2.23	0.15		
Tuberculosis	0.00	0.99		

[a]Reference for calculating the odds of other subcategories of variables.

ture needle, most repunctures were performed in patients with liver cirrhosis (11 of 12). In the cases of US-guided paracentesis with the routinely used puncture needle, repuncture was performed because of kinking of the sheath (11 of 12) or lack of definite penetration of the parietal peritoneum (1 of 12).

Discussion

US-guided paracentesis is safe and widely used to treat ascites. Recently, a new puncture needle with a hard plastic sheath and plastic wings was developed. Our study showed that the rate of repuncture was significantly lower in group A (6.1%; 95% CI, 2.3–13.8) than in group B (21.8%; 95% CI, 12.8–34.5) ($p=0.01$). Among the repuncture-associated factors, only the use of the newly developed puncture needle was significantly associated with the rate of repuncture ($p=0.02$).

The peritoneal cavity is the space between the parietal peritoneum and the visceral peritoneum. The parietal peritoneum lines the

abdominal wall and is penetrated in US-guided paracentesis [15]. The parietal peritoneum has elasticity [16], which can prevent penetration of the plastic sheath and result in repuncture. However, the newly developed puncture needle for paracentesis has a hard plastic sheath, which may help penetrate the parietal peritoneum and reduce the kinking of the sheath during drainage. Plastic wings contribute to fixation stability following paracentesis.

Regarding the newly developed puncture needle, all repunctures were performed in patients with carcinomatosis peritonei. Loculated ascites is associated with malignancy and inflammation [17]. Due to the presence of loculated ascites, a large amount of ascites could not be drained, and a repuncture was necessary. Unlike the newly developed puncture needle, most repunctures were performed because of kinking of the sheath with the routinely used puncture needle.

Comparing the characteristics and periprocedural factors between the two groups, the duration of the procedure was significantly lesser in group A (median duration of 1 minute) compared to group B (median duration of 2 minutes) ($p = 0.03$). The longer procedural time associated with the routinely used puncture needle might be due to the relatively frequent repunctures. As the frequency of repuncture increases, the likelihood of complications may increase and may also affect patient satisfaction during or after the procedure.

In our results, the thickness of the abdominal wall was a significant factor associated with repuncture on univariate analysis. The newly developed puncture needle was slightly longer than the routinely used puncture needle, which was advantageous for puncture and drainage. However, there were no significant differences in the thickness of the abdominal wall between the two groups.

No complications occurred in either group. Although many patients with ascites present with increased PT or PT-INR, less than 1% of cases have major complications, such as hemoperitoneum [18,19]. In a previous study reviewing hemorrhagic complications following paracentesis in 4,729 cases, severe hemorrhage occurred in 0.2% of all procedures in patients with liver disease [20]. In addition, US-guided paracentesis is safer than bedside procedures [21,22]. All paracentesis procedures were performed under US guidance in our study, which resulted in no major complications following paracentesis.

Our study had several limitations. First, because this study was retrospective, and we only analyzed patients with therapeutic paracentesis, selection bias may exist. However, this study was consecutive, and we compared the periprocedural factors between the two groups. Second, our results were confined to therapeutic US-guided paracentesis. We did not investigate the efficacy and complications of diagnostic US-guided paracentesis. Generally, continuous drainage following sheath fixation is not necessary for diagnostic paracentesis, which acquires a small amount of ascites. There were no other differences in the procedural techniques between diagnostic and therapeutic paracentesis. The efficacy and complications of this new puncture needle could be comparable to that of the routinely used puncture needle in diagnostic US-guided paracentesis. Third, there were no specific criteria for choosing the type of puncture needle, and the choice was made randomly. A study on the indications for a new puncture needle for paracentesis may be necessary. Finally, the study included a small number of participants. Therefore, further prospective studies with larger sample sizes are necessary.

In conclusion, the new puncture needle with a hard plastic sheath and plastic wings can decrease the rate of repuncture and duration of US-guided therapeutic paracentesis without complications.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: IWS, SBH, SK, SYH, HYW; Formal analysis: IWS, SK, SBH, NKL, MRJ; Data curation: IWS, MRJ; Funding acquisition, Project administration, Resources, Supervision: SK; Methodology: IWS, SBH; Visualization, Software: IWS; Investigation: IWS, SK; Validation: SK, SYH, HYW, MRJ; Writing-original draft: IWS; Writing-review & editing: SK, SYH, HYW.

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Magnetic resonance imaging texture analysis for the evaluation of viable ovarian tissue in patients with ovarian endometriosis: a retrospective case-control study

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Background: Texture analysis has been used as a method for quantifying image properties based on textural features. The aim of the present study was to evaluate the usefulness of magnetic resonance imaging (MRI) texture analysis for the evaluation of viable ovarian tissue on the perfusion map of ovarian endometriosis.

Methods: To generate a normalized perfusion map, subtracted T1-weighted imaging (T1WI), T1WI and contrast-enhanced T1W1 with sequences were performed using the same parameters in 25 patients with surgically confirmed ovarian endometriosis. Integrated density is defined as the sum of the values of the pixels in the image or selection. We investigated the parameters for texture analysis in ovarian endometriosis, including angular second moment (ASM), contrast, correlation, inverse difference moment (IDM), and entropy, which is equivalent to the product of area and mean gray value.

Results: The perfusion ratio and integrated density of normal ovary were 0.52 ± 0.05 and 238.72 ± 136.21, respectively. Compared with the normal ovary, the affected ovary showed significant differences in total size ($p<0.001$), fractional area ratio ($p<0.001$), and perfusion ratio ($p=0.010$) but no significant differences in perfused tissue area ($p=0.158$) and integrated density ($p=0.112$). In comparison of parameters for texture analysis between the ovary with endometriosis and the contralateral normal ovary, ASM ($p=0.004$), contrast ($p=0.002$), IDM ($p<0.001$), and entropy ($p=0.028$) showed significant differences. A linear regression analysis revealed that fractional area had significant correlations with ASM ($r^2=0.211$), IDM ($r^2=0.332$), and entropy ($r^2=0.289$).

Conclusion: MRI texture analysis could be useful for the evaluation of viable ovarian tissues in patients with ovarian endometriosis.

Keywords: Endometriosis; Gadolinium; Magnetic resonance imaging; Ovary

Introduction

Endometriosis occurs in 6% to 10% of women of reproductive age, among whom approximately 30% to 50% are infertile [1,2]. Therefore, for a patient with endometriosis who wants to conceive through ovarian preservation, the surgeon should use the appropriate surgical method to avoid destruction due to blood coagulation or destruction of the ovarian blood vessels to reduce damage

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to the residual ovarian tissue [3]. In addition to advances in surgical technology, various studies on clinical data have been attempted to find preoperative biomarkers useful in predicting the likelihood of pregnancy after surgery. Therefore, the need for preoperative imaging to assess ovarian tissue around endometriosis is raised to minimize damage to the ovarian reserve.

Recently, the increasing prevalence of ovarian endometriosis in young nulliparous women, who desire to preserve their ovarian function raised the necessity of magnetic resonance imaging (MRI) examination. Because the ovaries contain several stages of follicles, they are easily identified in most women's pelvic MRIs during the reproductive period [4,5]. T2-weighted images (T2WI) are the most useful sequences in the diagnosis of disorders in the ovaries and ovarian follicles in women of reproductive age [6]. The ovarian stroma shows a contrast enhancement similar to that of the myometrium, and its contrast enhancement pattern on T1-weighted images (T1WI) correlated with age and menopausal status [6]. Cystic follicles and functional ovarian cysts were found frequently and with variable appearances. Most cysts show discrete enhancement of the wall. In contrast to poorly perfused endometrial cysts, regardless of T1 high signal intensity, remnant ovarian tissue could appear well perfused. However, when the endometriosis involves the ovary, the typical magnetic resonance (MR) findings were displacement of the affected ovarian tissue by cystic lesions with high signal intensity on T1WI and T2WI [7,8]. However, hemosiderin deposit due to repeated bleeding within the endometriosis can cause a change in MR signal [7,9,10]. Ultimately, ovarian reserve can be defined as the quantity and quality of the remaining follicular pools that can grow in the presence of gonadotropin. Therefore, evaluating the state of the residual ovary in the image can be a biomarker for evaluating ovarian reserve.

In the present study, the effect of ovarian tissue enhancement was normalized by dividing the subtracted contrast enhancement T1WI by contrast enhancement T1WI. In addition, integrated density was defined as the sum of the values of the pixels in the image or selection. Texture characteristics are the intrinsic properties of an image and provide an efficient image classification system by which subtle alterations in the gray level distribution of an image can be detected [11]. We investigated the parameters for texture analysis in ovarian endometriosis, including angular second moment (ASM), contrast, correlation, inverse difference moment (IDM), and entropy, which is equivalent to the product of area and mean gray value. Consequently, the aim of this study was to evaluate the usefulness of texture analysis for the normalized perfusion map of pelvic MRI for predicting remnant ovarian tissues in patients with endometriosis.

Methods

Ethical statements: The Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2017-06-012) approved the retrospective data collection and analysis. The need for informed consent was waived for the retrospective design of the study.

In this study, female patients who underwent ovarian cystectomy for endometrioma by surgery between January 2016 and December 2019 were included. After surgical cystectomy, histopathological examination was performed for final diagnosis in all the cases. To evaluate the diseased ovary in comparison with the normal ovary, the patients with endometriosis only on one side were included, and those with disease on the other side were excluded. Normal ovary was defined as that without endometriosis on preoperative ultrasonography and MRI.

All the examinations were performed on a 3.0-tesla MR machine (Skyra; Siemens Health Care, Erlangen, Germany). Before MRI examination, the patients underwent 6 hours of fasting followed by intramuscular administration of 20 mg of hyoscine butylbromide (Buscopan; Boehringer Ingelheim, Ingelheim am Rhein, Germany) to inhibit bowel movement. In the study, a set of 8-channel phased-array body coils was applied. We performed the MRI examination using the same parameters for field of view, slice thickness, echo time, repetition time for T1WI, and contrast-enhanced T1WI acquisition to generate a normalized perfusion map. To obtain a normalized perfusion image, the non-contrast-enhanced image was subtracted from the contrast-enhanced image and then divided by the contrast-enhanced image. As a result, each pixel constituting the normalized perfusion map was theoretically coded from 0 for no perfusion to 1 for complete perfusion (Fig. 1). Each region of interest (ROI) was measured by specifying an outline of the ovaries affected by endometriosis at the level with the largest area of the remaining ovary and the normal contralateral ovary on T2WI by one radiologist who was blinded to the clinical information. To measure only the perfusion of the surviving ovarian tissue, pixels corresponding to the endometriotic cysts with a low perfusion state of ≤ 0.2 and high perfusion state of ≥ 0.9 were removed using the threshold technique. The fractional area ratio was defined as the ratio of tissue area with a perfusion ratio between 0 and 0.2 to the total area.

The area, mean and standard deviation of signal intensity, and integrated density of the affected ovary with endometrioma were compared with those of the normal ovary. Integrated density, as the sum of all pixel intensities in the ROI, indicates the total

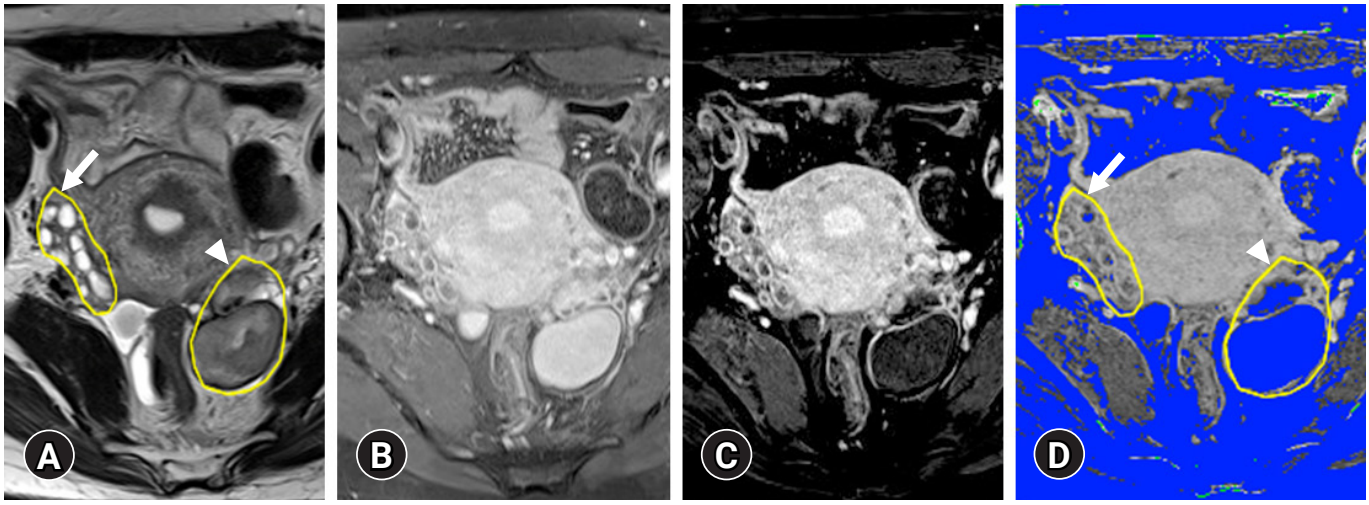

Fig. 1. (A) Region of interest (ROI) for normal ovary (arrow) and endometriosis (arrowhead) is defined on the T2-weighted image. (B, C) Division of the subtraction image by the contrast-enhanced T1-weighted image generates a normalized perfusion map. To measure only the perfusion of the surviving ovarian tissue, pixels corresponding to endometriotic cysts with a low perfusion state of 0.2 or less were removed using the threshold technique. (D) The saved ROI is applied to the normalized perfusion map.

amount of contrast enhancement effect in this study. The parameters included in the ASM, contrast, correlation, IDM, and entropy for the same ROI in the perfusion map, were calculated using the GLCM plugin using ImageJ (1.50i; National Institutes of Health, Bethesda, MD, USA; https://imagej.nih.gov/ij). Statistical analyses were performed using IBM SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA). The paired *t*-test was used to examine the difference in numerical variables from those in the texture analysis. Statistical significance was set at a *p*-value of < 0.05.

Results

This study included 25 patients with pathologically confirmed ovarian endometriosis after cystectomy. The mean age was 28.21 ± 5.71 years. Normal ovary was defined in all the patients. The normal ovaries showed variable-sized multiple cysts surrounded by solid ovarian stromal tissue on T2WI. At the level of the maximal diameter, normal ovaries showed 537.70 ± 331.80 mm^2 of area. Compared with the normal ovaries, ovaries affected by endometriosis had a higher number of pixels, with a perfusion ratio between 0 and 0.2 with poor perfusion due to the endometriotic cysts (Fig. 2). As a result, the perfused tissue area was 430.79 ± 272.98 mm^2 for the area of the tissue in the range of 0.2 to 0.9. The ratio of the fractional area with a perfusion ratio of 0.2 to 0.9 to the total area was 0.89 ± 0.11. The perfusion ratio and integrated density of the normal ovary were 0.52 ± 0.05 and 238.72 ± 136.21, respectively.

Compared with the normal ovary, the total size ($p < 0.001$), fractional area ratio ($p < 0.001$), and perfusion ratio ($p = 0.010$) of the affected ovary showed significant differences, but the perfused tissue area ($p = 0.158$) and integrated density ($p = 0.112$) had no significant differences (Table 1).

In the comparison with the parameters for texture analysis between the ovary affected by endometriosis and the contralateral normal ovary, ASM ($p = 0.004$), contrast ($p = 0.002$), IDM ($p < 0.001$), and entropy ($p = 0.028$) showed significant differences (Table 2). However, all the cysts showed a low perfusion ratio on the normalized perfusion map (Fig. 3). Linear regression analysis revealed a significant coefficient of determination between the fractional area with ASM ($r^2 = 0.211$), IDM ($r^2 = 0.332$), and entropy ($r^2 = 0.289$; Fig. 4). The standard coefficients of ASM, IDM, and entropy were −0.459 ($p = 0.021$), −0.577 ($p = 0.003$), and 0.538 (0.006), respectively (Table 3).

Discussion

Until now, the effect of contrast enhancement on the evaluation of endometriosis using MRI has been shown to differentiate between other hemorrhagic adnexal lesions, luteal cysts, ovarian abscesses, or potentially malignant tumors [12,13]. However, this study focused on the role of contrast agents in the evaluation of adjacent surviving ovarian tissue invaded by endometriosis. The perfusion map could be used for the analysis of viable tissue within this subset of cystic ovarian masses according to the severity of endometriosis for preoperative evaluation [14-16].

In the present study, the total perfusion ratio of the normal ovary ranged from 0.2 to 0.9 as compared with that of cysts caused by endometriosis, which was < 0.2 [17]. In this study, we suggest inte-

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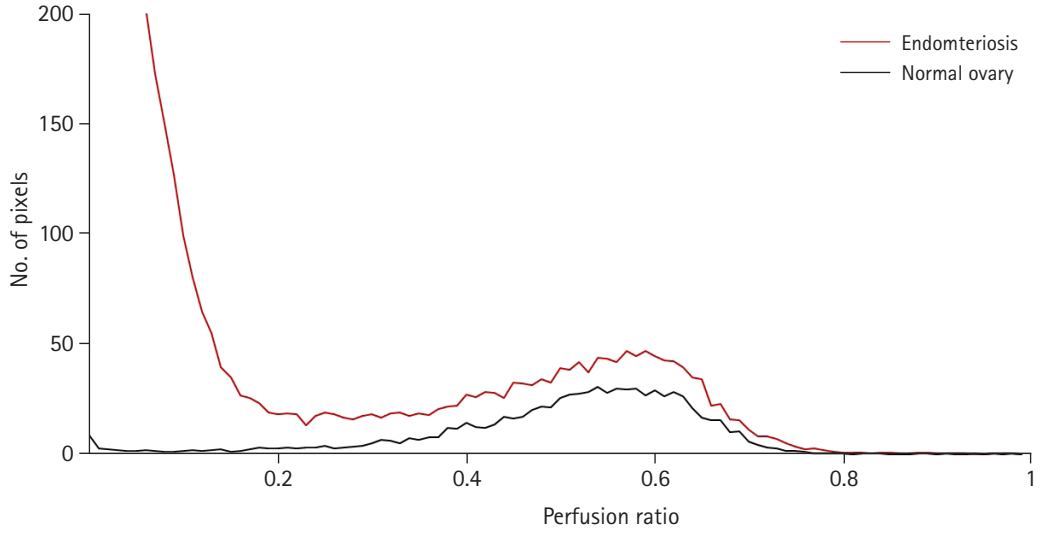

Fig. 2. Comparison of the number of pixels for the perfusion ratio between normal ovary (black line) and affected ovary by endometriosis (red line).

Table 1. Comparison of parameters of normalized perfusion map between affected ovary by endometriosis and contralateral normal ovary

Parameter	Affected ovary by endometriosis	Contralateral normal ovary	*p*-value[a]
Total area (mm^2)	2,050.40 ± 1,067.99	537.70 ± 331.80	< 0.001
Perfused tissue area (mm^2), 0.2 < perfusion ratio < 0.9	550.43 ± 270.22	430.79 ± 272.98	0.158
Fractional area ratio[b]	0.33 ± 0.19	0.89 ± 0.11	< 0.001
Perfusion ratio within perfused tissue area	0.49 ± 0.06	0.52 ± 0.05	0.010
Integrated density	290.25 ± 150.83	238.72 ± 136.21	0.112

Values are presented as mean ± standard deviation.
[a]Paired *t*-test. [b]Ratio of tissue area with perfusion ratio between 0 and 0.2 to the total area.

Table 2. Comparison of histogram analysis between affected ovary by endometriosis and contralateral normal ovary

Variable	Affected ovary by endometriosis	Contralateral normal ovary	*p*-value[a]
Angular second moment	0.10 ± 0.15	0.01 ± 0.03	0.004
Contrast	779.96 ± 396.83	1,040.45 ± 559.94	0.002
Correlation	0.00062 ± 0.00175	0.00066 ± 0.00154	0.440
Inverse difference moment	0.31 ± 0.18	0.14 ± 0.08	< 0.001
Entropy	6.40 ± 1.53	7.10 ± 0.75	0.028

Values are presented as mean ± standard deviation.
[a]Paired *t*-test.

grated density modified by area instead of pixel number. Although the further clinical study is needed, integrated density could be a potential biomarker of remnant ovarian tissue. In the present study, severe endometriotic invasion showed a smaller area with a moderate perfusion ratio similar to that of the ovary, which suggests that the perfusion map could predict remnant ovarian preserve. However, it is difficult to discriminate between the infiltration by the cyst accompanied by inflammatory changes due to endometriosis and the surrounding surviving ovarian tissue. Our results showed an increased pixel count at perfusion ratios between 0.4 and 0.9 in endometriosis, which suggests an increase in inflammatory changes in endometriosis and cystic lesions. These results may suggest that assessment of the degree of ovarian involvement may be helpful in determining the preoperative grade [14,15]. In this study, cysts were subtracted from the ovaries affected with endometriosis, and the remaining surviving ovarian tissues were compared with normal ovaries. The remainder after excluding the cyst site is presumed to be the changes caused by endometriosis, including inflammation and neovascularization, which will affect the texture analysis.

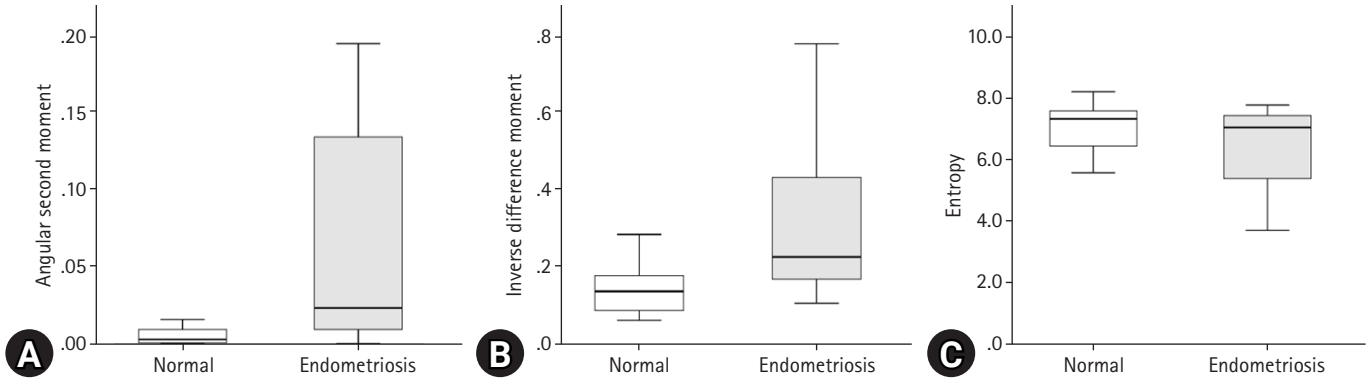

Fig. 3. Comparison of texture analysis parameters, including (A) angular second moment, (B) inverse difference moment, and (C) entropy, between affected ovary by endometriosis and the contralateral normal ovary.

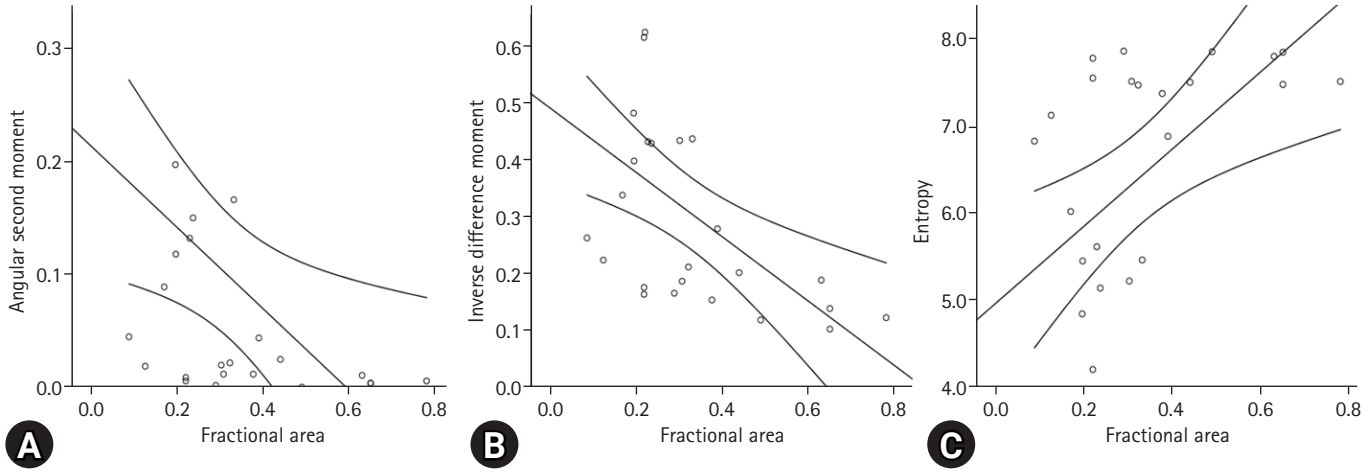

Fig. 4. Linear regression analysis of the parameters for texture analysis, including (A) angular second moment, (B) inverse difference moment, and (C) entropy, of the affected ovary according to fractional area.

Table 3. Linear regression analysis between parameters of texture analysis with fractional area of ovarian tissue affected by endometriosis

Model	Unstandardized coefficient		Standardized coefficient β	*t*	r^2	*p*-value[a]
	β	Standard error				
Angular second moment	–0.359	0.145	–0.459	–2.478	0.211	0.021
Inverse difference moment	–0.567	0.168	–0.577	–3.384	0.332	0.003
Entropy	4.430	1.448	0.538	3.061	0.289	0.006

[a]Paired *t*-test.

Texture analysis has been used as a method for quantifying image texture, which is concerned with the description of the image properties based on textural features [18]. Texture analysis of medical images has expanded its applications to segmentation of specific anatomical structures, detection of lesions, differentiation, and prognosis of pathological and healthy tissues [19]. ASM, also called uniformity or energy, represents image homogeneity. A high ASM value represents good homogeneity of the image and remarkable similarity of pixels. The IDM score implies the local homogeneity of the image. A high IDM score indicates uniformity in the gray level of the image. Entropy refers to the amount of image information required for image compression. The loss of image information or message can be measured by entropy. Texture analysis has been applied in various clinical areas and imaging methods but rarely applied in the evaluation of gynecological diseases, especially endometriosis, using MRI. Recently, histological analysis has been used to distinguish between cystic lesions of endometriosis and hemorrhagic cysts on MRI; therefore, images of selected le-

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sions were from T2WI [20]. However, the present study was conducted to compare infected endometrial tumors with normal ovaries; therefore, texture analysis was performed using a perfusion map based on contrast-enhanced T1WI.

However, this study has several limitations. First, the number of enrolled patients was too small for comprehensive understanding of the relationship between imaging results and clinical outcomes. For the validation of usefulness of texture analysis for prediction ability for pregnancy, a larger study population is mandatory. Second, the acquisition of perfusion maps requires that a trained radiologist strictly adheres to a specific protocol for obtaining an accurate image. Despite the need to create an image subtracted from correct pre- and postcontrast images, risk of disturbance caused by the patient's voluntary or involuntary movements remain [21,22]. Third, each ROI measurement was performed by a single observer, and the inter- and intraobserver variations were not assessed. However, these variations are expected to be small and barely affect the results of whole-volume measurements.

All the measurements and calculations after ROI measurement are made in the image postprocessing application, so these changes are limited and have little effect on texture analysis. Finally, the texture analysis result may vary depending on the image acquisition parameters, including image resolution, field size, and heterogeneity. Some of the features required to describe the structure of the tissue being examined can reflect the uneven sensitivity of the scanner, which can lead to inadequate description of the tissue.

This study focused on the role of texture analysis on perfusion imaging in patients with ovarian endometriosis. Normalized perfusion maps showed the extent of invasion of ovarian endometriosis to adjacent remnant ovarian tissue. The parameters of the perfusion map, including the perfusion ratio and integrated density in the residual ovary represented by the region with a perfusion ratio of 0.4 to 0.9, showed a correlation with the degree of endometrial invasion. In conclusion, texture analysis for the perfusion map of pelvic MRI could be useful for revealing the extent of endometrial invasion and viable remnant ovarian tissue. Until now, texture analysis of perfusion maps of pelvic MRI has been studied very rarely and may be a promising tool for preoperative evaluation of residual ovarian tissue in patients who wish to preserve their ovaries during surgical treatment.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Formal analysis, Visualization, Resources, Software, Supervision: HJL; Project administration: DL; Data curation, Methodology: all authors; Writing-original draft: all authors; Writing-review & editing: all authors.

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Impact of an emergency department resident strike during the coronavirus disease 2019 (COVID-19) pandemic in Daegu, South Korea: a retrospective cross-sectional study

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Background: To prepare for future work stoppages in the medical industry, this study aimed to identify the effects of healthcare worker strikes on the mortality rate of patients visiting the emergency department (ED) at six training hospitals in Daegu, South Korea.
Methods: We used a retrospective, cross-sectional, multicenter design to analyze the medical records of patients who visited six training hospitals in Daegu (August 21–September 8, 2020). For comparison, control period 1 was set as the same period in the previous year (August 21–September 8, 2019) and control period 2 was set as July 1–19, 2020. Patient characteristics including age, sex, and time of ED visit were investigated along with mode of arrival, length of ED stay, and in-hospital mortality. The experimental and control groups were compared using *t*-tests, and Mann-Whitney *U*-test, chi-square test, and Fisher exact tests, as appropriate. Univariate logistic regression was performed to identify significant factors, followed by multivariate logistic regression analysis.
Results: During the study period, 31,357 patients visited the ED, of which 7,749 belonged to the experimental group. Control periods 1 and 2 included 13,100 and 10,243 patients, respectively. No significant in-hospital mortality differences were found between strike periods; however, the results showed statistically significant differences in the length of ED stay.
Conclusion: The ED resident strike did not influence the mortality rate of patients who visited the EDs of six training hospitals in Daegu. Furthermore, the number of patients admitted and the length of ED stay decreased during the strike period.

Keywords: COVID-19; Emergency medical services; Employee strikes; Hospital mortality; Hospitals; Physicians

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Introduction

In August 2020, residents across the country went on strike to protest against the government's healthcare policies. Although a labor strike is a worker's right, healthcare worker strikes concern public welfare and are, therefore, a controversial social issue. A healthcare worker strike can cause public concern, as it has the potential to disrupt normal healthcare delivery, halt disease testing and treatment, and lead to increased overall mortality. However, previous studies have reported that mortality is not markedly altered during a healthcare worker strike. In a review by Cunningham et al. [1], four studies reported reduced mortality, and three studies reported no difference in mortality during a physicians' strike. A study conducted in Kilifi, Kenya, using data registered in the Kilifi Health and Demographic Surveillance system, revealed no considerable change in mortality during the six physician and nurse strikes that took place between 2010 and 2016. [2]. One Korean study from 2000 reported that emergency department (ED) use and length of ED stay decreased during an ED healthcare providers' strike [3]. The year 2020 was a period of dramatic changes for patients and healthcare providers alike because of the coronavirus disease 2019 (COVID-19) pandemic. Hartnett et al. [4] reported that the number of patients visiting the ED decreased, and the reason for ED visits showed marked changes during the COVID-19 pandemic.

Furthermore, another study reported that ED utilization declined out of fear of contracting COVID-19 at the ED and that the number of out-of-hospital cardiac arrests increased [5]. Amidst the pandemic, medical residents in South Korea went on strike for 19 days in opposition to the government's healthcare policies.

Previous studies have generally analyzed the relationship between strikes and patient mortality rates. In the present study, we investigated the effects of the resident strike during the COVID-19 pandemic on patient mortality, as well as the general characteristics of patients visiting the EDs of six teaching hospitals in Daegu, South Korea, ultimately presenting data to help respond to potential healthcare worker strikes in the future.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Kyungpook National University Hospital (IRB No. 2020-12-024) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived by the IRB owing to the retrospective nature of the study.

1. Study design, setting, population, and variables

This multicenter cross-sectional study retrospectively analyzed the medical records of six teaching hospitals in Daegu Metropolitan City from August 21 to September 8, 2020. Control period 1 (August 21–September 8, 2019) was set as the same period in the preceding year to reduce the seasonal influence. Control period 2 (July 1–19, 2020) was set to the same period to consider the impact of COVID-19. The start of control period 2 (July 2020) was set one month before the initiation of the strike (August 2020) for two reasons. First, in the early months of 2020, Daegu experienced a surge in COVID-19 cases. In those months, the effects of COVID-19 on patients' characteristics may be greater than the effects of the strike. The other reason was to choose a month with as minimal seasonal factors as possible. During control period 2, there were fewer than 100 COVID-19 cases per day.

In 2019, 252,608 patients visited the EDs of the six target hospitals. Prior to the strike, 83 physicians (46 specialists and 37 residents) worked in the ED. The resident strike participation rate was 100%, and during the strike, all residents in the ED were replaced by specialists. The target patient population included patients presenting to the EDs of six teaching hospitals during the strike and those presenting during the control periods. Patients who did not present to an ED to receive medical care (e.g., those who visited to retrieve their medical records, to obtain medication, or to cancel appointments) and those who were dead on arrival were excluded; patients who received cardiopulmonary resuscitation (CPR) on arrival were also excluded, as this can affect the primary outcome (in-hospital mortality). Patient age, sex, and ED visit time were examined. Factors related to ED visits, including mode of arrival to the ED, time of arrival, route of visit, triage, length of ED stay, disposition, and in-hospital death, were analyzed to determine their effect on the primary and secondary outcomes. The primary outcome was the in-hospital mortality rate, which was defined as death in the ED and death in the hospital following hospitalization. The secondary outcome was the length of ED stay, to examine the impact of the strike on the patient population.

2. Statistical analyses

Statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages. Continuous variables are presented as median values with interquartile ranges. When comparing the patient populations between the strike and control periods, normally distributed continuous data were analyzed by *t*-tests, and non-normally distributed continuous data were analyzed using the Mann-Whitney *U*-test. Categorical data were analyzed using the chi-square test and Fisher exact test. Multivariate logistic re-

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gression analysis was used to assess the effects of the predictors on the outcome, hospital mortality (by the period, hospital, Korean Triage and Acuity Scale [KTAS], mode of arrival, age, and patients per bed). All variables with a significance level of P less than 0.01 in the univariate analysis were included in the multivariate logistic regression model. Control period 2 was designated as a reference for intuitive understanding in the multivariate logistic regression analysis. The results of the logistic regression analysis are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was defined as a *p*-value of ≤ 0.05.

Results

A total of 31,357 patients were admitted to the ED during the study period. Patients who visited the ED for nontreatment purposes (patients who required CPR on arrival, visited for medical certification, were dead on arrival, and had canceled their appointment) were excluded. The number of patients who visited the ED was 13,100 during control period 1, 10,243 during control period 2, and 7,749 during the strike period (Fig. 1).

1. Comparison of control period 1 with the strike period

The median age of the patients was 50 years in control period 1 and 55 years in the strike period. The most common mode of arrival was individual transportation (n = 8,315, 63.5% vs. n = 4,675, 60.3%), followed by public ambulance services (n = 2,688, 20.5% vs. n = 1,861, 24.0%), and private ambulance services (n = 2,097, 16.0% vs. n = 1,213, 15.7%), with differences observed between the two periods. The ED route also differed between the two periods for direct visits (n = 10,638, 81.2% vs. n = 6,424, 82.9%) and transfers (n = 2,462, 18.8% vs. n = 1,325, 17.1%). According to KTAS, the number of patients with level 1 was 119 (0.9%) vs. 98 (1.3%), with level 2 was 922 (7.0%) vs. 699 (9.0%), and level 3 was 5,932 (45.3%) vs. 4,096 (52.9%). Length of stay (LOS) in the ED decreased from 3.2 hours (1.8–6.2 hours) to 3.0 hours (1.6–6.4 hours). The number of patients per bed significantly decreased from 1.01 to 0.53. Hospital mortality significantly increased from 258 (2.0%) to 195 patients (2.5%) (Table 1).

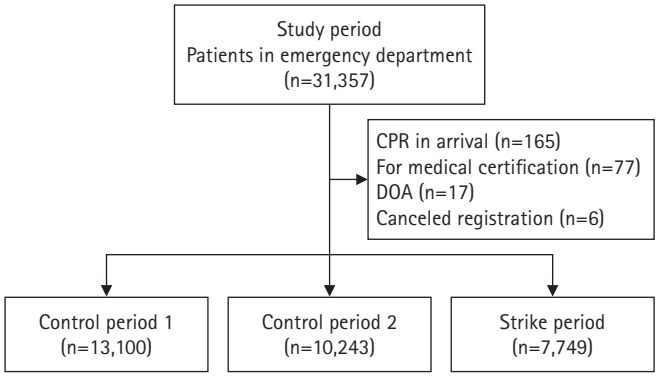

Fig. 1. Flow chart of enrolled patients. CPR, cardiopulmonary resuscitation; DOA, dead on arrival.

2. Comparison of control period 2 with strike period

The median age of patients was 54 years in control period 2 and 55 years in the strike period, and the difference was not statistically significant. The most common mode of arrival was individual transportation (n = 6,151, 60.1% vs. n = 4,675, 60.3%), followed by public ambulance services (n = 2,432, 23.7% vs. n = 1,861, 24.0%), and private ambulance services (n = 1,660, 16.2% vs. n = 1,213, 15.7%). The ED route differed between the two periods for direct visits (n = 8,269, 80.7% vs. n = 6,424, 82.9%) and transfers (n = 1,974, 19.3% vs. n = 1,325, 17.1%). Time from onset of symptoms to time of visit increased from 5.2 hours (1.3– 24.1 hours) to 6.2 hours (1.6–24.8 hours). The number of patients classified into KTAS level 1 was 112 (1.1%) vs. 98 (1.3%); level 2 was 849 (8.3%) vs. 699 (9.0%), level 3 was 5,412 (52.8%) vs. 4,096 (52.9%), and those assigned to levels 4 and 5 combined was 3,870 (37.8%) vs. 2,856 (36.8%), showing a reduced proportion of those with mild conditions. Patients' ED LOS decreased from 3.7 hours (2.0–7.6 hours) to 3.0 hours (1.6–6.4 hours). The number of patients per bed decreased from 0.81 patients (0.64–0.85 patients) to 0.53 patients (0.41–0.55 patients). Hospital mortality did not differ and was 2.5% in both the control and strike periods (Table 2).

3. Multivariate logistic regression of the associated factors for hospital mortality

Regarding hospital mortality by period, significant differences were observed in the univariate analysis for control period 1, but not in the multivariate analysis (Table 3). The OR for hospital mortality was 98.85 (95% CI, 61.97–157.65) for patients with KTAS level 1, 18.17 (95% CI, 11.93–27.66) for those with level 2, and 4.74 (95% CI, 3.15–7.13) for those with level 3. Regarding the mode of arrival, the OR for hospital mortality was 2.38 (95% CI, 1.89–2.99) for patients using a public ambulance service and 3.03 (95% CI, 2.40–3.81) for patients using a private ambulance service as opposed to those using individual transportation, indicating a significant difference. The OR for hospital mortality in terms of age was statistically significant at 1.04 (95% CI, 1.03–1.04), as was ED LOS at 1.03 (95% CI, 1.02–1.04).

Discussion

This study aimed to investigate the impact of a 19-day resident

Table 1. Demographic and clinical characteristics of the participants in control period 1 and the strike period

Characteristic	Control period 1 (August 21–September 8, 2019)	Strike period (August 21–September 8, 2020)	*p*-value
No. of patients	13,100	7,749	
Age (yr)	50 (22–68)	55 (31–71)	<0.01
Male sex	6,885 (52.6)	4,082 (52.7)	0.40
Vital sign			
Mean arterial pressure (mmHg)	94.7 (83.3–106.7)	96.7 (83.3–106.7)	<0.01
Heart rate (beat/min)	88 (76–105)	87 (76–103)	<0.01
Respiration rate (breath/min)	20 (20–20)	20 (18–20)	<0.01
Body temperature (℃)	36.8 (36.5–37.3)	36.9 (36.5–37.3)	<0.01
O_2 saturation (%)	98 (97–99)	98 (97–99)	0.36
Hospital			<0.01
A	2,652 (20.2)	1,442 (18.6)	
B	2,112 (16.1)	1,485 (19.2)	
C	1,754 (13.4)	805 (10.4)	
D	1,700 (13.0)	975 (12.6)	
E	1,725 (13.2)	1,147 (14.8)	
F	3,157 (24.1)	1,895 (24.5)	
Disease[a]	10,340 (78.9)	6,180 (79.8)	
Nondisease	2,753 (21.0)	1,563 (20.2)	
Mode of arrival			<0.01
Individual transportation	8,315 (63.5)	4,675 (60.3)	
Public ambulance service	2,688 (20.5)	1,861 (24.0)	
Private ambulance service	2,097 (16.0)	1,213 (15.7)	
Time of arrival			0.15
08:00–15:59	5,050 (38.5)	3,082 (39.8)	
16:00–23:59	5,526 (42.2)	3,170 (40.9)	
00:00–07:59	2,524 (19.3)	1,497 (19.3)	
Route of ED arrival			<0.01
Direct visit	10,638 (81.2)	6,424 (82.9)	
Transfer	2,462 (18.8)	1,325 (17.1)	
Onset to visit time (hr)	6.6 (1.4–28.7)	6.2 (1.6–24.8)	0.40
KTAS level			<0.01
1	119 (0.9)	98 (1.3)	
2	922 (7.0)	699 (9.0)	
3	5,932 (45.3)	4,096 (52.9)	
4, 5	3,870 (29.5)	2,856 (36.9)	
ED LOS (hr)	3.2 (1.8–6.2)	3.0 (1.6–6.4)	<0.01
Patients per bed	1.01 (0.67–1.08)	0.53 (0.41–0.55)	<0.01
Disposition from the ED[b]			<0.01
Discharge	9,164 (70.0)	5,197 (67.1)	
Transfer	404 (3.1)	264 (3.4)	
Admission	3,450 (26.3)	2,221 (28.7)	
Death	26 (0.2)	49 (0.6)	
Hospital mortality	258 (2.0)	195 (2.5)	0.01

Values are presented as number only, median (interquartile range), or number (%).
ED, emergency department; KTAS, Korean Triage and Acuity Scale; LOS, length of stay.
[a]Control period 1 vs. study period "unknown" 7 (0.1%) vs. 6 (0.1%). [b]Control period 1 vs. study period "others" 53 (0.4%) vs. 14 (0.2%), respectively.

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Table 2. Demographic and clinical characteristics of the participants in control period 2 and the strike period

Characteristic	Control period 2 (July 1–July 19, 2020)	Strike period (August 21–September 8, 2020)	*p*-value
No. of patients	10,243	7,749	
Age (yr)	54 (29–71)	55 (31–71)	0.07
Male sex	5,311 (51.9)	4,082 (52.7)	0.27
Vital sign			
Mean arterial pressure (mmHg)	93.7 (83.3–106.7)	96.7 (83.3–106.7)	<0.01
Heart rate (beat/min)	86 (76–103)	87 (76–103)	0.88
Respiration rate (breath/min)	20 (19–20)	20 (18–20)	<0.01
Body temperature (℃)	36.8 (36.5–37.3)	36.9 (36.5–37.3)	<0.01
O_2 saturation (%)	98 (97–99)	98 (97–99)	<0.01
Hospital			<0.01
A	1,969 (19.2)	1,442 (18.6)	
B	1,938 (18.9)	1,485 (19.2)	
C	1,343 (13.1)	805 (10.4)	
D	1,413 (13.8)	975 (12.6)	
E	1,215 (11.9)	1,147 (14.8)	
F	2,365 (23.1)	1,895 (24.5)	
Disease[a]	8,063 (78.7)	6,180 (79.8)	
Nondisease	2,176 (21.2)	1,563 (20.2)	
Mode of arrival			<0.01
Individual transportation	6,151 (60.1)	4,675 (60.3)	
Public ambulance service	2,432 (23.7)	1,861 (24.0)	
Private ambulance service	1,660 (16.2)	1,213 (15.7)	
Time of arrival			0.84
08:00–15:59	4,038 (39.4)	3,082 (39.8)	
16:00–23:59	4,235 (41.3)	3,170 (40.9)	
00:00–07:59	1,970 (19.2)	1,497 (19.3)	
Route of ED arrival			<0.01
Direct visit	8,269 (80.7)	6,424 (82.9)	
Transfer	1,974 (19.3)	1,325 (17.1)	
Time from onset to visit (hr)	5.2 (1.3–24.1)	6.,2 (1.6–24.8)	<0.01
KTAS level			<0.01
1	112 (1.1)	98 (1.3)	
2	849 (8.3)	699 (9.0)	
3	5,412 (52.8)	4,096 (52.9)	
4, 5	3,870 (37.8)	2,856 (36.8)	
ED LOS (hr)	3.7 (2.0–7.6)	3.0 (1.6–6.4)	<0.01
Patients per bed	0.81 (0.64–0.85)	0.53 (0.41–0.55)	<0.01
Disposition from the ED[b]			<0.01
Discharge	6,709 (65.5)	5,197 (67.1)	
Transfer	297 (2.9)	264 (3.4)	
Admission	3,122 (30.5)	2,221 (28.7)	
Death	66 (0.6)	49 (0.6)	
Hospital mortality	253 (2.5)	195 (2.5)	0.84

Values are presented as number only, median (interquartile range), or number (%).
ED, emergency department; KTAS, Korean Triage and Acuity Scale; LOS, length of stay.
[a]Control period 2 vs. study period "unknown" 4 (0.0%) vs. 6 (0.1%). [b]Control period 2 vs. study period "others" 47 (0.5%) vs. 14 (0.2%), respectively.

Table 3. Univariate and multivariate logistic regression analyses of associated factors for hospital mortality

Variable	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Period				
Control period 2	Reference		Reference	
Control period 1	0.79 (0.67–0.95)	0.01	1.04 (0.85–1.28)	0.71
Strike period	1.02 (0.84–1.23)	0.84	0.98 (0.69–1.38)	0.90
Hospital				
A	Reference		Reference	
B	0.61 (0.48–0.79)	<0.01	0.83 (0.63–1.09)	0.18
C	0.98 (0.77–1.25)	0.86	0.68 (0.47–1.01)	0.05
D	1.09 (0.87–1.38)	0.46	1.13 (0.77–1.65)	0.53
E	0.79 (0.61–1.02)	0.07	1.75 (1.27–2.40)	<0.01
F	0.49 (0.39–0.63)	<0.01	0.90 (0.69–1.17)	0.44
KTAS level				
4, 5	Reference		Reference	
3	10.88 (7.29–16.22)	<0.01	4.74 (3.15–7.13)	<0.01
2	49.69 (33.03–74.75)	<0.01	18.17 (11.93–27.66)	<0.01
1	287.0 (183.86–447.97)	<0.01	98.85 (61.97–157.65)	<0.01
Mode of arrival				
Individual transportation	Reference		Reference	
Public ambulance service	6.81 (5.50–8.42)	<0.01	2.38 (1.89–2.99)	<0.01
Private ambulance service	9.73 (7.86–12.05)	<0.01	3.03 (2.40–3.81)	<0.01
Age	1.05 (1.05–1.06)	<0.01	1.04 (1.03–1.04)	<0.01
Patients per bed	0.51 (0.37–0.70)	<0.01	0.78 (0.33–1.83)	0.59

OR, odds ratio; CI, confidence interval; KTAS, Korean Triage and Acuity Scale.

strike during the COVID-19 pandemic on the mortality and ED LOS of patients who visited the EDs of six teaching hospitals in Daegu, South Korea. Doctors do not strike frequently because of ethical concerns [6]. In particular, a physicians' strike is heavily criticized because of the belief that it will adversely impact patients (e.g., delay of scheduled surgeries, failure to provide proper care for emergency patients). Contrary to popular belief, however, a previous review did not observe a clear correlation between physician strikes and mortality [1].

In the present study, the number of patients who visited the EDs of the six teaching hospitals was affected during the strike; however, this relationship varied in previous studies. Salazar et al. [7] reported that there were no marked differences in the number of patients during a strike. In a 2016 study on a junior physicians' strike, Furnivall et al. [8] observed that the number of patients who actually visited a hospital fell short of the projections. These results could be attributed to the differences in methods of measuring the impact of strikes and various sociological factors, such as whether the strike emerged as a key issue in society.

Compared to the control periods, the patients' conditions were more severe during the strike period. That is, the number of patients classified as KTAS levels 1 or 2 increased during the strike period compared to that in the control periods. This result differs from that of a year 2000 study at Daejeon by Lee et al. [3], who reported an increased number of patients with mild conditions during a strike. The difference between the findings of this study and ours may be due to the low participation of primary care facility physicians in the present study's strike; thus, patients with mild conditions would have had no need to visit a tertiary hospital. Furthermore, the fact that patients with fever alone (no other symptoms) had limited access to primary care facilities during the pandemic may also have influenced the results.

COVID-19 is the first pandemic that has occurred since the Spanish flu in 1918. To the best of our knowledge, this is the first study to analyze resident strikes during such a period. We compared the impact of COVID-19 and residents' strikes on the ED. A previous study that analyzed the impact of COVID-19 on the ED reported similar outcomes [5], that is, the number of patients utilizing EDs declined. This decrease may have been due to people's fear of an increased risk of COVID-19 infection during ED visits.

We examined the impact of resident strikes on EDs in terms of mortality. In a previous study on the impact of physicians' strikes in

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public hospitals in Israel, Siegel-Itzkovich [9] analyzed the impact based on the number of funerals performed and reported that the number of funerals decreased compared to the previous 3 years without a strike. In a study regarding the effects of a physicians' strike in hospitals and polyclinics in Croatia, Erceg et al. [10] reported that there were no differences in the distributions of mortality and cause of death between the strike period and the comparison period. Ong'ayo et al. [2] analyzed the impact of strikes by healthcare providers in Kenya, including physicians, and their results showed that healthcare provider strikes were not correlated with patient mortality. Although the mortality rate in the strike period differed from that in control period 1, it did not differ from that in control period 2, which suggests that the difference in mortality was due to the pandemic. This is consistent with previous findings in which resident strikes did not lead to increased patient mortality. However, it should be noted that examining the impact of a strike on patients solely based on mortality is a limited approach, and additional studies are needed to develop more accurate measurement approaches.

The ED LOS decreased during the strike period compared to that in the control periods 1 and 2. This is in line with the results of a previous study on resident efficacy. Harvey et al. [11] reported that resident strikes led to a decrease in the ED LOS. Kim et al. [12] also reported that the LOS and number of tests and treatments performed in the ED declined. The decrease in ED LOS in our study may have been due to the fact that physicians avoided performing unnecessary tests and could quickly determine patient disposition. A previous study simultaneously observed a decrease in tests and procedures performed in the ED [3]; however, our study was limited in that it did not investigate the number of tests and procedures performed in the ED.

Although we were able to determine the mortality of patients who visited the ED during a resident strike in this study, a 19-day data collection may not have accurately portrayed the potential effect. We hypothesized that a reduction in the number of medical personnel may have a negative effect on patients' treatment outcomes. However, there are some points that require further investigation in future research, such as specialists filling in for residents, additional staff deployment from other departments, and additional factors such as differences in the number of diagnostic procedures performed.

One limitation of this study was its retrospective design, as a prospective review of medical records was not a viable study option. Furthermore, it was not possible to include all patients influenced by the resident strike or those who visited outpatient clinics rather than an ED. Another limitation was that the exact strike period and control period 2 for comparing mortality were not equivalent. Although we tried to use the same number of days for the study and control periods, they were not set to the same time of the year, which allowed for seasonal differences. Furthermore, we did not use a clear parameter to compare the increased workload in the ED due to the COVID-19 pandemic. We used mortality and ED LOS as our study parameters for comparison, although the work intensity increased even when working for the same number of hours, for example, extra time spent donning and removing personal protective equipment, such as N95 masks and face shields. In particular, before treating patients with fever and respiratory symptoms, more time was needed to replace personal protective equipment and N95 masks between patients. COVID-19 diagnostic testing was performed only at certain times and would have affected the patients' LOS. Finally, the parameters used in our study may not reflect the pandemic situation and were based on the parameters used in previous studies. Based on the results of this study, it is necessary to perform complex analyses of ED indicators in the setting of a pandemic in future studies.

In conclusion, our findings indicated that the resident strikes did not impact patient mortality in the EDs of the six teaching hospitals in Daegu, South Korea. During the strike, the number of patients visiting the ED and LOS in the ED decreased.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: YHC, HWR, JHK, TCJ, DEL; Data curation: SM, JHK, SHL, TCJ, DEL; Formal analysis: JWC, SM, JHK; Methodology, Project administration: YHC, HWR, SM, SHL; Investigation: SM, JHK, SHL, TCJ, DEL; Resources, Software: JWC, HWR, TCJ; Supervision, Validation, Visualization: HWR, SM, JHK; Writing-original draft: YHC, JWC, SM; Writing-review & editing: YHC, JWC, HWR, SM, DEL.

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Clinical investigation on acute pyelonephritis without pyuria: a retrospective observational study

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Background: The current guidelines for the diagnosis of acute pyelonephritis (APN) recommend that APN be diagnosed based on the clinical features and the presence of pyuria. However, we observed that some of the patients who are diagnosed with APN do not have characteristic clinical features or pyuria at the initial examination. We performed this study to investigate the characteristics of APN without pyuria.

Methods: A retrospective, cross-sectional study was conducted on 391 patients diagnosed with APN based on clinical and radiologic findings, between 2015 and 2019. The clinical features, laboratory results, and computed tomography (CT) findings were compared between patients with normal white blood cell (WBC) counts and those with abnormal WBC counts (WBC of 0–5/high power field [HPF] vs. >5/HPF) in urine.

Results: More than 50% of patients with APN had no typical urinary tract symptoms and one-third of them had no costovertebral angle (CVA) tenderness. Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) on urine microscopy. There was a negative correlation between pyuria (WBC of >5/HPF) and previous antibiotic use (odds ratio, 0.249; 95% confidence interval, 0.140–0.441; $p<0.001$), and the probability of pyuria was reduced by 75.1% in patients who took antibiotics before visiting the emergency room.

Conclusion: The diagnosis of APN should not be overlooked even if there are no typical clinical features, or urine microscopic examination is normal. If a patient has already taken antibiotics at the time of diagnosis, imaging studies such as CT should be performed more actively, regardless of the urinalysis results.

Keywords: Diagnosis; Emergency medical services; Pyelonephritis; Pyuria; Urinalysis

Introduction

Acute pyelonephritis (APN) is characterized by upper urinary tract infection (UTI) symptoms (fever and flank pain) and pyuria [1,2]. However, symptoms related to upper UTI may be ambiguous, and sometimes only fever may appear [3,4]. If the symptoms presented by the patient are ambiguous or no symptoms other than fever are present, an objective test confirming the presence of pyuria is an important factor in the diagnosis of APN [5-7]. However, it is known that some patients diagnosed with APN do not have pyuria [8], which is frequently encountered in clinical practice.

In this study, we investigated the number of white blood cells (WBC) observed in urine microscopy of female patients who were finally diagnosed with APN, to analyze how many patients with APN do not have pyuria, and to determine the differences in demographics, medical history, clinical features, physical examination findings, laboratory examination results, and abdominal computed

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tomography (CT) findings between APN with and without pyuria.

Methods

Ethical statements: This study was conducted as a retrospective, cross-sectional study after receiving approval from the Institutional Review Board (IRB) of Kangbuk Samsung Hospital (IRB No: 2020-11-030). The patient's name, hospital number, date of birth, and social security number were deleted after assigning a serial number to each to maintain anonymity.

1. Subjects

In addition to the clinical diagnosis of APN, abdominal CT findings compatible with APN were also necessary to target only patients with a clear APN diagnosis. Female patients aged 18 years or older who visited our emergency department (ED) between January 2015 and December 2019 and whose final discharge diagnosis was APN were sought. Then, the CT findings were reviewed to exclude cases that did not have findings compatible with APN or had obvious causes of infection other than APN. In addition, patients who visited the hospital with a double J stent, percutaneous nephrostomy, and an indwelling foley catheter were also excluded (Fig. 1).

2. Outcome measures

The urine WBC counts of the subjects determined by the microscopic study were arbitrarily classified into WBC 0–3/HPF, 4–5/HPF, 6–10/HPF, 11–20/HPF, and >20/HPF. We investigated the number of patients with APN having urine WBC counts in the normal range (0–5/HPF). After that, we compared the demographic characteristics, medical history, clinical features, physical examination findings, laboratory results, and CT findings between patients with normal WBC counts and those with abnormal WBC counts (0–5/HPF vs. >5/HPF). The patient's age, underlying disease, past APN diagnosis experience, time from symptom onset to diagnosis, and antibiotic use prior to the ED visit were determined under demographic characteristics and medical history. It was not possible to determine the dose, duration, and type of antibiotics administered, and it was defined as "previous antibiotics use" if the patient took antibiotics even once before visiting the emergency room. The symptoms of upper UTI (fever and flank pain) and lower UTI (dysuria, frequency, urgency and residual urine sense) were recorded under clinical features. Costovertebral angle (CVA) tenderness was investigated for physical examination findings. WBC, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, urine culture results, and blood culture results were investigated for laboratory findings. A positive urine culture test was defined as $>10^5$ colony-forming unit/mL. APN was defined as wedge-shaped low attenuation lesions from the renal medulla to the renal cortex and/or perinephric fat stranding on enhanced CT, and perinephric fat stranding on nonenhanced CT [9,10]. In addition, renal abscess formation and emphysematous change were considered APN. Those who had ureteritis or cystitis without APN were excluded from the study.

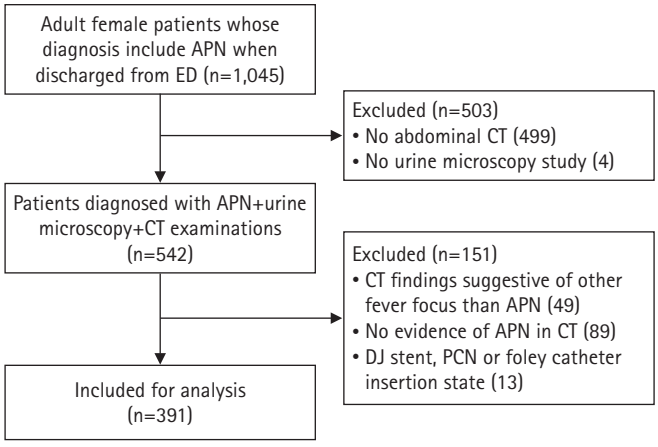

Fig. 1. Flow diagram of the enrolled patients. APN, acute pyelonephritis; ED, emergency department; CT, computed tomography; DJ, Double J; PCN, percutaneous nephrostomy.

3. Statistical analysis

Statistical analysis was performed using STATA (STATA 15.1, StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean and standard deviation, and categorical variables are described in terms of frequency (%). Continuous variables were compared using the Student *t*-test or Mann-Whitney *U*-test, while categorical variables were compared using the chi-square or Fisher exact test, according to the expected frequency. Statistical significance was set at $p < 0.05$. Logistic regression was performed to confirm the correlation of major variables according to the amount of WBCs observed in the urine microscopic study. Multivariate logistic regression was performed using the variables considered to have an important effect on the presence of pyuria, with a *p*-value of 0.05 or less in univariate analysis.

Results

1. General characteristics

The average age of patients was 58.5 years, and the average time to visit the emergency room after symptom onset was 69.3 hours. Sixty-two patients (15.9%) had already taken antibiotics at least

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once before visiting the ED. More than 90% of patients with APN had a fever or a history of fever. Approximately 43.2% of patients had upper UTI symptoms (back pain or flank pain), and only 39.9% of patients had lower UTI symptoms (dysuria, frequency, urgency, and residual urine sense) at the time of ED visit. More than 50% of patients with APN did not have either upper or lower UTI symptoms. On physical examination, CVA tenderness was observed in 269 patients (68.8%), and approximately one-third of patients did not have CVA tenderness despite APN.

A total of 223 patients underwent blood culture, and pathogens were identified in 80 patients (35.9%). Among the 138 patients who underwent urine culture, 99 (71.7%) had pathogenic bacteria.

On abdominal CT, 89 patients did not have findings compatible with APN despite the clinical diagnosis of APN. There were 49 patients who had other causes of infection without APN findings on abdominal CT despite the clinical diagnosis of APN. Abscess formation or emphysematous changes were observed on abdominal CT in 24 patients (6.1%). There were 175 patients (44.8%) with ureteritis and 131 patients (33.5%) with cystitis (Table 1).

Table 1. Demographic data

Characteristic	Data
No. of patients	391
Age (yr)	58.5 ± 18.7
Symptom onset to ED (hr)	69.3 ± 109.1
Past medical history	
Diabetes mellitus	118 (30.2)
Hypertension	152 (38.9)
Chronic kidney disease	14 (3.6)
Previous APN history	92 (23.5)
Previous antibiotics use at least once before ED visit	62 (15.9)
Clinical presentation	
Fever	361 (92.3)
Back pain or flank pain	169 (43.2)
Lower UTI symptom	
Dysuria	142 (36.3)
Frequency	185 (47.3)
Urgency	89 (22.8)
Residual urine sense	97 (24.8)
CVA tenderness	269 (68.8)
Abdomen CT finding	
Abscess formation or emphysematous change	24 (6.1)
Ureteritis	175 (44.8)
Cystitis	131 (33.5)
Culture	
Urine culture positive	99/138 (71.7)
Blood culture positive	80/223 (35.9)

Values are presented as number only, mean ± standard deviation, or number (%).
ED, emergency department; APN, acute pyelonephritis; UTI, urinary tract infection; CVA, costovertebral angle; CT, computed tomography.

2. Comparison of patients with normal (0–5/HPF) and abnormal WBC count (>5/HPF) in urine microscopic study

Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) despite the clinical and CT diagnosis of APN, whereas 77.5% of patients had abnormal WBC counts (> 5/HPF) on urine microscopic analysis (Table 2).

When comparing APN with normal WBC (0–5/HPF) and with abnormal WBC (> 5/HPF), there were no differences in age, underlying disease, duration from symptom onset to diagnosis, previous history of APN, upper UTI symptoms (fever and flank pain), lower UTI symptoms (dysuria, frequency, urgency, and residual urine sense), physical examination findings, blood WBC count, CRP, procalcitonin, and positive blood culture results. The variables that showed statistical differences were prior use of antibiotics, neutrophil percentage, NLR, and positive urine culture. Abscess formation or emphysematous changes in abdominal CT showed no difference, while ureteritis or cystitis showed a significant difference. Patients with APN accompanied by ureteritis or cystitis on CT showed a significantly higher prevalence of abnormal WBC counts (> 5/HPF) on urine microscopic examination (Table 3).

3. Logistic regression analysis

Table 4 shows the results of the univariate and multivariate logistic regression analyses. Among the variables with a $p < 0.05$ in univariate analysis, previous antibiotic use, ureteritis, and cystitis were presumed to have an important effect on pyuria, and multivariate logistic regression analysis was performed using these variables. There was no multicollinearity between ureteritis and cystitis (phi coefficient = 0.200). There was a strong and independent negative correlation between WBC of > 5/HPF and previous antibiotic use at the time of diagnosis (odds ratio [OR]), 0.249; 95%

Table 2. Degree of leukocyte in urine microscopy study among acute pyelonephritis confirmed patients in the emergency department

Degree of WBC	Data
0–3/HPF	46 (11.8)
4–5/HPF	42 (10.7)
6–10/HPF	61 (15.6)
11–20/HPF	68 (17.4)
> 20/HPF	174 (44.5)

Values are presented as number (%).
WBC, white blood cell; HPF, high power field.

Table 3. Comparison of patients with normal (0–5/HPF) and abnormal WBC count (>5/HPF) in urine microscopic study

Variable	White blood cell (/HPF)		*p*-value
	≤5 (n=88)	>5 (n=303)	
Age (yr)	57.1±19.5	58.9±18.5	0.425
Diabetes mellitus	31 (35.2)	87 (28.7)	0.241
Hypertension	35 (39.8)	117 (38.6)	0.844
Chronic kidney disease	3 (3.4)	11 (3.6)	1.000
Symptom duration (hr)	65.4±91.8	70.4±113.7	0.706
Previous antibiotics use	29 (33.0)	33 (10.9)	<0.001
Previous APN history	22 (25.0)	70 (23.1)	0.712
Fever	78 (88.6)	283 (93.4)	0.139
Flank pain or back pain	41 (46.6)	128 (42.2)	0.469
CVA tenderness	61 (69.3)	208 (68.7)	0.905
Lower UTI symptom			
Dysuria	31 (35.2)	111 (36.6)	0.809
Frequency	38 (43.2)	147 (48.5)	0.378
Urgency	15 (17.0)	74 (24.4)	0.146
Residual urine sense	25 (28.4)	72 (23.8)	0.374
Laboratory finding			
WBC (counts/μL)	11,566±5,018	12,600±4,653	0.072
Neutrophil (%)	81±8.9	83.7±7.6	0.006
NLR	9.9±6.3	13±9.9	0.006
CRP (mg/dL)	11.1±8	12.6±8.8	0.163
Procalcitonin (ng/mL)	5.6±14.9	5.7±12.5	0.961
Positive urine culture	12/26 (46.2)	87/112 (77.7)	0.001
Ciprofloxacin resistant	8/12 (66.7)	68/87 (78.2)	0.377
ESBL positive	2/12 (16.7)	22/87 (25.3)	0.514
Positive blood culture	11/44 (25.0)	69/179 (38.5)	0.093
CT finding			
Abscess formation or emphysematous change	9 (10.2)	15 (5.0)	0.069
Ureteritis	27 (30.7)	148 (48.8)	0.003
Cystitis	17 (19.3)	114 (37.6)	0.001

Values are presented as mean ± standard deviation or number (%).
WBC, white blood cell; HPF, high power field; APN, acute pyelonephritis; CVA, costovertebral angle; UTI, urinary tract infection; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; CT, computed tomography.

confidence interval [CI], 0.140–0.441; $p<0.001$). If antibiotics were used at least once before visiting the emergency room, the chance of pyuria in urinalysis was reduced by 75.1%. None of the clinical signs or symptoms correlated with pyuria. Among the blood test results, neutrophil percentage and NLR showed a minimal positive correlation. For every one-unit increase in neutrophil percentage and NLR, the probability of pyuria was predicted to increase by 3.3% and 5.1%, respectively. The probability of pyuria was significantly higher in cases with ureteritis or cystitis on CT than in those without ureteritis or cystitis. In particular, in bilateral ureteritis, the OR for pyuria reached 9.7 (95% CI, 2.2–41.7; $p=0.002$) compared to cases without ureteritis.

Discussion

This study showed that a relatively large proportion of patients with a confirmed diagnosis of APN based on clinical and radiological findings did not have typical clinical features and WBC counts on urine microscopic examination were within the normal range. Unlike the current guidelines for diagnosing APN based on clinical features and pyuria, this result suggests that it is difficult to exclude the diagnosis of APN based on clinical features and pyuria alone.

Eighty-eight patients (22.5%) had normal WBC counts (0–5/HPF) on urine microscopic examination despite the clinical and CT diagnosis of APN. Among the several variables investigated, even a single use of antibiotics before visiting the ED was found to

Table 4. Logistic regression analysis

WBC of >5/HPF	OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Previous antibiotics use	0.249 (0.140–0.441)	<0.001	0.249 (0.138–0.45)[a]	<0.001
Fever	1.814 (0.816–4.035)	0.144	1.916 (0.821–4.469)[a]	0.133
Flank pain or back pain	0.838 (0.520–1.351)	0.469	1.033 (0.618–1.727)[a]	0.900
Dysuria	1.063 (0.647–1.745)	0.809	1.089 (0.63–1.883)[a]	0.760
Frequency	1.240 (0.769–2.000)	0.378	1.176 (0.7–1.976)[a]	0.539
Residual urine sense	0.785 (0.461–1.339)	0.375	0.904 (0.507–1.611)[a]	0.731
Urgency	1.573 (0.851–2.907)	0.149	1.513 (0.787–2.908)[a]	0.214
CVA tenderness	0.969 (0.580–1.620)	0.905	1.105 (0.639–1.912)[a]	0.721
WBC (×1,000/μL)	1.05 (0.995–1.108)	0.073	1.054 (0.996–1.115)[a]	0.068
Neutrophil (%)	1.038 (1.009–1.068)	0.009	1.033 (1.003–1.065)[a]	0.030
NLR	1.059 (1.018–1.102)	0.005	1.051 (1.009–1.094)[a]	0.017
Lactate	1.140 (0.659–1.973)	0.639	1.04 (0.595–1.817)[a]	0.891
CRP	1.021 (0.992–1.051)	0.164	1.014 (0.984–1.045)[a]	0.374
Procalcitonin	1.001 (0.977–1.025)	0.960	1.001 (0.975–1.026)[a]	0.964
Abscess formation or emphysematous change	0.457 (0.193–1.084)	0.075	0.511 (0.201–1.301)[a]	0.159
Ureteritis	2.157 (1.301–3.578)	0.003	2.244 (1.328–3.789)[b]	0.003
Unilateral ureteritis	1.574 (0.928–2.672)	0.093	1.645 (0.95–2.848)[b]	0.076
Bilateral ureteritis	9.445 (2.226–40.072)	0.002	9.663 (2.239–41.698)[b]	0.002
Cystitis	2.519 (1.413–4.490)	0.002	2.412 (1.334–4.36)[b]	0.004

WBC, white blood cell; HPF, high power field; OR, odds ratio; CI, confidence interval; CVA, costovertebral angle; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.
[a]Adjusted for previous antibiotics use, ureteritis, and cystitis. [b]Adjusted for previous antibiotics use.

be highly correlated with normal urine WBC counts despite having APN. Therefore, prior use of antibiotics before ED visit should always be checked while taking a patient's history for APN diagnosis. If the patient has already taken antibiotics, it is reasonable to diagnose APN based on the results of imaging tests such as CT rather than the results of urinalysis.

On the other hand, the presence of abnormal WBC count showed a significant positive correlation with the presence of accompanying ureteritis or cystitis on CT. UTI is a retrograde ascending infection in which uropathogens arising from fecal flora, progress through the urethra and bladder to the ureter and kidney [11,12]. Clinical features appear in the form of urethritis and cystitis at the onset of UTI; hence, typical symptoms of lower UTI, such as dysuria, frequency, residual urine sense, and urgency are observed. However, as UTI progresses to ureteritis and pyelonephritis, upper UTI symptoms (fever and flank pain) appear. As lower UTI progresses to APN, the uropathogens may move from the lower urinary tract to the upper region of the tract; hence, bacteria and inflammation no longer remain in the lower urinary tract. However, in other cases, bacteria and inflammation may remain in the lower urinary tract. We assumed that if bacteria and inflammation remain in the lower urinary tract in patients with APN, cystitis should be observed along with APN findings on CT, and urine WBC count may be high.

This study showed that more than half of patients with APN had neither upper UTI symptoms nor lower UTI symptoms, and approximately one-third of patients had no CVA tenderness. It is known that elderly patients with APN can only have a fever without typical symptoms of UTI [3,4]. However, in this study, the subjects were from a relatively younger age group with an average age of 58.5 ± 18.7 years, which indicates that even in young female patients, typical upper UTI symptoms and lower UTI symptoms may not appear in APN. Physicians should always keep in mind that clinical features and physical examination may be ambiguous, and pyuria may not be present in patients with APN.

The current APN diagnosis and treatment guidelines recommend that APN be diagnosed clinically based on the clinical features and the presence of pyuria, and to perform imaging studies only if the patient does not show clinical improvement after 72 hours of antibiotic treatment [1,2,13]. However, complicated APN requiring intervention or maintenance on a longer period of antibiotic treatment (kidney abscess, emphysematous change, ureter stone, etc.) is only identified after CT scans [8,14-16]. Moreover, as shown in the results of this study, there were many cases without APN findings or other infection sources than APN on CT, despite the clinical suspicion of APN. In this study, 16.4% of cases (89 of 542) had no evidence of APN on CT, and 9.0% of patients (49 of 542) with the clinical suspicion of APN had other sources

of infection than APN on CT. For these reasons, the effectiveness of CT in APN diagnosis is gradually increasing. The authors recommend to actively perform CT on patients from their initial visit if APN cannot be ruled out, rather than insisting on the current guidelines that defer imaging studies.

The main limitation of this study could be the selection bias. First, since this study was not intended for all patients with clinically suspected APN, but only for patients who had confirmed APN based on CT scan, there is a possibility that a selection bias could have occurred. Some patients may not have undergone CT because their symptoms, physical examination findings, and urine microscopy results were clearly suggestive of APN. These patients could have been included in the study if they had undergone CT. Second, this study included only patients who visited the ED; hence, patients who visited the outpatient clinic were excluded. Third, this was a single-center, retrospective study. Additionally, we have not studied whether there are differences in treatment and clinical prognosis between patients with and without pyuria.

More than half of the patients with confirmed APN did not have typical symptoms or signs of UTI, and about one-quarter of the patients did not have pyuria. Usage of antibiotics before ED visit was strongly and independently correlated with normal WBC counts on urinalysis. The diagnosis of APN should not be overlooked even if there are no typical clinical features, or a urine microscopic analysis is normal. If no other cause of fever can be found and APN cannot be completely excluded, imaging tests such as CT should be more actively performed regardless of clinical features or presence of pyuria, especially if the patient has already taken antibiotics at the time of diagnosis.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: all authors; Data curation, Investigation: HKS, JHL, DHS, JUN; Formal analysis: HKS, JHL, JUN, SKH, PCC; Supervision: DHS, JUN, SKH, PCC; Writing-original draft: HKS, JHL; Writing-review & editing: HKS, JHL, DHS, JUN, SKH, PCC.

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Increase in blood glucose level and incidence of diabetic ketoacidosis in children with type 1 diabetes mellitus in the Daegu-Gyeongbuk area during the coronavirus disease 2019 (COVID-19) pandemic: a retrospective cross-sectional study

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Background: The coronavirus disease 2019 (COVID-19) outbreak in the Daegu-Gyeongbuk area in 2020 has caused difficulties in the daily life and hospital care of children with type 1 diabetes mellitus (T1DM). We detected an increase in blood sugar levels in these children and the number of patients hospitalized with more severe diabetic ketoacidosis (DKA) compared to those before COVID-19.
Methods: This single-center study was conducted at Kyungpook National University Children's Hospital. The following patient groups were included; 45 returning patients diagnosed with T1DM and undergoing insulin treatment for more than 2 years and 20 patients newly diagnosed with T1DM before and after COVID-19 were selected by age matching. Returning patients before and after the outbreak were selected, and changes in hemoglobin A1c (HbA1c) levels were retrospectively reviewed. The HbA1c levels and severity of symptoms in newly diagnosed patients during hospitalization were examined.
Results: HbA1c levels in returning patients with T1DM were significantly increased after COVID-19 (before, 7.70%±1.38% vs. after, 8.30%±2.05%; $p=0.012$). There were 10 and 10 newly diagnosed patients before and after COVID-19, respectively. The proportion of patients with drowsiness and dyspnea at the time of admission was higher after COVID-19 than before (before, 2 of 10 vs. after, 4 of 10). The HbA1c levels were higher in newly diagnosed patients hospitalized after COVID-19 than before (before, 11.15% vs. after, 13.60%; $p=0.036$).
Conclusion: Due to COVID-19 in the Daegu-Gyeongbuk area, there was an increase in blood glucose levels in children with T1DM and in the incidence of severe DKA in newly diagnosed diabetes mellitus patients.

Keywords: COVID-19; Diabetic ketoacidosis; Type 1 diabetes mellitus

Introduction

In December 2019, atypical pneumonia of unknown cause was first reported in Wuhan, Hubei Province, China [1-3]. In January 2020, the World Health Organization termed this condition as coronavirus disease 2019 (COVID-19), which began to spread rapidly, and eventually, it was declared a pandemic on March 11, 2020 [4].

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In Korea, the first imported case of COVID-19 was confirmed on January 20, 2020 [5]. After the first case in the Daegu-Gyeongbuk area was reported on February 18, 2020, there was a rapid increase in the number of patients, which was the first large outbreak in countries other than China [6,7]. Consequently, difficulties in daily life and hospital care in the Daegu-Gyeongbuk area became prominent.

It has been reported that COVID-19 has led to a high mortality rate among adult patients with diabetes mellitus (DM) [8-10]. However, no severe cases of COVID-19 requiring hospitalization have been reported among children and adolescent patients with type 1 DM (T1DM) [11]. The International Society for Pediatric and Adolescent Diabetes stated that diabetic care should be provided while avoiding hospitalization and emergency room visits to prevent infection [12]. However, we observed an increase in overall blood glucose levels compared to the levels before COVID-19 in patients with T1DM in the Daegu-Gyeongbuk area and also encountered new patients who were hospitalized with more severe diabetic ketoacidosis (DKA). This study aimed to investigate the changes in blood glucose levels and clinical manifestations in pediatric patients with T1DM in the Daegu-Gyengbuk area where there was a large outbreak of COVID-19.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No: 2020-09-023) in accordance with the Declaration of Helsinki. Informed consent was waived by the IRB due to the use of anonymized data and the retrospective design.

1. Subjects and methods

The study subjects were children aged < 19 years diagnosed with T1DM at Kyungpook National University Children's Hospital in the Daegu-Gyeongpuk area. A total of 65 patients, including 45 returning patients, 10 newly diagnosed patients during the COVID-19 outbreak, and 10 age-matched patients before the COVID-19 outbreak were included in the control group. A retrospective chart review was conducted. For returning patients undergoing insulin treatment for more than 2 years, patients who had visit records between 3 and 6 months before and after the outbreak were selected. The parameters (age, sex, and changes in hemoglobin A1c [HbA1c] and body mass index [BMI]) before and after COVID-19 were compared. HbA1c levels were analyzed between the similar age and pubertal groups. The age of the patients was divided into 0–4, 5–9, 10–14, 15–18 years old, and was defined as pubertal age from 10 years of age for girls and 11 years of age for boys. For newly diagnosed patients, 10 new patients who were hospitalized after the COVID-19 outbreak were examined for HbA1c levels and severity of symptoms at hospitalization. As a control group of newly diagnosed patients, a total of 10 age-matched patients with T1DM who visited our hospital 4 years prior to the COVID-19 outbreak were selected. Clinical signs reflecting DKA severity at the time of admission, altered mental status, presence of dyspnea, and laboratory parameters such as HbA1c levels, initial serum glucose, venous blood gas analysis (pH, pCO_2, HCO_3^-), hemoglobin, blood urea nitrogen, and creatinine were assessed. The severity criteria were as follows: the biochemical criteria for the diagnosis of DKA were blood glucose level of > 200 mg/dL, venous pH of < 7.3, serum bicarbonate level of < 15 mmol/L, and ketonemia or ketonuria of ≥ 2+. The severity of DKA was categorized based on the degree of acidosis as follows: (1) mild: venous pH of < 7.3 or serum bicarbonate level of < 15 mmol/L; (2) moderate: pH of < 7.2, serum bicarbonate level of < 10 mmol/L; and (3) severe: pH of < 7.1, serum bicarbonate level of < 5 mmol/L [13].

2. Statistical analysis

Continuous values are presented as the mean ± standard deviation. Among the returning patients, the differences in BMI and HbA1c between the two groups were analyzed using the *t*-test. Due to the small number of newly diagnosed T1DM patients, the distributions of DKA severity, age, sex, HbA1c, glucose, pH, and bicarbonate levels were compared between the groups using Wilcoxon rank-sum tests; the results are reported as medians. All statistical analyses were conducted using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

Results

1. Changes in body mass index and hemoglobin A1c levels in returning patients with type 1 diabetes mellitus

There were 45 subjects with T1DM, consisting of 22 females and 23 males (1:1 ratio), with a mean age of 15.8 ± 6.13 years. There were one patient aged 0 to 4 years, five patients aged 5 to 9 years, 21 patients aged 10 to 14 years, and 18 patients aged 15 to 18 years. As baseline characteristics, initial random glucose was 413.53 ± 202.62 mg/dL and C-peptide was 0.65 ± 0.56 ng/mL (range, 0.4–2.2 ng/mL). At least one autoantibody was identified in 37 of 45 patients (82.2%). Anti-islet cell antibody (ICA) was identified in two patients (4.4%), glutamic acid decarboxylase anti-

body (GADA) in 21 patients (46.7%), and insulin autoantibody in 14 patients (31.1%). Six patients (13.3%) were positive for both ICA and GADA. One patient (2.2%) tested positive for all three antibodies.

When the data were compared during a period of 3 to 6 months before and after the COVID-19 outbreak, no significant difference was found in average BMI (21.62 ± 6.17 kg/m^2 vs. 21.06 ± 4.97 kg/m^2, p = 0.250). The HbA1c levels were significantly increased after the COVID-19 outbreak (before, 7.70% ± 1.38% vs. after, 8.30% ± 2.05%; p = 0.012) (Table 1). HbA1c levels increased significantly after COVID-19 and tended to be higher in the pubertal group (before, 7.83% ± 1.56% vs. after, 8.46% ± 2.40%; p = 0.025) than in the prepubertal group (before, 7.03% ± 0.90% vs. after, 7.23% ± 1.24%; p = 0.565).

2. Comparison of diabetic ketoacidosis severity in patients with newly diagnosed type 1 diabetes mellitus

There were 10 age-matched patients newly diagnosed with T1DM before the onset of the COVID-19 outbreak and 10 patients diagnosed after the outbreak. The frequency of DKA tended to be higher during puberty (Fig. 1). The COVID-19 outbreak period was spring and early summer, and the patients in the age-matched control group before COVID-19 visited the hospital at 2:4:2:2 in spring, summer, autumn, and winter.

The 10 newly diagnosed patients before the outbreak comprised one male and nine female subjects, with a median age of 12.0 years. Four patients were confirmed with DKA at the time of admission, of whom two patients showed severe clinical symptoms such as altered mental status, dyspnea, and tachypnea. Based on DKA severity, patients were classified as follows: two patients had mild disease, and two patients had moderate disease. Two patients required care from the pediatric intensive care unit (PICU). After the outbreak, there were 10 children with newly diagnosed T1DM (six males and four females), with a median age of 11.5 years. Six patients had DKA at the time of admission, of whom four showed severe symptoms. When classified according to

Table 1. Baseline characteristics and comparison of BMI and HbA1c in patients with T1DM 3–6 months before and after COVID-19 pandemic

Characteristic	Data
No. of patients	45
Age (yr)	15.83 ± 6.13
Sex, male:female	23:22
Initial random glucose (mg/dL)	413.53 ± 202.62
C-peptide (ng/mL)	0.65 ± 0.56
Patients with identified autoantibodies	
ICA	2 (4.4)
GADA	21 (46.7)
IAA	14 (31.1)
ICA+GADA	6 (13.3)
ICA+GADA + IAA	1 (2.2)
Autoantibody negative	8 (17.8)
BMI (kg/m^2)	
Before COVID-19	21.62 ± 6.17
After COVID-19	21.06 ± 4.97
p-value	0.250
HbA1c (%)	
Before COVID-19	7.70 ± 1.38
After COVID-19	8.30 ± 2.05
p-value	0.012[a]

Values are presented as number only, mean ±standard deviation, or number (%).
BMI, body mass index; HbA1c, hemoglobin A1c; T1DM, type 1 diabetes mellitus; COVID-19, coronavirus disease 2019; ICA, islet cell antibody; GADA, glutamic acid decarboxylase antibody; IAA, insulin autoantibody.
[a] p < 0.05.

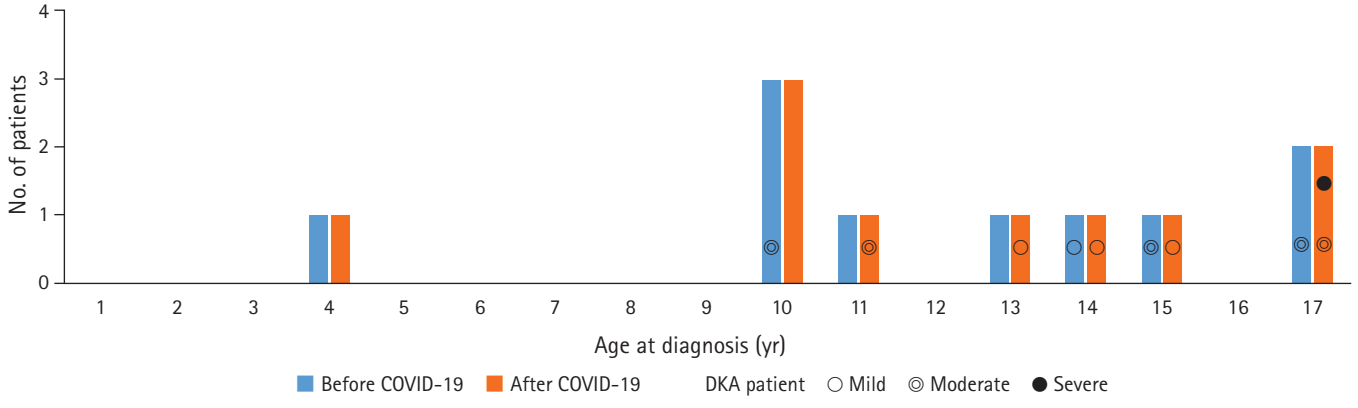

Fig. 1. Distribution by age of newly diagnosed type 1 diabetes mellitus patients before and after the coronavirus disease 2019 (COVID-19) outbreak. Non-diabetic ketoacidosis (DKA) patients were not indicated, and DKA patients were indicated according to severity.

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DKA severity, three patients had mild disease, two had moderate disease, one patient had severe disease, and three patients required PICU care (Fig. 2).

HbA1c levels of newly diagnosed T1DM patients were significantly higher in patients hospitalized after the COVID-19 outbreak than in those hospitalized before the outbreak (before, 11.15% vs. after, 13.60%; $p=0.036$) (Table 2). Moreover, random serum glucose levels were higher in patients with T1DM after COVID-19 (before, 300 mg/dL vs. after, 371 mg/dL; $p=0.203$). The levels of pH and bicarbonate were lower after COVID-19, but not statistically significant (pH: before, 7.40 vs. after, 7.25, $p=0.333$; bicarbonate: before, 19.50 mmol/L vs. after, 10.50 mmol/L, $p=0.221$).

Discussion

In this study, we detected a significant increase in HbA1c levels in children with T1DM when social distancing was being implemented due to the COVID-19 outbreak in the Daegu-Gyeongbuk area. Moreover, there were increases in the total number of patients with newly diagnosed T1DM, HbA1c levels, DKA incidence, and DKA severity after the COVID-19 outbreak compared to those before the outbreak. In particular, the number of patients in the pubertal group was higher than that in the prepubertal group, and the HbA1c levels, DKA frequency, and severity were also higher.

It is well known that natural disasters such as hurricanes and earthquakes have a significant impact on DM management [14-17]. In a study examining glucose control in patients with DM in

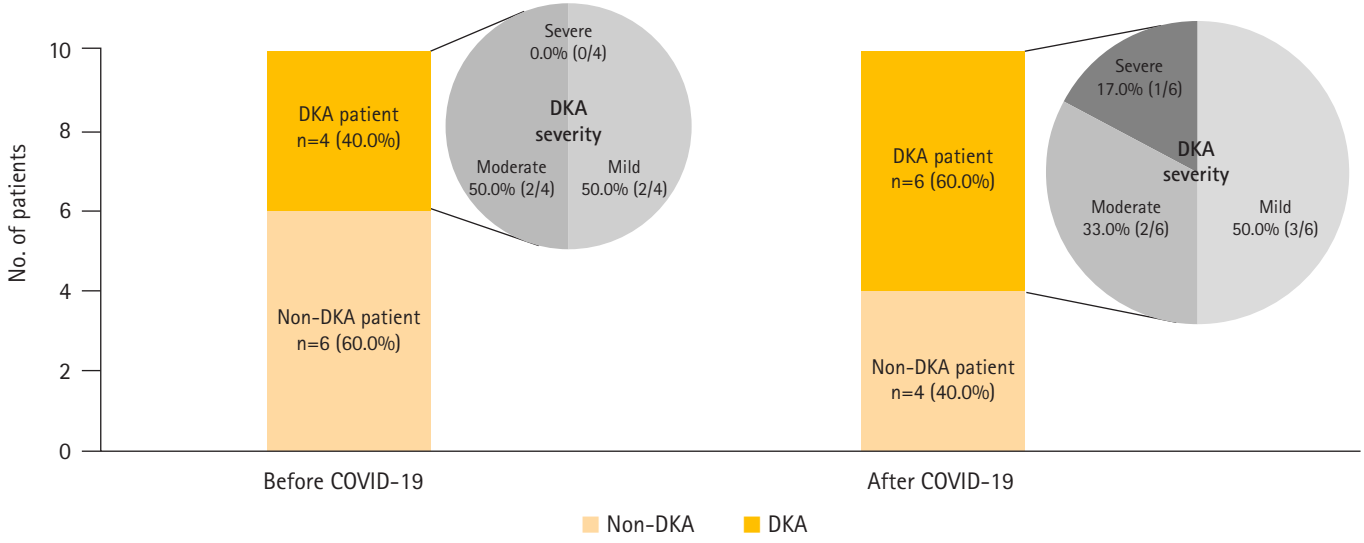

Fig. 2. Comparison of ratio of diabetic ketoacidosis (DKA) and DKA severity in newly diagnosed type 1 diabetes mellitus patients hospitalized before and after the coronavirus disease 2019 (COVID-19) outbreak.

Table 2. Comparison of HbA1c in newly diagnosed T1DM patients hospitalized before and after the COVID-19 outbreak

Variable	Before COVID-19	After COVID-19	*p*-value
No. of patients	10	10	
DKA (mild:moderate:severe)	4 (2:2:0)	6 (3:2:1)	0.317
Age (yr)	12.0 (4.0–17.0)	11.5 (3.90–17.0)	0.439
Sex, male:female	1:9	6:4	0.414
HbA1c (%)	11.15 (7.40–14.70)	13.60 (11.70–16.00)	0.036[a]
Glucose (mg/dL)	300 (176–608)	371 (116–915)	0.203
pH	7.40 (7.06–7.44)	7.25 (6.83–7.45)	0.333
Bicarbonate (mmol/L)	19.50 (5–26)	10.50 (2–25)	0.221

Values are presented as number only or median (range).
HbA1c, hemoglobin A1c; T1DM, type 1 diabetes mellitus; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis.
[a] $p<0.05$.

connection with the Great East Japan Earthquake Disaster, HbA1c levels did not increase significantly by actively controlling the drugs through regular outpatient visits [18]. However, the effects of the COVID-19 pandemic on glycemic control in patients with DM and patient management guidelines are not well established. In India, a total lockdown was implemented for 21 days, from March 24, 2020, to prevent the spread of COVID-19; a systematic study revealed that blood sugar levels and DM-related complications were increased during this period [19]. The present study also demonstrated a significant increase in HbA1c levels in children with T1DM after the outbreak. Therefore, we suggest a possible explanation for this phenomenon. Wang et al. [20] reported a decrease in physical activity during the COVID-19 outbreak in students due to limitations in daily life. It has already been reported that students are less physically active, have more screen time, and display irregular sleeping patterns when they are not attending school, such as during weekends and breaks [21,22]. As such, there were restrictions on daily life, including school attendance, as observed in this study, which led to a decrease in physical activity and changes in lifestyle habits. In fact, patients and their guardians at the outpatient clinic cited irregular lifestyle habits as the cause of the increase in blood sugar levels. Moreover, there were no significant changes in BMI, suggesting that the increase in blood sugar level was due to irregular lifestyle changes rather than increased food intake. MacMillan et al. [23] reported that these lifestyle changes have a detrimental impact on blood sugar control. In addition, Nansel et al. [24] reported that dietary control, such as intake of foods with high fiber and low glycemic index and carbohydrate-containing foods improves glycemic control, suggesting that irregular eating habits due to lifestyle changes cause an increase in blood sugar levels. Furthermore, irregular eating habits may interfere with regular insulin injections. Verma et al. [25] reported that COVID-19 lockdown resulted in an increase in blood sugar levels in patients with T1DM because of the difficulty in prescribing blood sugar measuring devices and insulin injections. In this study, there were no cases in which children could not receive insulin treatment due to the unavailability of insulin shots. However, this may be because the insulin dose was not properly controlled by checking blood sugar levels due to irregular lifestyles.

In this study regarding the frequency and severity of DKA in newly diagnosed patients, the HbA1c levels and DKA severity increased after COVID-19. The frequency and severity of DKA increased compared to the previous age-matched patients. In a study conducted by Rabbone et al. [26] in 53 clinics in Italy, it was observed that the proportion of newly diagnosed T1DM patients with severe DKA significantly increased from 44.3% in 2020 to 36.1% in 2019 ($p = 0.030$). A German study conducted by Kamrath et al. [27] also showed that the rates of DKA and severe DKA were higher during the COVID-19 outbreak. In the case of patients with newly diagnosed DM in this study, even when symptoms such as polyurea and polyphagia occurred, because of concerns about infection when visiting a medical institution or when going outside, the patients did not visit the hospital until the disease progressed and the symptoms were severe enough to cause problems in their daily life, such as dyspnea and altered mental status. Moreover, we analyzed the cause of the increased DKA severity before and after the COVID-19 outbreak. In Korea, schools conduct health checkups for all students in the spring, among which, urine analysis is conducted for the 1st and 4th grades of elementary school, the 1st grades of middle school, and the 1st grades of high school [28]. Due to the COVID-19 outbreak in the Daegu-Gyeongbuk area, there were daily life restrictions and delays in school attendance and admissions. During that time, students were unable to attend schools for a considerable period of time to prevent infection during the COVID-19 pandemic; hence, they were unable to undergo health checkups, as this period fell from March to April, which marks the beginning of a new school year in Korea. Furthermore, 1.4% of the students had high blood sugar levels according to the 2019 Student Health Examination Sample Statistics [28]. As such, most of the patients with newly diagnosed DM who have no symptoms or show mild symptoms are identified during school checkups and are asked to visit the hospital. In this study, health checkups in school were not possible during the COVID-19 outbreak. In the control group before the COVID-19 outbreak, two out of 10 patients were referred for hospital treatment due to abnormal findings in the screening test and were diagnosed with T1DM when symptoms were mild. School screening is useful for detecting type 2 DM with relatively mild symptoms and a long latent period of asymptomatic progression. However, it is meaningful because it can be detected through school examinations in the early stage of type 1 DM, when symptoms are not severe. This COVID-19-induced lockdown led to the omission of screening, and the symptoms were recognized only after the onset of severe DKA.

If symptoms of DM occur in both newly diagnosed patients and previously diagnosed patients, it is important to visit a hospital and check the progress before the symptoms worsen. Regular glucose monitoring and insulin medication are important for glycemic control in pediatric T1DM patients after the acute symptoms have improved. For this, it is important to check the progress of periodic outpatient visits [29]. In an Italian study conducted by Tornese et al. [30], there were cases of good glycemic control in patients with T1DM through continuous glucose monitoring (CGM) and insu-

lin pump along with physical activity and diet control through telemedicine. This study is limited by the lack of statistical data on the reasons for poor blood glucose control. Specifically, there were no studies on the activity, total intake, and insulin dose of the patients. The daily insulin dose, number of daily blood sugar test checks, and rate of CGM application were not investigated. Further research is needed, and more careful patient observation is required while following general DM guidelines during the COVID-19 epidemic. This includes checking the readings of blood sugar and insulin doses through frequent and regular follow-up and monitoring of physical activity and diet.

This retrospective chart review was conducted at a single center. When searching for an age-matched control group for newly diagnosed T1DM patients in the COVID-19 period, patients who visited the hospital in the closest season as possible were selected, but it was difficult to completely match and analyze patients by season by performing a single-center study with small sample size. Further multicenter analysis with a larger number of patients will be needed to identify factors in addition to COVID-19 that may have an influence, such as seasonality. Gender was also considered, but it was difficult to match because of the small number of patients. One more limitation is the lack of data on patients who did not visit the hospital within the study period. However, as the data were collected from a region with a severe COVID-19 outbreak, we believe that this study will be helpful in examining the incidence rate, symptom severity, and changes in the prevalence rate and degree of glycemic control of DM in children and adolescents.

In conclusion, this study reports the incidence of increased blood sugar levels and newly diagnosed cases of T1DM in children with severe DKA due to the COVID-19 situation in the Daegu-Gyeongbuk area. In the future, a large-scale, long-term follow-up study and active blood sugar management in patients with T1DM are required during the COVID-19 pandemic.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: MSL, CWK, JEM; Data curation: MSL, RL, JEM; Formal analysis: MSL; Investigation, Software, Validation: MSL, JEM; Writing-original draft: MSL, RL; Writing-review & editing: CWK, JEM.

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Case report

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Multilocular cystic hemangioma of the liver mimicking mucinous cystic neoplasm: a case report

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Hepatic hemangiomas infrequently exhibit atypical imaging features, which may cause diagnostic confusion with hepatic malignancies and lead to unnecessary surgery. We report a rare case of multilocular cystic hemangioma of the liver mimicking a mucinous cystic neoplasm of the liver in a 48-year-old female, focusing on computed tomography and magnetic resonance imaging features and their differential diagnosis.

Keywords: Cavernous hemangioma; Liver neoplasms; Magnetic resonance imaging; Multidetector computed tomography

Introduction

Cavernous hemangiomas are the most common benign tumors of the liver [1,2]. Mostly, imaging studies are sufficient for a definite diagnosis of typical cavernous hemangioma, and this lesion does not require surgical resection [1,2]. Infrequently, cavernous hemangiomas showing atypical imaging features are confused with other malignant hepatic tumors, which will subsequently require unnecessary surgery [3,4]. Cavernous hemangiomas containing fluid and multiple septa are rare. To our knowledge, there have been a few case reports on the imaging features of a multilocular cystic hemangioma of the liver [5-8]. In our case report, we present atypical imaging features of a multilocular cystic cavernous hemangioma with pathologic correlation.

Case

Ethical statements: This retrospective study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No: 2012-012-097), and the requirement for informed consent from the patient was waived by the IRB.

A 48-year-old female presented with lower abdominal pain and menorrhagia, and multiple uterine myomas were detected during a transvaginal ultrasound examination. She underwent contrast-enhanced abdominal computed tomography (CT) in the obstetrics and gynecology department for a preoperative examination of

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uterine myomas. On a CT scan, a hepatic tumor was incidentally found. CT scan revealed an approximately 14-cm multiseptated cystic mass containing some enhancing irregular septa in the right lobe of the liver (Fig. 1). For a detailed investigation of the hepatic tumor, gadoxetic acid-enhanced magnetic resonance imaging (MRI) of the liver was performed, which also revealed a huge multiseptated cystic mass with T1-hypointensity and T2-hyperintensity, identical to that of the fluid. Some hemorrhagic locules showing T1-hyperintensity and T2-hypointensity were noted (Fig. 2A, 2B). Enhancement of the irregular septa within the tumor was observed, but no solid enhancing nodules were detected (Fig. 2C). She did not complain of any symptoms related to the hepatic tumor. Laboratory tests, including liver function tests and tumor markers such as cancer antigen (CA) 125, carcinoembryonic antigen, alpha-fetoprotein, and CA 19-9 were unremarkable. No metastasis was found on the chest or abdominal CT.

Based on these imaging features, we considered the possibility of a mucinous cystic neoplasm (MCN) of the liver. Under high suspicion of hepatic MCN and consideration of large tumor size, the surgeon decided to perform immediate surgery without cytologic aspiration or biopsy. Bisectionectomy of the liver (resection of Couinaud segments 5 and 6) was performed. Histological examination of the resected tumor specimen revealed a well-defined multiseptated cystic mass in the liver, containing fluid, necrosis, and hemorrhage (Fig. 3A). Microscopic findings showed a multilocular cystic mass composed of variable-sized cystic spaces (Fig. 3B) and a cystic wall lined by flattened or cuboidal endothe-

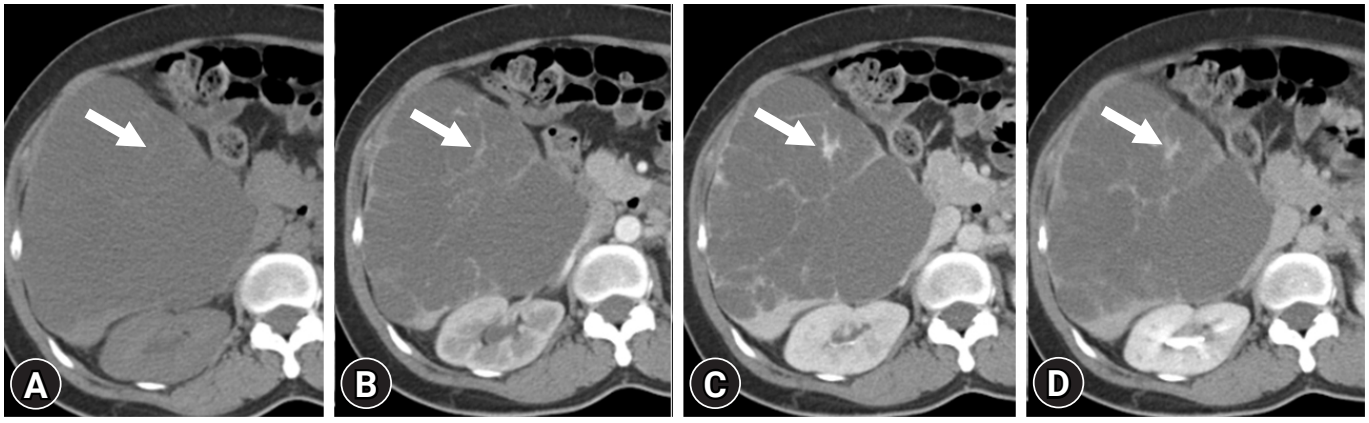

Fig. 1. Computed tomography (CT) findings of a multilocular cystic hemangioma of the liver in a 48-year-old female. Contrast-enhanced dynamic-phase abdominal CT scans show a huge septated cystic mass in the right lobe of the liver. (A) Nonenhanced, (B) arterial phase, (C) portal venous phase, and (D) delayed phase. Enhancement of the septa within the mass (arrows) is noted.

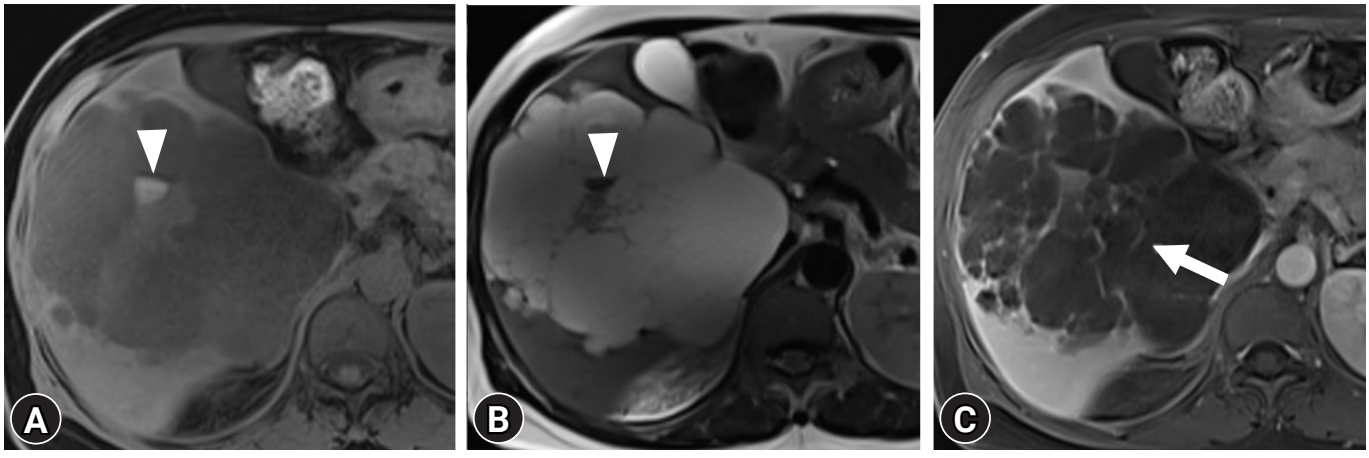

Fig. 2. Magnetic resonance imaging findings of a multilocular cystic hemangioma of the liver in a 48-year-old female. (A) T1-weighted and (B) T2-weighted images show a multiseptated cystic mass containing variable signal intensity. Most locules present as T1-hypointensity and T2-hyperintensity, identical to signal intensity of fluid. Some T1 hyperintense locules present as T2-hypointensity, suggesting subacute hemorrhage (arrowheads). (C) Contrast-enhanced fat-suppressed T1-weighted image shows septal enhancement (arrow).

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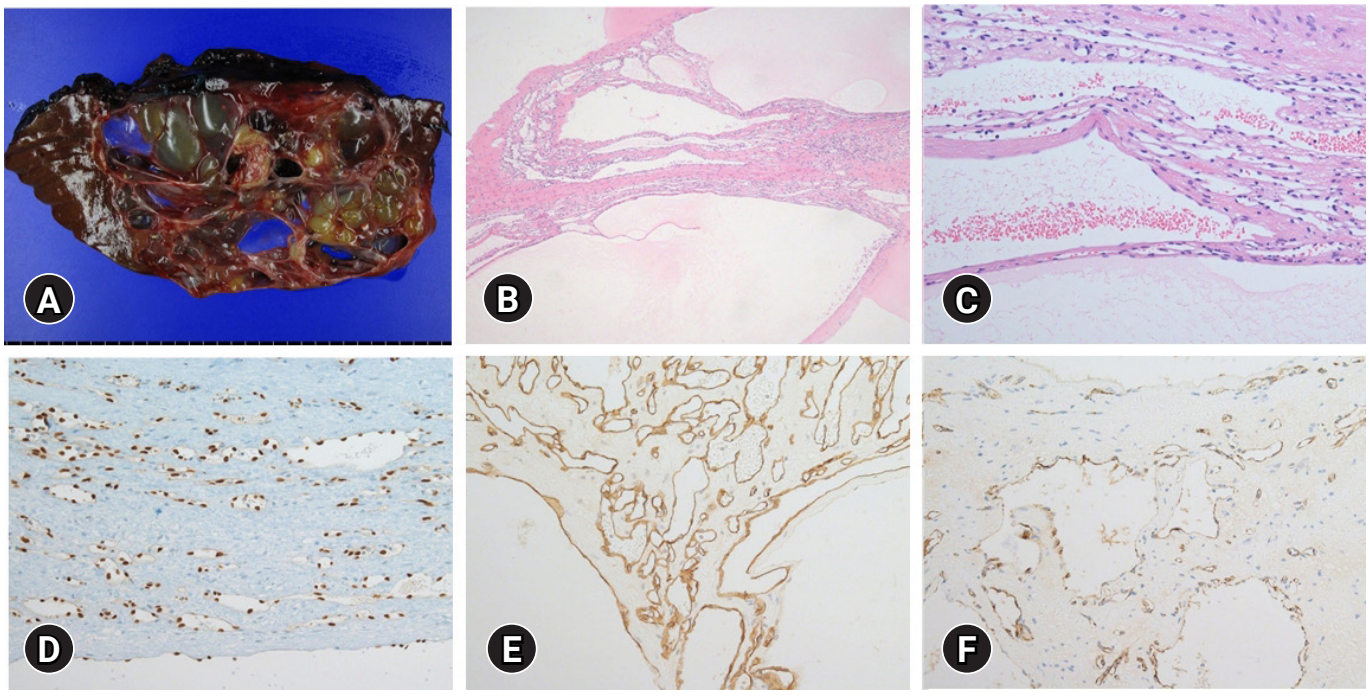

Fig. 3. Histopathologic findings of a multilocular cystic hemangioma of the liver in a 48-year-old female. (A) The cut section of the gross specimen shows multiple cystic loculi separated by multiple septa. (B) Low-power magnification shows a multilocular cystic mass composed of medium to small-sized cystic space (hematoxylin and eosin [H&E] stain, ×40). (C) High-power magnification shows the cystic wall lined by flattened or cuboidal endothelial cells without cytologic atypia and supported by fibrotic stroma (H&E stain, ×200). On immunohistochemical staining, the endothelial cells are positive for vascular endothelial cell markers such as (D) ETS-related gene (ERG), (E) CD34, and (F) factor VIII (immunohistochemical stain, x200 [D-F]), but negative for biliary epithelial cell markers such as cytokeratin 7 (CK 7) and CK 19 (not shown).

lial cells without cytologic atypia and supported by stroma (Fig. 3C). On immunohistochemical staining, the endothelial cells were positive for vascular endothelial cell markers (ETS-related gene [ERG], CD34, and factor VIII), but negative for biliary endothelial cell markers (cytokeratin 7 [CK 7] and CK 19) (Fig. 3D–F). The final diagnosis was a multilocular cystic cavernous hemangioma.

Discussion

Vilgrain et al. [3] described less frequent atypical imaging patterns of liver hemangiomas, such as large heterogeneous giant hemangiomas, rapidly filling hemangiomas, calcified hemangiomas, hyalinized hemangiomas, cystic or multilocular hemangiomas, hemangiomas with fluid-fluid levels, and pedunculated hemangiomas. According to Vilgrain et al. [3], our case may be categorized as cystic or multilocular hemangioma.

To our knowledge, only four cases of multilocular cystic hemangioma of the liver along with their CT and/or MRI findings, have been reported previously [5-8]. The size of the mass in the previous cases was approximately between 3.5 cm and 6 cm. The common imaging features were a well-defined multilocular cystic lesion showing hypoattenuation on CT and bright hyperintensity on T2-weighted MRI. It also showed a lobulated margin and some irregular septa. Three reports described the enhancing portion of the tumor, and among these, Cha et al. [8] performed dynamic-phase contrast-enhanced CT, which did not show globular enhancement seen in typical hemangiomas, but delayed gradual enhancement was noted in the central portion [5,6,8]. Another case did not show any enhancement on contrast-enhanced imaging [7]. Similar to previous cases, our case also showed a multilocular cystic lesion with bright T2 hyperintensity, lobulated margins, and some irregular septa. However, the mass in our case was larger (about 14 cm) than those in previously reported cases, and there was no enhancing portion except for the septa.

Multilocular cystic hepatic lesions are commonly detected on CT and MRI; however, they are nonspecific and cause potential challenges for differential diagnosis [9,10]. MCN is a rare neoplasm of the liver. Complete resection is required because of its malignant potential. The MCN of the liver appears as a large, solitary, multilocular cystic lesion with well-circumscribed margins

and internal septa. Enhancement is commonly observed along the walls and internal septa. Some enhancing solid portions may exist in mucinous cystadenocarcinomas. It has been reported exclusively in middle-aged female patients with ovarian-like stroma within the tumor [9,10]. Hepatocellular carcinoma (HCC) may lead to extensive necrosis or hemorrhage, which can manifest as an atypical multilocular cystic mass. Noticeably, even multilocular cystic HCC demonstrates mural nodules with arterial enhancement and delayed washout pattern or delayed capsular enhancement, which is indicative of typical HCC. Moreover, a hepatic mass in cirrhosis should first be considered HCC [9,10]. Multilocular cystic metastasis can be caused by extensive necrosis of hepatic metastasis, especially from a neuroendocrine tumor, melanoma, or gastrointestinal stromal tumor, or abundant mucin production from mucinous adenocarcinoma of the ovary or colorectum. Enhancing irregular septa or walls may present viable tumor cells within the cystic metastasis. However, because these imaging findings are usually nonspecific compared with other multilocular cystic neoplasms, knowledge of their primary malignancy is the most important [9,10]. Non-neoplastic hepatic lesions include hepatic abscesses, echinococcal cysts, intrahepatic hematomas, and bilomas. Hepatic abscesses generally show characteristic imaging features, such as the cluster sign or double target sign, and are associated with febrile conditions. A typical echinococcal cyst appears as a mother cyst and peripheral daughter cysts, which are associated with endemic areas. Intrahepatic hematoma or biloma may be associated with trauma or iatrogenic injuries [9,10]. Therefore, in our case, considering the past history of no primary malignancy, trauma, or travel, and that the patient was asymptomatic and a middle-aged female, MCN of the liver was the most likely preoperative diagnosis.

The pathogenesis of hemangioma multilocularity remains unknown. According to previous literature, it may be caused by cystic degeneration secondary to thrombus formation, necrosis or hemorrhage, and scar formation within cavernous hemangioma [6,7]. Similar to previous reports, our imaging features are also correlated with macroscopic appearance, showing a multiseptated cystic lesion containing fluid, necrosis, and hemorrhage. In our case, septa showed delayed enhancement that might be a fibrous stroma rather than centripetal filling-in enhancement in typical hemangioma [8].

Multilocular cystic hemangiomas are extremely rare and difficult to differentiate from other cystic hepatic lesions. Therefore, it is important to be familiar with the fact that hemangiomas can rarely be seen as multilocular cystic hepatic lesions. If other differential diagnoses in multilocular cystic hepatic lesions are excluded, the possibility of atypical hemangioma is suspected, and preoperative biopsy can be performed to avoid unnecessary extended hepatic resection.

Notes

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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Author contributions

Conceptualization, Project administration: SK, NKL; Data curation, Formal analysis: SBH, SJL, HIS; Funding acquisition: NKL; Writing-original draft: NKL; Writing-review & editing: SK, NKL.

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Case report

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Mega cisterna magna in bipolar mood disorder: a case report

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Mega cisterna magna (MCM), one of the members of the Dandy-Walker complex, is a developmental malformation of the posterior fossa that is larger than 10 mm but morphologically does not affect the vermis and cerebellar hemispheres. Reports of psychiatric disorders associated with this anomaly are rare. We present the case of a patient with MCM who presented with a psychotic manic attack and was diagnosed with bipolar disorder. A 28-year-old female, single housewife, university graduate, presented with irritability, decreased sleep and appetite, distraction, and agitation. The patient also had a delusion of reference. In the clinical follow-up, an increase in energy and an increase in the amount of speech were observed. Her neurological examination was normal, and cranial magnetic resonance imaging revealed an MCM. The relationship and clinical significance of MCM with psychosis and mood disorders have not yet been fully elucidated. It is not known whether this association is accidental or based on etiological commonality. The purpose of this case report is to review the relationship between the cerebellum and psychiatric symptoms and to contribute to the literature.

Keywords: Cerebellum; Mania; Mood disorders; Posterior cranial fossa; Psychotic disorders

Introduction

Bipolar disorder is a chronic disease with elevation, depression, and recovery periods and is accompanied by psychotic symptoms during episodes of illness. The cerebellum is thought to play a role in the pathophysiology of bipolar disorder. It is located in the posterior cranial fossa, behind the fourth ventricle, pons, and medulla oblongata. The tentorium, which is an extension of the dura mater, separates the cerebellum from the cerebrum. The cerebellum, which is the largest structure of the central nervous system after the cerebrum, has anatomically and physiologically different functional parts and consists of highly ordered neuronal units sharing the same basic cerebellar microcircuit [1]. The cerebellum is responsible for coordinating movement, maintaining balance and posture, muscle tone, and motor learning. In addition, the cerebellum is linked to many brain areas related to cognition and behavior, such as the dorsolateral prefrontal cortex, medial frontal cortex, anterior cingulate, and posterior hypothalamus, particularly through the thalamus. It is thought that noradrenergic, serotonergic, and dopaminergic afferents from the nuclei in the brainstem may play a role in the regulation of sensory, procedural, linguistic, and emotional activities through cerebellar connections with limbic and cortical association areas. This information suggests that the cerebellum contributes significantly to mood regulation and that cerebellar

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anomalies may be involved in the pathophysiology of mood disorders [2].

Cisterna magna is the subarachnoid space located behind the medulla oblongata under the cerebellum. This space allows the cerebrospinal fluid (CSF) to be transferred from the fourth ventricle to the foramina. Mega cisterna magna (MCM), which is a developmental malformation of the posterior fossa, is known for the cisterna magna being larger than 10 mm, morphologically normal vermis and cerebellar hemispheres, and no hydrocephalus [3,4].

MCM is observed in approximately 1% of postnatal brain images. The incidence of isolated MCM in the community is not clearly known, as it is asymptomatic. The coexistence of MCM and psychiatric disorders is rare and possibly coincidental. However, the relationship between these two is striking when evaluated in terms of the effect of the cerebellum on psychiatric symptoms and mood regulation, and more studies are needed to reveal the causal relationship between them.

This study aimed to present the case of a patient who presented with a manic episode of bipolar disorder associated with MCM, to review the relationship between the cerebellum and psychiatric symptoms, and to contribute to the literature.

Case

Ethical statements: Ethical approval for the study was obtained from the non-invasive ethics committee of Sakarya University Faculty of Medicine (No: 02.03.2021-E.14816).

A 28-year-old female, single housewife, university graduate, was brought with complaints of irritability, decreased sleep and appetite, distraction, reference delusion, and agitation that started 10 days before her hospitalization. The patient, who was referred to our service with a prediagnosis of psychotic attack by a psychiatry consultant doctor in the emergency department, with a haloperidol injection, had reduced self-care, looked agitated, and was sleepy. The patient, who did not have a psychiatric history before, had a hypomania attack 2 years ago for 2 to 3 days with complaints of irritability, decreased sleep and appetite, decreased attention, and concentration.

On mental state examination, the patient was conscious, oriented to place-time-person, and was not willing to communicate, but could establish eye contact. The agitated patient's affect was labile, and her mood was irritable. Her speech was reduced and fit for purpose, and her tone of voice was natural. She spoke defensively. The flow of thought and associations was accelerated. Her attention and concentration were reduced. The patient's thought content had a reference delusion that people were texting her on television. Her perception was not disordered. Near and distant memories were normal. Knowledge and intelligence were correlated with the education level. Abstract thinking was natural. Judgment and insight were reduced. Her psychomotor activity was increased. Neurological deficits were not observed during her neurological examination. There was no history of smoking, alcoholism, or other substance abuse. No significant pathological findings associated with the perinatal history were observed. The patient was born through vaginal delivery at term. She had no known disease or hospitalization history during her infancy. Her psychomotor development was normal. No family history of any neurological or psychiatric illness was found. For psychological assessment, the Minnesota Multiphasic Personality Inventory (MMPI) and intelligence quotient (IQ) tests were performed on the patient. The IQ test results were in the normal intelligence range. In the MMPI personality test, a psychopathological increase was not observed in the subtests and the general test profile.

In the first week after her admission to our service, while her anamnesis was taken, the patient had almost no speech and insomnia. On the clinical impression of the patient, elevated mood, increased amount of speech and energy, distraction, thought flow, and acceleration in associations were observed. The patient was diagnosed with bipolar disorder manic episode.

The hemogram and biochemical values were within normal limits. Replacement therapy was initiated for low vitamin D levels. In cranial magnetic resonance imaging (MRI), a 2 cm wide MCM variation with the same intensity as the CSF in the T1A and T2A sequences was detected in the infravermian area, extending posteriorly between both cerebellar hemispheres (Fig. 1).

The patient was started on quetiapine (100 mg), haloperidol (10 mg), and biperiden (2.5 mg) injection therapy. On the third day of hospitalization, 10 mg of olanzapine was added to the treatment. The dose of olanzapine was gradually increased to 20 mg over 2 weeks. The doses of haloperidol and biperiden were tapered. During the third week of the hospitalization, the patient's psychotic symptoms regressed and 300 mg of lithium was added to the treatment for the ongoing mood symptoms. When the lithium dose was gradually increased to 900 mg, the patient's affective symptoms regressed, and the blood lithium level was measured as 0.72 at the time of discharge. The patient, who was in a good clinical condition and had no homicidal or suicidal thoughts, was discharged.

Discussion

According to the Diagnostic and Statistical Manual of Mental Dis-

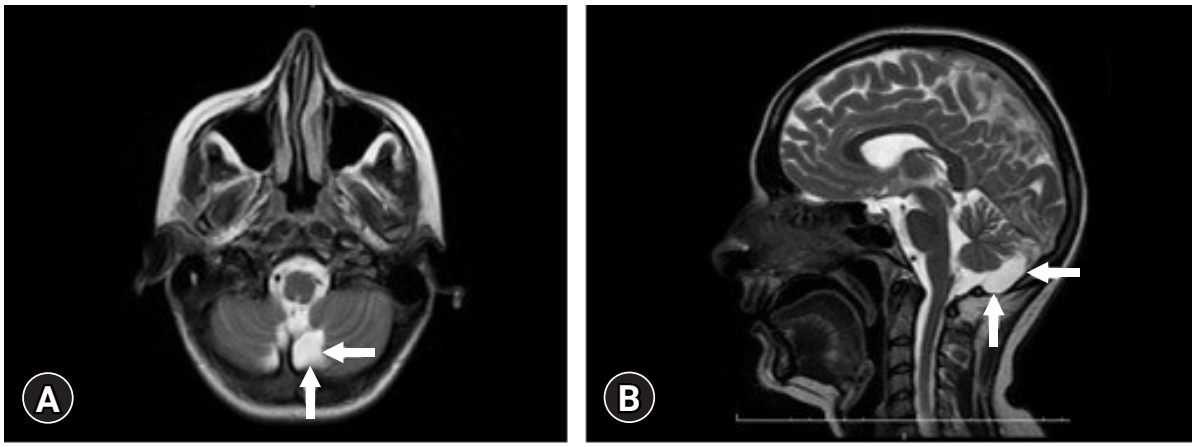

Fig. 1. The unenhanced T2-weighted brain magnetic resonance imaging scans of (A) the axial and (B) sagittal planes show mega cisterna magna (arrows) with the same intensity as the cerebrospinal fluid extending from the interhemispheric area to the posterior, which is more prominent in the left cerebellar hemisphere.

orders, fifth edition (DSM-5) criteria, affective episodes lasting longer than 1 week (shorter if resulted in hospitalization) are diagnosed as manic episodes of bipolar mood disorder [5]. This case meets the bipolar disorder criteria in terms of symptom severity and duration according to the DSM-5 criteria. The patient did not have any known alcohol or psychoactive substance use. This was confirmed by toxicological analysis of the urine. Moreover, no anomaly was found in the vermis and cerebellar hemispheres on MRI, and no neurological deficits were detected. These findings are consistent with the diagnosis of MCM. When a search was conducted using the keywords 'mega cisterna magna' on Google Scholar and PubMed databases, it was found that this anomaly is associated with psychiatric disorder; Langarica and Peralta [6], Ferentinos et al. [7], Turan et al. [8], Kumar et al. [9], Karayılan and Erol [4], Kani et al. [10], Erzin [11], Balcioğlu et al. [12], and Öztürrk et al. [13]. Only two of these case reports were associated with manic episodes; Turan et al. [8] and Öztürrk et al. [13]. Previous case reports have mentioned that there may be a relationship between MCM and psychiatric symptoms. This relationship is more evident in malformations affecting the vermis and cerebellar hemispheres [14,15]. However, in proton magnetic resonance spectroscopy, it was observed that the levels of gamma-aminobutyric acid (GABA) were decreased in the cerebellar tissue of patients diagnosed with unipolar and bipolar disorder. Another postmortem study showed that Purkinje cells were significantly reduced in the frontal lobe of the cerebellum in a patient with bipolar disorder. It has also been suggested that abnormal GABA proteins play an important role in the expression and migration of GABAergic Purkinje cells during cerebellar development [16-18].

Although there is no cerebellar parenchymal anomaly that can be detected by imaging and neurological examination, postmortem findings of MCM as a developmental anomaly have been investigated in cases such as stillbirth, but there is no postmortem neuropathological study of adult patients with MCM [19]. Although this case cannot be evidence of a causal relationship alone, the relationship between the neuroanatomical location of the variation and mood regulation and psychiatric symptoms brings to mind an underlying etiology that may point out a causal relationship. Therefore, further studies are needed to establish a causal relationship between the effects of structural disorders, such as MCM, on cerebellar mechanisms and psychiatric disorders. These studies may be particularly valuable in guiding studies on the pathophysiology and treatment of mood and psychotic disorders.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: EY, YG, EMK, ABY; Investigation: ABY; Data curation: SK, YG; Formal analysis: YG, ABY; Methodology: EY; Supervision: YG, ABY; Writing - original draft: EY; Writing - review & editing: all authors.

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Adrenal insufficiency development during chemotherapy plus anti-programmed death receptor-1 monoclonal antibody (tislelizumab) therapy in patients with advanced gastric cancer: two case reports

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Immune checkpoint inhibitor (ICI)-associated adrenal insufficiency is rare but may become a serious adverse event in patients treated with ICIs. The present case report documents two cases of adrenal insufficiency developed during chemotherapy plus tislelizumab (百泽安, Baize'an; BeiGene Ltd.) therapy in patients with advanced gastric cancer. Adrenal insufficiency developed after 6 and 13 cycles of treatment and was well controlled with hydrocortisone. The patients also developed hypothyroidism, which was managed with levothyroxine. Two patients showed a partial response, and one patient out of two achieved a near-complete response, sustaining over 11 months. Increased awareness of ICI-related adrenal insufficiency is crucial for early detection and prompt management of patients treated with ICIs.

Keywords: Adverse events; Immune checkpoint inhibitors; Stomach neoplasms; Tislelizumab

Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide, even though rapid advances in treatment options have improved its prognosis [1]. Remarkable progress in tumor biology has led to the development of new therapeutics that target critical aspects of oncogenic pathways or the immune system. However, the prognosis of patients treated with standard treatment for advanced gastric cancer remains poor [2]. Programmed cell death protein 1 (PD-1) is a cell surface receptor that plays a significant role in downregulating the immune system and promoting self-tolerance by suppressing T-cell activity. Antibodies that block the interaction between PD-1 and programmed death-ligand 1 (PD-L1) allow the immune system to attack cancer cells. Anti-PD-1 and anti-PD-L1 antibodies have revolutionized the treatment of melanoma and non-small cell lung cancer (NSCLC) and are being evaluated in a broad range of other cancers, including gastric cancer.

Tislelizumab (百泽安, Baize'an; BeiGene Ltd., Beijing, China) is a humanized monoclonal antibody (mAb) with high affinity and specificity for PD-1 that was engineered to minimize binding to Fc-γ receptor I (FcγRI) on macrophages to greatly reduce anti-

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body-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy [3].

The use of immune checkpoint inhibitors (ICIs) in cancer therapy is complicated by numerous mechanism-based toxicities, termed immune-related adverse events (irAEs), affecting dermatological, gastrointestinal, hepatic, endocrine, and other systems. Adrenal insufficiency is an irAE and may manifest as nonspecific symptoms. Delay in diagnosis and inadequate care can lead to serious complications. Although it is necessary to elucidate the detailed clinical features of this adverse event (AE) for early detection, the clinical features of anti-PD-1 therapy-induced adrenal insufficiency remain poorly described.

Two cases of adrenal insufficiency are described in this study that developed during chemotherapy plus anti-PD-1 mAb (tislelizumab) therapy in patients with advanced gastric cancer in the clinical trial setting.

Cases

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No: 2019-05-021). Informed consent was obtained from the patients.

1. Case 1

A 58-year-old male was diagnosed with clinical T4N3M1, stage IV Her-2 negative gastric adenocarcinoma, with portal vein tumor thrombosis. He underwent palliative chemotherapy with capecitabine (1,000 mg/m^2 twice daily, D1–D14), oxaliplatin (130 mg/m^2, D1), and tislelizumab (200 mg/m^2, D1) at 3-week intervals. He received palonosetron (0.25 mg) and dexamethasone (10 mg), intravenously, before the infusion of oxaliplatin for the prevention of emesis. The initial treatment was well tolerated, and follow-up scans showed a partial response. He developed severe fatigue, and his serum sodium level was 109 mmol/L (range, 135–145 mmol/L) after six cycles of treatment. Further investigations revealed the following: random urinary sodium, 64 mmol/L; free T3, 0.39 pg/mL (range, 2.00–4.40 pg/mL); free T4, 0.15 ng/dL (range, 0.89–1.8 ng/ dL); and thyroid-stimulating hormone (TSH) 136.50 mIU/L (range, 0.3–4.0 mIU/L). The levels of antithyroglobulin antibody and antithyroid peroxidase were 70.60 U/mL (range, 0–60 U/mL) and 55.02 U/mL (range, 0–60 U/mL), respectively. Thyroid ultrasonography showed atrophic changes in both lobes of the thyroid gland. The random serum adrenocorticotropic hormone (ACTH) level was 20.23 pg/mL (range, 0–60 pg/mL), and a rapid ACTH test was conducted. Before the administration of 250 μg of synthetic ACTH (cosyntropin), serum cortisol was < 0.5 μg/dL (range, 3.09–22.4 μg/dL). Postadministration values were 2.27 and 3.56 μg/dL, at 30 and 60 minutes, respectively. Magnetic resonance imaging (MRI) of the brain showed no abnormalities in the pituitary gland (Table 1). The patient was diagnosed with hypothyroidism and adrenal insufficiency. The patient received levothyroxine (0.15 mg) per day and 10 mg of hydrocortisone twice daily. His serum sodium level improved to 138 mmol/L after 1 week of treatment, and the patient reported improvement in fatigue. Follow-up investigations were conducted after 6 weeks of treatment and revealed the following: free T3, 3.03 pg/mL; free T4, 1.41 ng/dL; TSH, 13.10 mIU/L; and random serum cortisol, 14.77 μg/dL. Currently, the patient shows a near-complete response to treatment with capecitabine and tislelizumab. Hypothyroidism and adrenal insufficiency are well controlled with levothyroxine (0.15 mg) per day and hydrocortisone twice daily (10 mg on awakening and 5 mg in the early evening).

2. Case 2

A 59-year-old man was diagnosed with clinical T3N2M1, stage IV Her-2 negative gastric adenocarcinoma, with multiple metastases to the left paraaortic lymph node and liver. He underwent six cycles of palliative chemotherapy with capecitabine (1,000 mg/m^2 twice daily, D1–D14), oxaliplatin (130 mg/m^2, D1), and tislelizumab (200 mg/m^2, D1) and seven cycles of capecitabine and tislelizumab from December 2019 to September 2020, resulting in a partial response. He received palonosetron (0.25 mg) and dexamethasone (10 mg), intravenously, before the infusion of oxaliplatin for the prevention of emesis.

He developed severe weakness and mild dizziness after 13 cycles of treatment. Further investigations revealed the following: serum sodium, 123 mmol/L; free T3, 4.44 pg/mL; free T4, 1.05 ng/dL; and TSH 8.28 mIU/L. Additional tests for antithyroid antibodies and thyroid ultrasonography were not performed. Random serum cortisol was found to be 0.79 μg/dL and serum ACTH was 51.90 pg/mL (Table 1). The patient was diagnosed with subclinical hypothyroidism and adrenal insufficiency. The patient was administered levothyroxine (0.05 mg per day) and hydrocortisone (10 mg) twice daily. His serum sodium level improved to 137 mmol/L after 1 week of treatment, and he reported improved condition and restarted treatment with capecitabine and tislelizumab. Follow-up investigations were conducted after 6 weeks of treatment and revealed the following: serum sodium, 135 mmol/L; free T3, 4.62 pg/mL; free T4, 1.46 ng/dL; TSH, 3.67 mIU/L; and random serum cortisol 9.15 μg/dL. His disease progressed after 16 cycles of treatment. Currently, the patient receives second-line treatment with ramucirumab and paclitaxel. Hypothyroidism and adrenal in-

Table 1. Summary of patient characteristics and clinical symptom, laboratory result, and imaging

Case	Age (yr) /sex	Diagnosis	Time of symptom onset	Presenting symptom	Laboratory result	Imaging result
1	58/M	AGC with portal vein tumor thrombosis	Cycle 6	Severe fatigue	Pretreatment free T3: 3.29 pg/mL Pretreatment free T4: 1.43 ng/dL Pretreatment TSH: 0.67 mIU/L Serum sodium: 109 mmol/L Random urinary sodium: 64 mmol/L Free T3: 0.39 pg/mL Free T4: 0.15 ng/dL TSH: 136.50 mIU/L Antithyroglobulin antibody: 70.60 U/mL Antithyroid peroxidase: 55.02 U/mL Rapid ACTH test[a]	Thyroid ultrasonography: atrophic changes in both lobes of the thyroid gland Brain MRI: no abnormality in the pituitary gland
2	59/M	AGC with multiple metastases to left paraaortic lymph node and liver	Cycle 13	Severe weakness and mild dizziness	Pretreatment free T3: 3.25 pg/mL Pretreatment free T4: 1.12 ng/dL Pretreatment TSH: 5.81 mIU/L Serum sodium: 123 mmol/L Free T3: 4.44 pg/mL Free T4: 1.05 ng/dL TSH: 8.28 mIU/L Random serum cortisol: 0.79 μg/dL Random serum ACTH: 51.90 pg/mL	

M, male; AGC, advanced gastric cancer; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; MRI, magnetic resonance imaging.
[a]Serum cortisol is <0.5, 2.27, 3.56 μg/dL at 0, 30, 60 minutes, respectively; serum ACTH is 20.23 pg/mL at 0 minute.

sufficiency are well controlled with levothyroxine (0.05 mg) per day and hydrocortisone twice daily (10 mg on awakening and in the early evening).

Discussion

ICIs are now considered the standard of care for melanoma, NSCLC, and renal cancer. An increasing number of agents are available, and the list of indications is growing, including gastric cancer. Tislelizumab is a humanized IgG4 anti-PD-1 mAb that has been developed for the treatment of hematological malignancies and advanced solid tumors [4]. The low affinity of tislelizumab for FcγRI may result in improved anticancer efficacy. ICIs have been shown to cause a unique set of toxicities, irAEs, which are different from those previously reported for cytotoxic agents. ICIs may affect peripheral tolerance to autoantigens, resulting in autoantibody formation, which could be associated with irAEs in various organs. Endocrine AEs are the most common irAEs. The majority of irAEs are mild to moderate and self-limiting, but a few of them, including adrenal insufficiency, can lead to potentially life-threatening events [5].

ICI-related adrenal insufficiency is a rare disease, and a systematic review reported that the incidence of adrenal insufficiency of any grade was 0.7%, and the incidence of grade 3 or higher was only 0.2% [6]. However, recognition is important because it may be severe or life-threatening. There is no clearly defined time frame for the development of adrenal insufficiency. It can develop in the first month of treatment, but some cases have been reported several years after treatment. In this study, adrenal insufficiency developed after six and 13 cycles of treatment in cases 1 and 2, respectively. The presentation of adrenal insufficiency may vary from asymptomatic laboratory abnormalities to serious medical conditions [7]. Symptoms are also vague and nonspecific; fatigue, dizziness, and anorexia are frequent symptoms, and refractory hypotension and altered state of consciousness may present in severe cases. Hyponatremia and hyperkalemia are frequently reported. Hyponatremia is mediated by increased release of antidiuretic hormone (ADH), which results in water retention and a dilutional decrease in serum sodium levels [8]. The increased secretion of ADH is caused by cortisol deficiency; hence, cortisol deficiency results in the increased hypothalamic secretion of corticotropin-releasing hormone, an ADH secretagogue [9]. Increased ADH secretion is also attributed in part to the reduction in systemic blood pressure and cardiac output. In addition, cortisol directly suppresses ADH

secretion [10]. Differential diagnoses may include central (immune-mediated hypophysitis with secondary adrenal insufficiency, hypophyseal metastasis) and peripheral (adrenal metastasis, adrenal hemorrhage) potential causes, while infections, drugs, and infiltrative diseases should also be considered. Laboratory tests and imaging studies, including morning cortisol, ACTH, ACTH-stimulation test, adrenal gland computed tomography, and hypophysis MRI, may be helpful for differential diagnosis. Management should include holding ICIs until a patient is stabilized, hydrocortisone, and fluid resuscitation based on clinical severity. ICIs with appropriate hormone replacement can be continued.

Some studies have suggested an association between irAEs and clinical benefits, but it has not yet been identified [11,12]. Hussaini et al. [13] reported a positive association between the development of irAEs and objective response rate (ORR), progression-free survival, and overall survival (OS). They also reported that grade 3 or 4 irAEs were associated with better ORR but worse OS. In our case studies, both patients showed a partial response. One patient achieved a near-complete response, and the response has been sustained for over 11 months. Further studies are required to investigate the association between irAEs and the efficacy of ICIs and to improve the control of irAEs and the clinical practice of ICIs.

This study presented two cases of adrenal insufficiency that developed during tislelizumab therapy in patients with advanced gastric cancer. The guidelines of the American Society of Clinical Oncology recommend testing for TSH and free T4 every 4 to 6 weeks as part of routine clinical monitoring or for case detection in symptomatic patients, but regular monitoring for adrenal insufficiency is not recommended [14]. Therefore, increased awareness of ICI-related adrenal insufficiency is crucial for early detection and prompt management in patients treated with ICIs.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Case report

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Coinfection of *Sphingomonas paucimobilis* meningitis and *Listeria monocytogenes* bacteremia in an immunocompetent patient: a case report

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This report describes a case of coinfection of *Sphingomonas paucimobilis* meningitis and *Listeria monocytogenes* bacteremia in a 66-year-old immunocompetent female patient. The patient had undergone traditional procedures, including acupuncture, which possibly caused the coinfection. During treatment with susceptible antibiotics for bacterial meningitis, she developed hydrocephalus on the third day. Consequently, the patient recovered with a mild neurological deficit of grade 4 motor assessment in both upper and lower extremities at discharge. *S. paucimobilis* and *L. monocytogenes* are rare pathogens in developed countries, occurring only during environmental outbreaks. *S. paucimobilis* meningitis is rarely reported. Hence, the various presentations of *S. paucimobilis* meningitis and the antibiotic regimen for its treatment are hereby reported, in addition to a review of other similar reported cases. This case is a possible traditional procedure-related infection. Appropriate oversight and training should be emphasized regarding preventive measures of this kind of infection. A team approach with neurologists and neurosurgeons is imperative in treating patients with hydrocephalus-complicated meningitis.

Keywords: Bacteremia; Coinfection; *Listeria*; Meningitis; *Sphingomonas*

Introduction

Sphingomonas paucimobilis is a gram-negative, nonfermenter, and community-acquired bacteria [1]. *Sphingomonas* spp. has been isolated from seawater, river water, wastewater, mineral water, and water-based hospital equipment [2]. Several hospital outbreaks of *S. paucimobilis*, mainly catheter-associated infections, have been reported [3,4]. Although *S. paucimobilis* has low virulence, it may still cause meningitis and bacteremia. *S. paucimobilis* infection involving the central nervous system can manifest as meningitis and ventriculitis.

Listeria monocytogenes is a gram-positive pathogenic bacterium found in soil and water [5]. Community-acquired infections generally occur during foodborne outbreaks [6]. Common *L. monocytogenes* infections have been reported as gastrointestinal tract infections, meningitis, and bacteremia [6,7]. Infections in neonates and the elderly have higher rates of mortality and morbidity [6,7].

This case report described the case of an immunocompetent host with *S. paucimobilis* meningitis and *L. monocytogenes* bacteremia.

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Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: 2020-01-018). Written informed consent was obtained for publication of this case report and accompanying images.

A 66-year-old woman complained of fever, slight drowsiness, and neck stiffness for 5 days. The patient complained of no gastrointestinal symptoms. Eight days before her admission, she had received acupuncture more than 100 times and moxibustion cupping on both sides of her posterior neck. She had no history of diabetes, hypertension, or corticosteroid use. Thirteen months before this event, the patient had received her final adjuvant chemotherapy for breast cancer after mastectomy. One day before her admission, she had visited a nearby hospital, and the brain magnetic resonance imaging (MRI) findings were unremarkable and showed no meningeal enhancement. The hospital referred her to a tertiary hospital for further evaluation of her neck stiffness as she had no Kernig or Brudzinski signs. There were few round thin bruise-like lesions from the previous cupping procedure without tenderness or swelling on inspection. Her vital signs were as follows: blood pressure, 160/100 mmHg; heart rate, 75 beats/min; respiratory rate, 20 breaths/min; and body temperature, 39.1°C. Her initial Glasgow Coma Scale (GCS) score was 15, while her motor assessment result was grade 5. Her sensory assessment result was unremarkable. The initial cerebrospinal fluid (CSF) analysis results revealed a white blood cell (WBC) count of 429/μL (polymorphonucleocytes [PMN], 62%), red blood cell count of 100/μL, glucose of 11 mg/dL, adenosine deaminase of 19.7 IU/L, protein level of 369.51 mg/dL, and an opening pressure of 100 mmHg. The fluid was yellowish with a turbid nature. For culture, an uncentrifuged CSF sample was inoculated onto one blood agar plate (Komed Corp., Ltd., Seongnam, Korea), one chocolate agar plate (Komed Corp., Ltd.), and BBL Fluid thioglycollate medium (BD, Sparks, MD, USA).

Identification and antimicrobial susceptibility tests were performed using VITEK 2 (software version 08.01; bioMérieux, Marcy-l'Étoile, France). The laboratory blood results were as follows: WBC of 11,520/μL, hemoglobin of 13 g/dL, high-sensitivity C-reactive protein of 18.791 mg/dL, erythrocyte sedimentation rate of 33 mm/hr, glucose of 174 mg/dL, and total protein of 6.08 g/L. For blood culture, each bottle of two blood culture media sets (BACT/ALERT SA & SN; bioMérieux) was inoculated with 10 to 15 mL of blood. The identification process was performed using VITEK MS (bioMérieux). VITEK 2 was used for antimicrobial susceptibility tests for the blood culture. The patient was diagnosed with bacterial meningitis. She received antibiotic treatment with vancomycin and ceftazidime. Intravenous dexamethasone sodium phosphate (0.6 mg/kg/day every 6 hours) was given for 5 days.

On her third hospitalization day (HD), her mental status deteriorated, and she was intubated. Subsequently, brain computed tomography (CT) showed signs consistent with hydrocephalus (Fig. 1), and an emergency external ventricular drainage (EVD) was inserted. On HD 5, the culture results of the initial CSF sample revealed *S. paucimobilis*, which was susceptible to cefotaxime (minimal inhibitory concentration [MIC] ≤ 1), ciprofloxacin (MIC = 0.5), ceftazidime (MIC = 8), and cefepime (MIC ≤ 1) but resistant to colistin (MIC ≥ 16). Two bottles of the initial blood culture results revealed *L. monocytogenes* susceptible to ampicillin (MIC ≤ 0.25) and vancomycin (MIC = 0.5) but resistant to ciprofloxacin (MIC = 1) and oxacillin (MIC ≥ 4). The treatment was switched to ampicillin/sulbactam and ceftriaxone on the HD 6.

The patient's mental status and laboratory findings gradually improved. On the 14th HD at 3:25 PM, the EVD was removed, as she responded to all verbal questions and directions (intact place, time, and person orientation, and her motor grade was 4), and she was transferred from the intensive care unit to a general ward. Two hours after EVD was removed, the patient exhibited a sudden deterioration of mental status (deep drowsiness) and presented with an enlarged left ventricle, which was seen on brain CT and received a second EVD insertion. CSF analysis results were as follows: WBC count of 12/μL (PMN, 90%), red blood cell count of 3,500/μL, glucose of 61 mg/dL, and protein level of 29.28 mg/dL. The fluid was pinkish. Later, the neurosurgery team inserted a ventriculoperitoneal (VP) shunt. On HD 28, her GCS score was 15; her motor assessment results were all grade 4; her Mini-Mental State Examination (MMSE) score was 11; her functional ambulation categories (FAC) score was 2. She was transferred to a rehabilitation hospital on HD 91. About 5 months later, the patient's status improved to a GCS score of 15, motor grades 4, a FAC score of 3.5, and an MMSE score of 21.

Overall, the patient's antibiotic regimen consisted of ceftriaxone (2 g every 12 hours) and vancomycin (1 g every 12 hours) for 6 days, followed by switching to ampicillin/sulbactam (3 every 6 hours) and ceftriaxone (2 g every 12 hours) for 21 days. Thus, her antibiotic treatment lasted for a total of 26 days.

Discussion

S. paucimobilis can be isolated from seawater, river water, invertebrates residing in water, and water distribution systems, including hospital environments [2]. This organism is often responsible for

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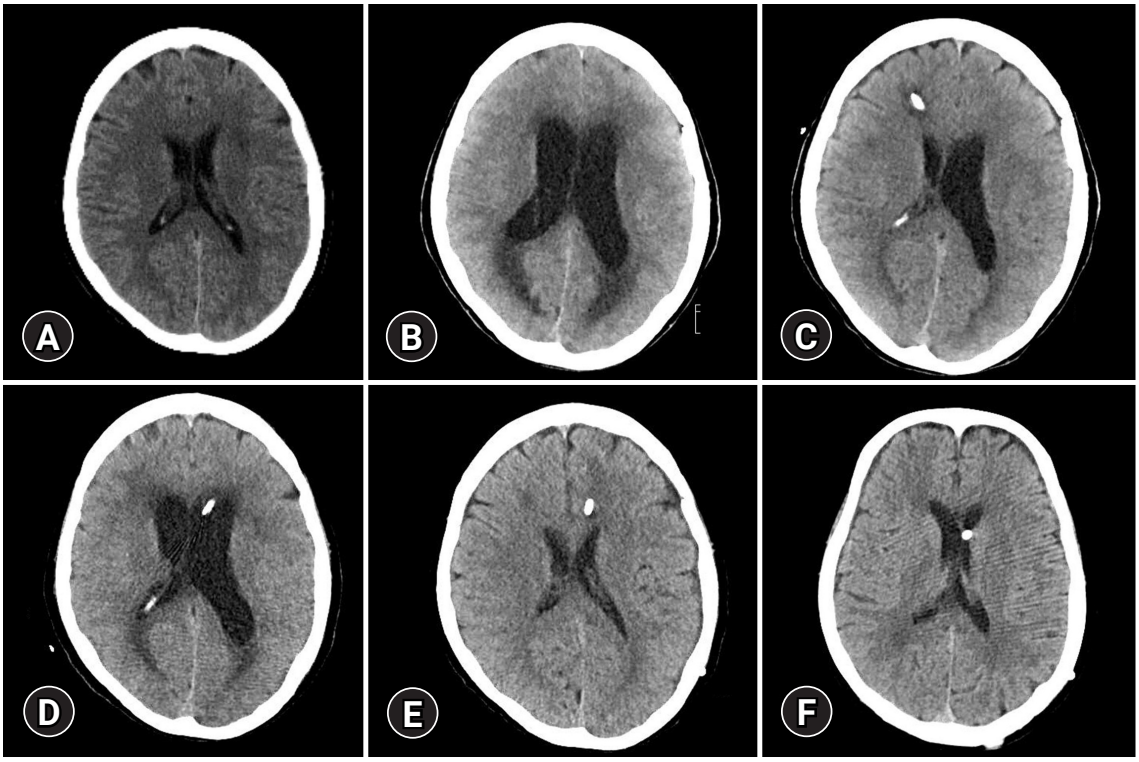

Fig. 1. Computed tomography images of the brain. (A) On hospitalization day (HD) 1, without enlarged ventricles; (B) on HD 3, with the enlarged ventricle; (C) on HD 10, with the enlarged left ventricle and emergency external ventricular drainage, inserted at right Kocher's point; (D) on HD 32, with the enlarged ventricle and emergency external ventricular drainage, inserted at left Kocher's point; (E) on HD 45, with a normal ventricle size and ventriculoperitoneal (VP) shunt inserted at left Kocher's point; and (F) 4 months after discharge, with normal-sized ventricles and VP shunt.

catheter-associated infections and hospital outbreaks [3,4]. *S. paucimobilis* infection usually occurs in severely ill patients, including immunocompromised patients, due to its low virulence. Most case reports of *S. paucimobilis* infection presented with primary bacteremia and were often associated with catheter-associated infections [3,4,8]. Only a few cases of *S. paucimobilis* central nervous system infection have been reported (Table 1) [4,9-15]. When this pathogen infects the central nervous system and the adjacent tissue, the prognosis varies from baseline function recovery to severe disability and even death [9-11]. The treatment duration for meningitis caused by gram-negative bacteria has not been clearly defined [16].

Table 1 contains nine case reports of *S. paucimobilis* meningitis, including this case. Bacterial meningitis is challenging to diagnose due to its various clinical signs and symptoms [17]. Among these reports, some had normal radiological findings with atypical clinical presentations of meningitis during the first clinical visit, like this case [13,15]. Four out of nine *S. paucimobilis* meningitis cases were complicated with hydrocephalus [4,10,13].

L. monocytogenes, a foodborne pathogen, is relatively common. More than 70% of listeriosis cases occur in patients with recognized underlying diseases, such as liver disease, cancer, and diabetes [18]. In the current case, the patient had no gastrointestinal symptoms. However, it must be noted that she had breast cancer, for which she had received the last adjuvant chemotherapy 13 months before. Her history of breast cancer and age of 66 years had thus increased her risk of listeriosis [18]. Furthermore, there are several cases of listeriosis that are linked to traditional procedures such as acupuncture [19]. Mixed infections in adult bacterial meningitis were reviewed by Chang et al. [20]. The authors analyzed 12 cases of CSF polymicrobial culture results. They concluded that mixed-infection adult bacterial meningitis was mainly of a nosocomial nature and associated with underlying conditions such as VP shunt.

Two different pathogens were obtained in the CSF and blood from the initial evaluation in the presented patient. Given her past medical history, a coinfection with *S. paucimobilis* meningitis and *L. monocytogenes* bacteremia without gastrointestinal signs and symptoms suggested a possible procedure-related infection from the acupuncture and cupping after moxibustion.

Xu et al. [19] reviewed 308 cases of acupuncture, moxibustion, and cupping that were associated with adverse events. One of the most common adverse events in these cases was infection. Traditional procedures, including acupuncture, are often performed by

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Table 1. Case reports of *Sphingomonas paucimobilis* meningitis

Study	Age (yr) /sex	Country/year	Immunologic status and history	Radiological finding	CSF/Whole blood culture result	Treatment and duration	Outcome
Hajiroussou et al. [9]	39/M	United Kingdom/1979	Immunocompetent	Not mentioned in the report	*Sphingomonas paucimobilis*/ *S. paucimobilis*	Streptomycin, rifampicin, isoniazid for 4 days	Recovery to baseline
Tai and Velayuthan [10]	31/M	Malaysia/2014	Immunocompetent, open wound in the leg	In CT, meningeal enhancement, and cerebral edema	*S. paucimobilis*/not commented in the report	Ceftriaxone, acyclovir, anti-TB medication for 3 days	Death
Bolen et al. [11]	39/F	United States/2015	Immunocompromised	In MRI, diffuse periventricular T2 hyperintensities along the lateral ventricles and the third ventricle consistent with ventriculitis	*S. paucimobilis*/not commented in the report	Vancomycin, ceftriaxone, ampicillin for 21 days	Recovery to baseline
Deveci et al. [12]	14.5/M	Turkey/2017	Immunocompetent	In MRI, meningeal contrasting of the frontal region, T2 signal increase, findings of mucosal thickening, and leveling in paranasal sinuses	*S. paucimobilis*/ negative result	Vancomycin, ceftriaxone for 14 days	Recovery to baseline
Göker et al. [4]	48/F	Turkey/2017	Immunocompetent	Basal ganglia and intra-ventricular hemorrhage. No evidence of infection	*S. paucimobilis*/not commented in the report	Meropenem for 46 days	Death
Mehmood et al. [13]	50/F	United States/2018	Immunocompetent	Unremarkable neck CT and brain MRI	*S. paucimobilis*/not commented in the report	Meropenem for 21 days	Recovery to baseline
Ciftci et al. [14]	13/F	Turkey/2018	Immunocompetent, with VP shunt placed ten years ago	Not mentioned in the report	*S. paucimobilis*/not commented in the report	Vancomycin, meropenem, VP shunt removal, levofloxacin for 35 days	Recovery to baseline
Orozco-Hernández et al. [15]	3/M	Colombia/2019	Immunocompetent, exposure to contaminated water	Unremarkable brain CT	*S. paucimobilis*/ negative result	Ceftriaxone for 14 days	Recovery to baseline
Current case	66/F	South Korea/2021	Immunocompetent, final chemotherapy 1-year ago due to breast cancer	Unremarkable initial brain MRI, brain CT on HD 3 showed signs of hydrocephalus	*S. paucimobilis/Listeria monocytogenes*	Ceftriaxone and vancomycin switched to ampicillin/ sulbactam and ceftriaxone on HD 6 for 21 days	Bed-ridden with VP shunt, recovering without permanent neurological deficit

CSF, cerebrospinal fluid; M, male; F, female; CT, computed tomography; TB, tuberculosis; MRI, magnetic resonance imaging; VP, ventriculoperitoneal; HD, hospitalization day.

unlicensed people without medical training. There are many open classes and YouTube videos teaching and promoting traditional procedures to the public that do not discuss the concepts of infectious diseases or regulations issued by proper authorities. Public bath places equipped with cupping and moxibustion are ubiquitous. Furthermore, in reviewing this case and other case reports of procedure-related infection, licensed medical practitioners are also responsible for procedure-related infections. The risk of infectious diseases in these settings should be emphasized through proper supervision and education from qualified authorities.

For patients like this, close observation is recommended to initiate surgical treatment without delay. Constant neurological observation, prompt surgical responses, and a suitable antibiotic regimen are essential for treating *S. paucimobilis* meningitis complicated with hydrocephalus.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Methodology, Investigation, Visualization, Resources, Supervision: SWB; Data curation, Validation: SWB, JHL; Writing-original draft: SWB; Writing-review & editing: SWB, JHL.

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Case report

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Enteritis cystica profunda with lipoma in the second portion of the duodenum: a case report

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Enteritis cystica profunda (ECP), a rare and benign condition, is defined as the displacement of the glandular epithelium into the submucosa and more profound layers of the small intestinal wall leading to the formation of mucin-filled cystic spaces. ECP frequently occurs in the ileum or jejunum and is associated with diseases such as Crohn disease and Peutz-Jeghers syndrome. ECP also develops in the absence of known pathology. ECP in the duodenum is very rare and mostly occurs without associated conditions. In this report, we present a rare case of ECP without an associated disease, in the second portion of the duodenum distal to the ampulla of Vater and coexisting with lipoma within the polypoid lesion.

Keywords: Duodenum; Enteritis cystica profunda; Lipoma

Introduction

Enteritis cystica profunda (ECP), a rare and nonneoplastic condition, is defined as the displacement of the glandular epithelium into the submucosa or more profound layers of the small intestinal wall and characterized by mucin-filled cystic spaces [1]. ECP occurs mainly in the ileum or jejunum and is related to diseases such as Crohn disease and Peutz-Jeghers syndrome [2-14]. ECP also develops without associated conditions [15-20]. ECP in the duodenum is rare and mostly occurs without an associated pathological condition, unlike ECP in the ileum or jejunum [15-18]. So far, there have been only six reports on ECP in Korea [2,3,15-18]. One report described a case of ECP coexisting with lipoma in the duodenal bulb [18]. In the foreign literature, ECP cases are also rare, and only one case of ECP coexisting with lipoma in the ileum has been reported [4-12,19]. The authors detected an approximately 3.5 × 1.5 × 1.0 cm elongated polyp in the second portion of the duodenum distal to the ampulla of Vater (AOV), through esophagogastroduodenoscopy, in a patient without an underlying disease. The polyp was removed using endoscopic snare polypectomy. Histopathological examination confirmed the polyp as an ECP with lipoma. Therefore, the authors report this along with the literature review because this is a rare case in which ECP coexists with lipoma, without an associated condition, in the second portion of the duodenum, which is different from the previously reported case [18] with lipoma in the duodenal bulb.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Maryknoll Hospital (IRB No: 2021-308), and the requirement for informed consent from the patients was waived by the IRB.

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A 78-year-old female without any underlying disease or symptoms underwent esophagogastroduodenoscopy during a health examination. Esophagogastroduodenoscopy revealed an elongated polypoid lesion (3.5 × 1.5 × 1.0 cm) with erosions (Fig. 1). The polyp was in the second portion of the duodenum, distal to the AOV. On gross examination, the lower part of the polyp was presumed to be a lipoma, and the upper part to be Brunner gland hyperplasia. Biopsy using cold forceps demonstrated chronic duodenitis with gastric metaplasia. Therefore, she was hospitalized for further examination and polypectomy. There was no history of Crohn disease or Peutz-Jeghers syndrome. Vital signs were as follows: blood pressure, 100/70 mmHg; pulse rate, 72 beats/min; respiration rate, 18 breaths/min; and body temperature, 36.7°C. She had normal consciousness and a healthy appearance. Physical examination revealed normal conjunctivae, anicteric sclerae, and no other abnormal findings were observed. Heart sounds, bowel sounds, and chest auscultation were normal. There was no tenderness or palpable mass on the neck, abdomen, or other lymph nodes. There were no noted findings on limb or neurological examination. In the peripheral blood test, the white blood cell count was 5,800/mm^3, hemoglobin was 14.2 g/dL, and platelet count was 279,000/mm^3. The results of blood chemistry were as follows: aspartate aminotransferase/alanine aminotransferase, 42/31 IU/L; alkaline phosphatase, 83 IU/L; total protein, 7.6 g/dL; albumin, 4.8 g/dL; total bilirubin, 0.55 mg/dL; amylase, 63 U/L; lipase, 26 U/L; blood urea nitrogen, 20.5 mg/dL; and creatinine, 0.7 mg/dL. The electrolyte values were as follows: sodium, 141 mM/dL; potassium, 4.4 mM/dL; and chloride, 103 mM/dL. The results of the immunoassay test were negative for hepatitis B surface antigen, negative for hepatitis B surface antibody, negative for hepatitis C virus antibody, and serum tumor markers were: alpha-fetoprotein, 3.69 ng/mL; carcinoembryonic antigen, 1.70 ng/mL; and carbohydrate antigen 19-9, 13.98 U/mL. An axial computed tomography image showed focal fat within the duodenum, indicating a lipoma (Fig. 2). Endoscopic snare polypectomy was performed (Figs. 3, 4). Histology confirmed the diagnosis of ECP with a lipoma. Cystically dilated mucosal glands were seen in the submucosa, in which mature adipocytes deposit to produce like mass (Fig. 5). The main component of the polyp was lipoma; therefore, it was presumed that ECP occurred within the lipoma.

Discussion

Cystica profunda (CP) is a rare condition, defined as the displacement of the glandular epithelium into the submucosa or more profound layers of the gastrointestinal wall, characterized by the formation of benign mucin cysts [1]. When the condition occurs in the colon, it may be termed colitis CP, in the stomach, gastritis CP, and in the small intestine, ECP [1]. The most common type is colitis CP, followed by ECP and gastritis CP [1,4]. ECP develops most frequently in the ileum or jejunum with associated diseases [2-14,19]. However, ECP in the duodenum is the least common and is mostly without causative conditions [15-18]. In Korea, six cases of ECP have been reported [2,3,15-18]. Four cases [15-18] occurred in the duodenum without any associated condition, and the others [2,3] in the ileum or jejunum with Peutz-Jeghers syndrome. One of the four cases demonstrated ECP with lipomas in the duodenal bulb [18]. In the literature of other

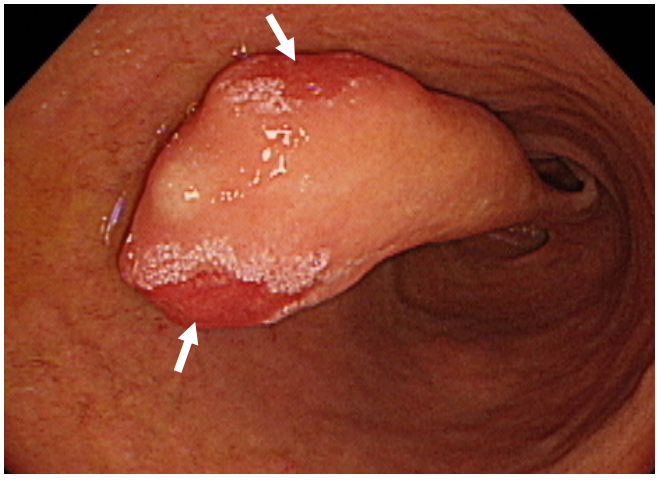

Fig. 1. Esophagogastroduodenoscopy findings. The elongated polyp is in the second portion of the duodenum distal to the ampulla of Vater and covered with normal surrounding mucosa. There are erosions (arrows) on the head of the polyp.

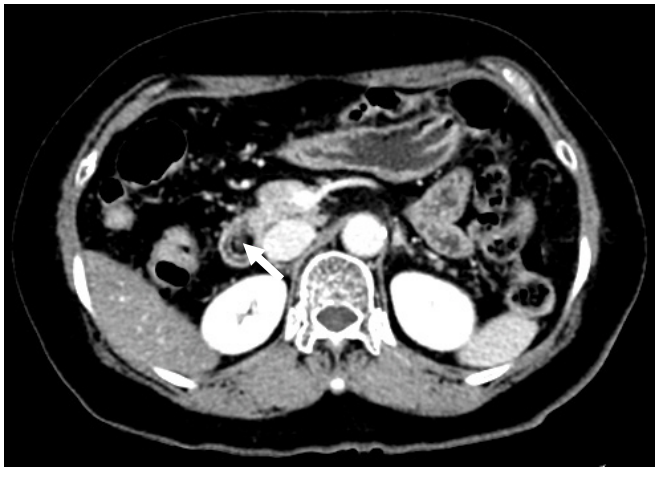

Fig. 2. Abdominal computed tomography (CT) findings. Axial CT image shows a focal fat-density mass (arrow) in the second portion of the duodenum, which indicates lipoma.

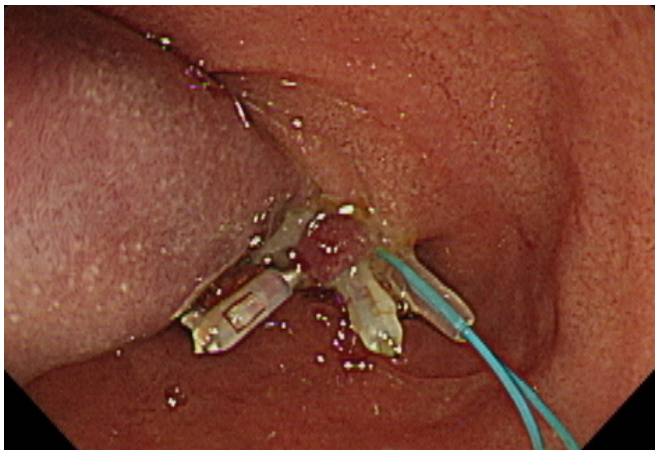

Fig. 3. Endoscopic polypectomy. The polyp is captured by a hemoclip and detachable snare and then resected by the snare.

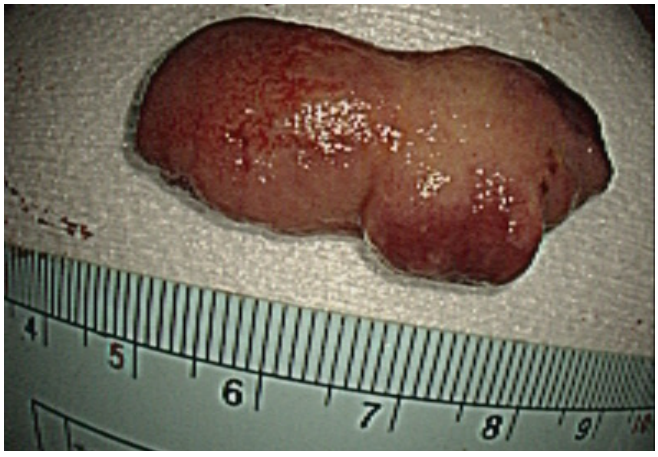

Fig. 4. Gross findings. The polyp measures about 3.5×1.5×1.0 cm.

countries, only one case demonstrating ECP with lipoma in a polypoid lesion that was found on the leading edge of ileocolic intussusception has been reported [19]. It is rare to find ECP in the duodenum without an associated condition and coexisting with lipoma. In the literature of Korea and other countries, this is the third case of lipoma, but in the second portion of the duodenum distal to the AOV, unlike the others in the duodenal bulb or ileum [18,19].

The etiology of CP remains unclear. However, because CP mostly coexists with a specific condition, the condition is presumed to be the etiology [1]. Some common etiologies of CP include inflammatory bowel disease, Peutz-Jeghers syndrome, prolapse, severe infection, ischemia, and trauma [1]. CP is also found in therapeutically irradiated tissues along with surgical anastomosis site and rarely occurs without an etiology [1]. ECP generally develops with Crohn disease and Peutz-Jeghers syndrome, rarely with

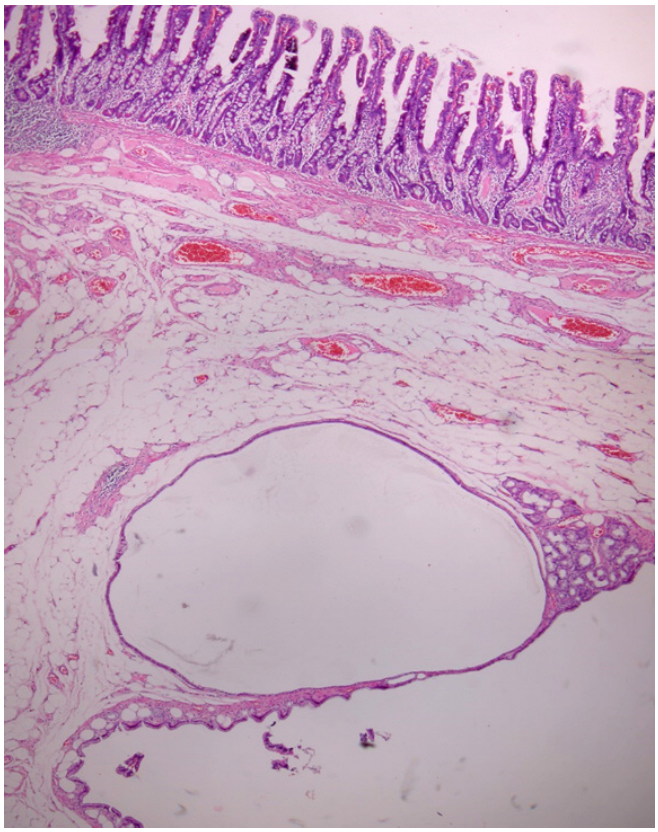

Fig. 5. Histological findings. The coexistence of cystically dilated mucosal glands and mature adipocytes is present in the submucosa (hematoxylin and eosin stain, ×40).

conditions such as hamartoma, trauma, and primary eosinophilic enteritis, and sometimes without any underlying condition [2-20]. These pathological conditions result in a persistent chronic injury, that, through ulceration and repair, leads to entrapment of glands deep in the intestinal wall [1]. The mechanisms of misplacement may include herniation, implantation after ulceration, mucosal microdiverticula, and reepithelialization of fistulae, and entrapped glands in the intestinal wall can reach the subserosa [1]. Glands entrapped in the intestinal wall commonly undergo dilatation and mucin-filled cystic changes and often have a loss of epithelium due to pressure atrophy [1]. Acellular mucin pools are then left behind and may show calcium deposition or even ossification [1]. This case did not have any associated diseases or lipomas. Based on the etiology, mechanism, and histological results, it is presumed that the lipoma had occurred and underwent persistent chronic injury, leading to the development of ECP.

The cytologic features of the glands in CP are usually bland, and the benign characteristics of CP include the presence of hemosiderin, foreign body giant cells, lack of cytologic atypia, lack of desmoplasia, presence of lamina propria, rounded contours of the epithelial border, and a rim of a single layer of cells along the edge of

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the mucin pool [1]. In this case, cystically dilated mucosal glands were seen in the submucosa, with deposits of mature adipocytes to produce a mass. The epithelium of the ECP is composed of a mucinous columnar epithelium. In addition, atypical epithelial cells or malignant cells are not seen in ECP. It is not difficult to histologically distinguish ECP from malignancy. To date, it is a predominant view that CP is not a precancerous lesion [1].

CP is detected in the form of a polypoid lesion, through esophagogastroduodenoscopy, gastrointestinal series, endoscopic ultrasound, computed tomography, or magnetic resonance imaging, and can be diagnosed in an excised specimen by surgical operation or endoscopic polypectomy [15]. In this case, an elongated polypoid lesion that was covered with normal surrounding mucosa and erosions on the head was observed endoscopically in the second portion of the duodenum distal to the AOV. When pressed by biopsy forceps, it sank smoothly, showing a positive pillow sign. Therefore, it was presumed to be a lipoma with Brunner gland hyperplasia. After endoscopic snare polypectomy, ECP with lipomas was confirmed by histology.

Patients may be asymptomatic or may present with signs or symptoms of the associated condition or ECP, such as abdominal pain, dyspepsia, diarrhea, bleeding, obstruction, and intussusception [9]. ECP itself does not require specific treatment; however, surgical resection or endoscopic polypectomy can sometimes be performed to resolve the symptoms or to exclude malignant tumors [15]. In this case, the patient had no symptoms or signs. To rule out malignancy, the lesion was removed using endoscopic polypectomy.

The authors report a rare case of ECP in a healthy patient without any particular underlying disease who had a polypoid lesion in the second portion of the duodenum, distal to the AOV, which was suspected to be simple lipoma at first but was histopathologically diagnosed as ECP within lipoma through endoscopic snare polypectomy.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: all authors; Data curation, Investigation: BJS; Formal analysis, Supervision: TYP; Validation: SKP, HUP; Resources: HUP; Writing-original draft: BJS; Writing-review & editing: BJS, TYP.

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Case report

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Stent graft treatment of an ilioenteric fistula secondary to radiotherapy: a case report

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Fistulas between the arteries and the gastrointestinal tract are rare but can be fatal. We present a case of an ilioenteric fistula between the left external iliac artery and sigmoid colon caused by radiotherapy for cervical cancer, which was treated with endovascular management using a stent graft. A 38-year-old woman underwent concurrent chemoradiotherapy for cervical cancer recurrence. Approximately 9 months later, the patient suddenly developed hematochezia. On her first visit to the emergency room of our hospital, computed tomography (CT) images did not reveal extravasation of contrast media. However, 8 hours later, she revisited the emergency room because of massive hematochezia with a blood pressure of 40/20 mmHg and a heart rate of 150 beats per minute. At that time, CT images showed the presence of contrast media in almost the entire colon. The patient was referred to the angiography room at our hospital for emergency angiography. Inferior mesenteric arteriography did not reveal any source of bleeding. Pelvic arteriography showed contrast media extravasation from the left external iliac artery to the sigmoid colon; this was diagnosed as an ilioenteric fistula and treated with a stent graft. When the bleeding focus is not detected on visceral angiography despite massive arterial bleeding, pelvic arteriography is recommended, especially in patients with a history of pelvic surgery or radiotherapy.

Keywords: Angiography; Fistula; Iliac artery; Radiotherapy; Stents

Introduction

Arterioenteric fistulas are uncommon but life-threatening emergencies that require immediate intervention. They connect large arteries and the gastrointestinal tract and can be categorized into primary and secondary forms. Primary arterioenteric fistulas are extremely rare with an incidence of approximately 0.07% in the general population, as revealed by a large autopsy series [1]. Surgery is the standard treatment for arterioenteric fistulas. However, in emergencies, endovascular treatments such as stent graft exclusion can be applied. In the current report, we present the case of a patient with a primary arterioenteric fistula between the left external iliac artery and sigmoid colon caused by radiotherapy, which was managed successfully with endovascular treatment using a stent graft.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Pusan National University Yangsan Hospital (IRB No: 05-2021-071) in accordance with the Declaration of Helsinki, and the requirement for informed consent from the patient was waived by the IRB.

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A 38-year-old female patient was admitted to our hospital with sudden hematochezia. She had a history of radical trachelectomy with bilateral pelvic lymph node dissection for stage IB1 cervical cancer and concurrent chemoradiotherapy for recurrence 9 months prior. She was in a stable condition with a heart rate of 72 beats per minute (bpm) and blood pressure of 100/60 mmHg when she visited the emergency room (ER) of our hospital for the first time. Her hemoglobin level was 9.2 g/dL; hematocrit, 25.9%; platelet count, 139,000/μL, and prothrombin time-international normalized ratio (PT-INR), 0.97. Physical examination findings were nonspecific. Sigmoidoscopy revealed no active bleeding. Computed tomography (CT) (Fig. 1A) revealed a thickened wall of the distal ileum and rectosigmoid colon, suggesting radiation-related inflammation. In addition, she no longer complained of hematochezia. Therefore, the patient was discharged.

Eight hours later, she revisited the ER because of massive hematochezia. Her hemoglobin level was 9.5 g/dL; hematocrit, 27.2%; platelet count, 101,000/μL; and PT-INR, 1.22. Her blood pressure was 70/40 mmHg, and her vitals stabilized after loading with normal saline. However, she complained of sudden massive hematochezia, and her vitals became unstable, with a blood pressure of 40/20 mmHg and a heart rate of 150 bpm. The patient remained in hypovolemic shock despite massive transfusion. CT was reperformed, which revealed the presence of contrast media in almost the entire colon in the delayed phase (Fig. 1B).

She was referred to the angiography room of the hospital for emergency angiography. Inferior mesenteric arteriography (Fig. 2A) revealed extremely narrow caliber vessels without definite extravasation. Therefore, pelvic arteriography was performed. An arteriogram (Fig. 2B) showed contrast extravasation from the left external iliac artery into the sigmoid colon. This was considered an ilioenteric fistula. A 9 mm × 5 cm Viabahn stent graft (WL Gore and Associates, Flagstaff, AZ, USA) was inserted into the left external iliac artery, followed by ballooning with a 6 mm × 4 cm balloon (Mustang, Boston Scientific, Natick, MA, USA). However, extravasation was still visible, and the patient remained in an unstable condition. Therefore, we inserted another Viabahn stent graft (9 mm in diameter and 10 cm in length) (Fig. 2C). Continuous extravasation was observed despite further ballooning (Fig. 2D). We assumed that the stent graft could not fully expand, and extravasation continued because she was in a hypovolemic state. It was thought that when the patient's vital signs recovered, the stent graft would attach to the vessel wall. Therefore, despite continuous extravasation, we decided to stop the procedure because her vital signs were stable.

She remained in the intensive care unit for 4 days after the procedure. Her vital signs were stable, and her hemoglobin level stabilized to 16.1 g/dL. Antibiotics and anticoagulants were also administered. She was discharged approximately 1 month later, without any additional bleeding episodes. A month later, she visited the hospital because of swelling of her left leg. Lower extremity CT venography (Fig. 3) showed a patent lumen of the stent graft with no extravasation of contrast media. At that time, we considered the swelling to be lymphedema.

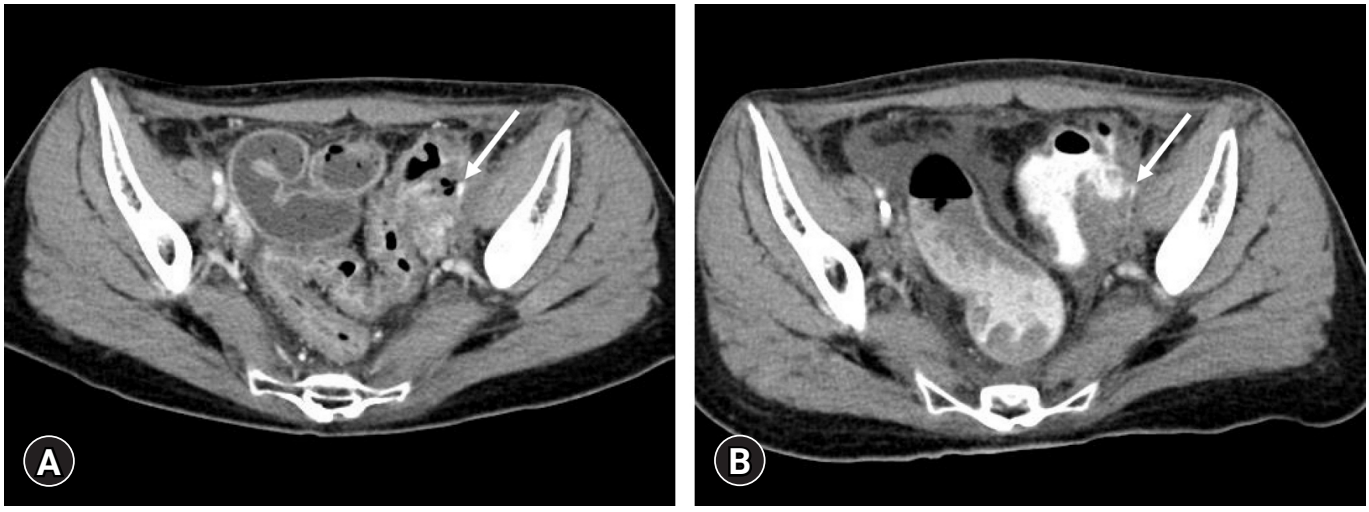

Fig. 1. (A) Computed tomography (CT) image demonstrates thickened wall of the distal ileum and rectosigmoid colon, suggesting radiation-related inflammation, on the first visit. The narrowed left external iliac artery (arrow) contacts air bubbles in the bowel lumen. (B) CT image show the presence of contrast media in almost the entire colon in the delayed phase on the second visit. The left external iliac artery (arrow) is extremely narrow. Considering (A), rupture of the left external iliac artery is retrospectively suspected.

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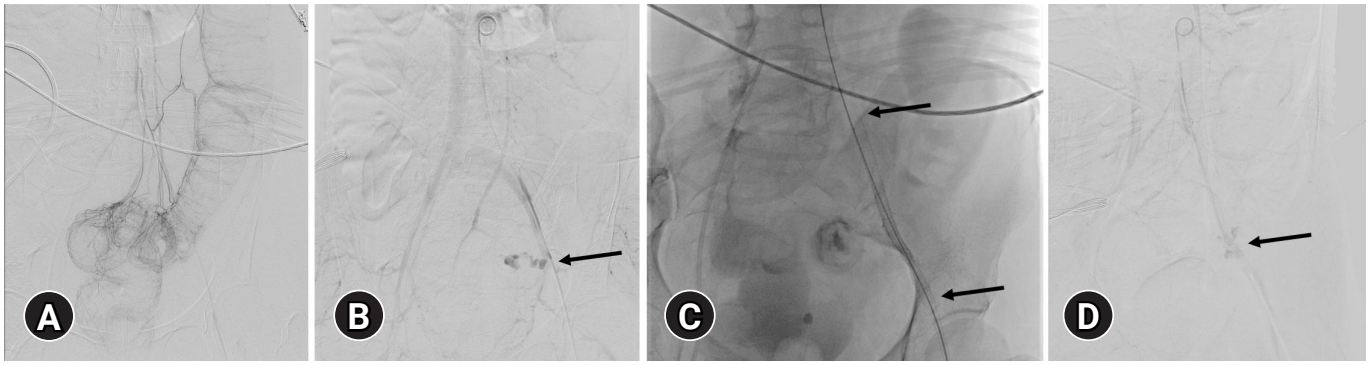

Fig. 2. (A) Inferior mesenteric arteriography shows significantly narrow vessels without definite contrast media extravasation. (B) The pelvic arteriography shows extravasation (arrow) from the left external iliac artery into the sigmoid colon. (C) A Viabahn stent graft (5 cm in length; WL Gore and Associates, Flagstaff, AZ, USA) is placed in the left external iliac artery to stop the extravasation, but continuous extravasation is observed despite repeated ballooning. Therefore, another Viabahn stent graft (10 cm in length) is inserted sequentially (arrows at the end of the stent graft). (D) After stent graft placement, ballooning is repeated to put the stent graft and vessel wall together. However, slight extravasation (arrow) is seen on the final angiography. We stopped the procedure because the patient's condition was stable at that time.

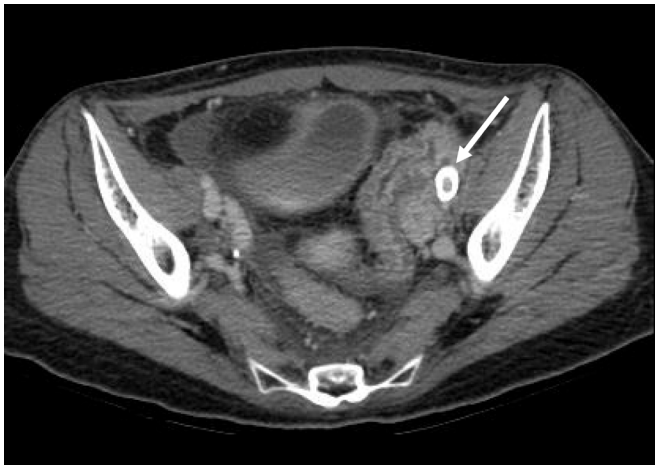

Fig. 3. Approximately 1 month later, lower extremity computed tomography venography shows a patent stent graft (arrow) in the left external iliac artery. Contrast media extravasation is not visible.

Discussion

A fistula between the major arteries and the gastrointestinal tract is not common but is often life-threatening. Primary arterioenteric fistulas most frequently result from aneurysmal disease but may also be associated with peptic ulcer disease, malignancy, radiation therapy, trauma, diverticulitis, appendicitis, and pancreatic pseudocysts. Secondary fistulas develop after vascular surgery for abdominal aortic aneurysm or aortoiliac occlusive disease and are observed 10 times more often than primary fistulas [2]. Therefore, primary arterioenteric fistulas are extremely rare, with an incidence of 0.07% in the general population [3]. Primary fistulas most commonly occur between the aorta and the esophagus or duodenum and rarely between the iliac artery and the intestine.

Bleeding from a fistula may be minor or intermittent, and there is a symptom-free period before it opens. When a fistula opens, rapid and massive bleeding can be seen [4]. To demonstrate the origin of bleeding from an arterioenteric fistula, CT should be performed while massive bleeding occurs, at which time extravasation of contrast media into the bowel lumen is visible. Therefore, the diagnosis is challenging. According to the literature, CT has varying sensitivity (40%–90%) and specificity (33%–100%) for the diagnosis of arterioenteric fistulas [5].

The standard treatment for an arterioenteric fistula is surgery, including removal of all infected tissue, repair of the bowel defect, and revascularization of the vessel to the lower extremity. It is associated with high morbidity and mortality rates [6,7]. Consequently, less invasive endovascular treatments, such as stent graft exclusion, have been introduced. Antoniou et al. [8] reviewed 33 articles on arterioenteric fistulas published between 1990 and 2008 and found that 41 patients were treated with stent grafts. Complications occurred in 21 patients, of whom 18 developed infections. The authors concluded that stent graft exclusion should not be performed as a final treatment; however, it can be applied as a bridge option to surgical treatment, especially in patients with signs of infection or in emergencies.

Massive gastrointestinal bleeding necessitates emergency angiography, usually celiac, superior mesenteric, and inferior mesenteric arteriographies. However, nonvisceral arteries can be a bleeding focus in postoperative or cancer patients, as in our patient. Therefore, aortography and pelvic arteriography should be performed in such cases [9].

In conclusion, angiography of the aortoiliac arteries is needed when identifiable bleeding sources are not detected on visceral angiography in cases of massive arterial bleeding, especially in postoperative or cancer patients. In addition, endovascular management using a stent graft for arterioenteric fistulas can be a good treatment option for emergencies.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: JYJ, JHK; Formal analysis: UBJ, JYH; Funding acquisition: JYJ; Resources: JYJ, TUK, HSR; Supervision: UBJ; Writing - original draft: JYJ; Writing - review & editing: all authors.

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- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software

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