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Aims and scope

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Function of hepatocyte growth factor in gastric cancer proliferation and invasion

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Cancer incidence has been increasing steadily and is the leading cause of mortality worldwide. Gastric cancer is still most common malignancy in Korea. Cancer initiation and progression are multistep processes involving various growth factors and their ligands. Among these growth factors, we have studied hepatocyte growth factor (HGF), which is associated with cell proliferation and invasion, leading to cancer and metastasis, especially in gastric cancer. We explored the intercellular communication between HGF and other surface membrane receptors in gastric cancer cell lines. Using complimentary deoxyribonucleic acid microarray technology, we found new genes associated with HGF in the stomach cancer cell lines, NUGC-3 and MKN-28, and identified their function within the HGF pathway. The HGF/N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene (c-MET) axis interacts with several molecules including E-cadherin, urokinase plasminogen activator, KiSS-1, Jun B, and lipocalin-2. This pathway may affect cell invasion and metastasis or cell apoptosis and is therefore associated with tumorigenesis and metastasis in gastric cancer.

Keywords: Cell proliferation; Hepatocyte growth factor; Neoplasm metastasis; Stomach neoplasm

Introduction

Cancer initiation and progression involve a multistep process. Cancer initiation requires germline mutation, amplified oncogene, mutated suppressor genes, or hormone action, while cancer progression and metastasis require various growth factors, including epidermal growth factor (EGF), hepatocyte growth factor (HGF), and vascular endothelial growth factors (VEGFs), as well as proteases and adhesion molecules (Table 1) [1-6]. Cell surface receptors can bind growth factors and other ligands, which activate the receptors and transduce the signals by activating a tyrosine kinase inhibitor, thereby regulating cell functions such as cell survival, cell proliferation, protein synthesis, and angiogenesis [7].

HGF, an effector on cells expressing the N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene (c-MET) tyrosine kinase receptor, is produced by mesenchymal cells and acts on cells of epithelial origin in paracrine or autonomic fashion [8]. Studies have shown that overexpression or over-activation of HGF can lead to misplaced or inappropriately timed angiogenic and mitogenic signals. c-MET is a cell surface membrane receptor composed of a 50 kDa α-chain and a 145 kDa β-chain [9]. MET activity is observed during embryogenesis and organogenesis in normal cells and is also activated in degenerative diseases such lung and renal fibrosis and liver cirrhosis [10]. Although the HGF/c-MET axis plays a principal role in normal cell development, aberrant activation of this axis is thought to be involved in cell invasion and metastasis in most types of human cancers [11]. We have studied the HGF/c-MET pathway and the associated tumor invasion and proliferation in gastric cancer for several years and here, we review our experiment results.

Table 1. Gowth factors in cancer progression

Growth factor	Property	Receptor	Study
Vascular endothelial growth factor	Endothelial mitogen, survival factor, and permeability inducer produced by many types of tumor cells	Flk-1/KDR (VEGFR-2), Flt-1 (VEGFR-1) (both present on activated endothelium)	Veikkola and Alitalo [1]
Transforming growth factor-α (TGF-α)	Endothelial mitogen and angiogenesis inducer; inducer of vascular endothelial growth factor expression	Epidermal growth factor-R	Schmitt and Soares [2]
Fibroblast growth factor	Endothelial mitogen, angiogenesis inducer, and survival factor; inducer of Flk-1 expression	FGF-RI-4	Botta et al. [3]
Epidermal growth factor (EGF)	Weak endothelial mitogen; inducer of vascular endothelial growth factor expression	Epidermal growth factor-R	Mooradian and Diglio [4]
Hepatocyte growth factor/scatter factor (HGF/SF)	Endothelial mitogen, motogen, and angiogenesis inducer	c-MET	Lamszus et al. [5]
Interleukin-8	*In vivo*-acting, possibly indirect angiogenesis inducer	Interleukin-8R presence on endothelial cells remains uncertain	Desbaillets et al. [6]

VEGFR, vascular endothelial growth factor receptor; c-MET, N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene.

Interaction of HGF and other molecular proteins in gastric cancer

1. E-cadherin and β-catenin

MET has been demonstrated to interact with other cell surface receptors, including integrins, human epidermal growth factor receptor, and FAS receptor, to enhance downstream signaling and tumorigenesis. We previously reported that the expression of E-cadherin (ECD) and urokinase plasminogen activator (uPA) is associated with the development of pancreatic cancer [12]. ECD is a transmembrane glycoprotein that is responsible for calcium-dependent intercellular adhesion by homotypic interaction and is one of the principal elements of the cytoskeleton. Decrease or loss of ECD is frequently associated with cell-to-cell disengagement, tumor invasion, and metastasis [13,14]. ECD functions to dephosphorylate β-catenin, thus inhibiting the binding of intracellular ECD to catenin proteins. It has been suggested that HGF reduces cell-to-cell adhesion by dephosphorylation of the ECD/catenin complex and ECD shedding [15]. We hypothesized that HGF/c-MET may interact with ECD to promote tumorigenesis through the activation of matrix metalloproteinase-7 (MMP-7), which degrades many cellular matrix proteins and adhesion molecules (Fig. 1). To confirm this hypothesis, we investigated the association between HGF/c-MET, ECD, and MMP-7 in two stomach cancer cell lines, NUGC-3 and MKN-28. Western blot and reverse transcription PCR analyses showed that treatment of these cells with HGF reduced the expression of ECD. These results suggested that HGF may stimulate the extracellular cleavage of ECD, thereby increasing the shedding of the soluble fragment and decreasing the 120-kDa full-length ECD in the total cell lysates [16]. MMP-7, which is known to be expressed predominantly by tumor cells in various cancers, was increased by HGF treatment and knockdown of MMP-7 expression in the stomach cancer cell lines resulted in no extracellular cleavage of ECD as well as decreased *in vitro* cell invasion. These results suggest that HGF may interact with ECD, leading to the activation of the MMP-7 pathway and increased cell invasion.

2. Urokinase plasminogen activator

uPA is a member of the family of serine proteases and is known to participate in cell migration and tissue remodeling. uPA overexpression has been reported in lung, colon, and breast cancers [17-19]. Many studies have shown that blocking the expression of uPA or inhibiting its binding to the uPA receptor (uPAR) suppresses tumor cell invasion and metastasis in various cancer cell lines [20,21]. We measured uPAR expression in 26 patients with stomach cancer before and after surgery and found that uPAR expression was significantly decreased after surgery ($p < 0.05$). We also found that the survival rate of patients with gastric tumors expressing uPAR was significantly lower than that of patients with tumors not expressing uPAR ($p = 0.035$) [22]. We hypothesized that uPA is also associated with tumor progression in gastric cancer and we explored the relationship between HGF and uPA in gastric cancer tumorigenesis. We found that HGF induced reactive oxygen species generation, which regulates uPA production and tumor invasion via mitogen-activated protein (MAP) kinase [23]. Previous studies have also examined the connection between HGF and uPA. One study showed that histone deacetylase (HDAC) regulates HGF-induced expression of both uPA and MMP-9 through a protein kinase C (PKC) dependent pathway in

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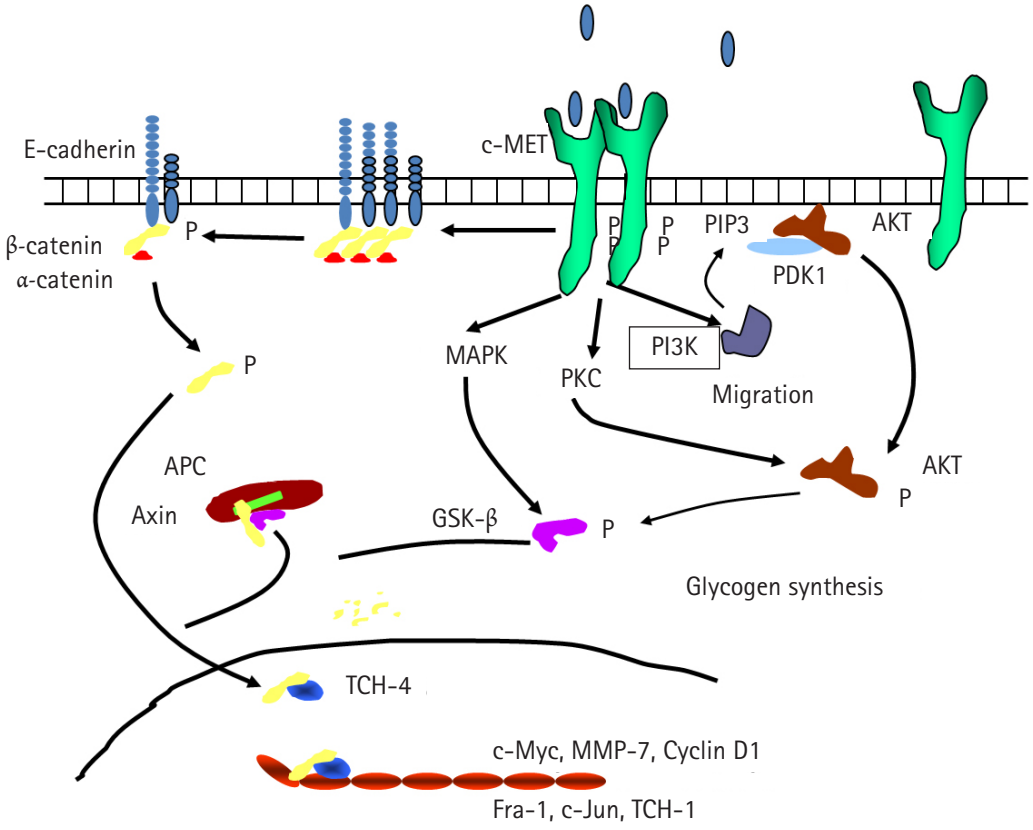

Fig. 1. Schematic diagram of the relationship between hepatocyte growth factor and E-cadherin. APC, adenomatous synthase kinase-binding protein; AKT, protein kinase B; c-MET, N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene tyrosin kinase receptor; GSK-β, glycogen synthase kinase β; MAPK, mitogen-activated protein kinase; MMP-7, matrix metalloproteinase-7; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphinositol-3 kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; TCF-1, transcription factor 1; TCF-4, transcription factor 4.

gastric cancer [24]. Another study showed that survivin, a member of the inhibitor of apoptosis family, increases HGF-induced uPA expression and seems to play a role in gastric cancer tumorigenesis [25].

3. New HGF regulatory genes

To find new HGF regulatory genes and identify their role in HGF-induced stomach cancer cell survival, we screened for genes induced by HGF using complimentary deoxyribonucleic acid (cDNA) microarray technology in the stomach cancer cell lines, NUGC-3 and MKN-28 (Fig. 2). We selected the genes that were up or downregulated by more than three-fold in NUGC-3 and MKN-28 cells during HGF treatment (Table 2) and determined their function in conjunction with HGF.

Bcl-2 associated agonist of cell death (BAD), a BH3-only proapoptotic Bcl-2 family protein, has been found to be upregulated in response to HGF treatment. BAD functions by inactivating anti-apoptotic Bcl-2 proteins [26]. cDNA microarray analysis results have confirmed that BAD is upregulated at the RNA and protein levels following HGF treatment. Our data showed that HGF induced BAD overexpression and enhanced BAD phosphorylation, thereby inhibiting apoptosis and promoting cancer cell survival [27].

KiSS-1 was also upregulated in response to HGF treatment. KiSS-1 is a putative metastasis suppressor gene and its expression is increased in several human malignancies including melanoma [28] and breast cancer [29]. One study also reported that overexpression of KiSS-1 in breast cancer cells results in a more aggressive phenotype [30]. Consistent with these results, we found that HGF induced the overexpression of KiSS-1 in a p38-dependent manner. In addition, KiSS-1 suppressed MMP-9 expression and decreased cell invasion *in vitro*, suggesting it may act as a metastasis suppressor gene in gastric cancer [31].

Jun B was also upregulated in response to HGF treatment. Jun B belongs to the June gene family (c-Jun, JunB, and JunD), whose members encode the activator protein-1 (AP-1) family of tran-

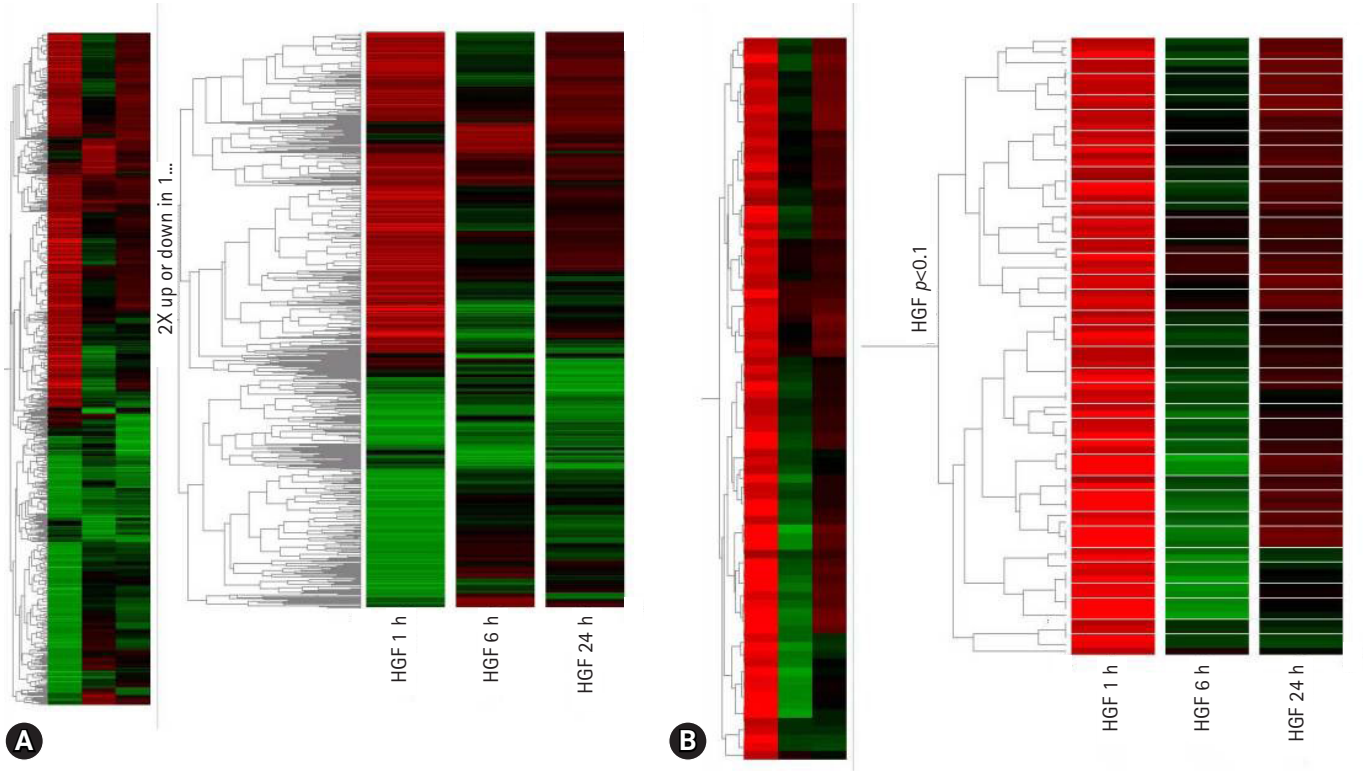

Fig. 2. (A) Genetree showing genes up or downregulated by at least 2-fold after 1 hour, 6 hours, and 24 hours of hepatocyte growth factor (HGF) treatment. (B) Genetree of t-test.

Table 2. Genes induced by hepatocyte growth factor using complimentary deoxyribonucleic acid microarray

Gene otology	Name	Fold
Transcript variant 1	Homo sapiens Bcl-2 agonist of cell death (BAD)	3.71
Transcript variant 2	Homo sapiens histone diacetylate 5 (HDAC5)	3.26
Metastasis suppressor	KiSS-1	9.3
Single strand break repair	Homo sapiens X-ray repair complementing defective repair in Chinese hamster cell 1 (XRCC1)	3.1
Inflammatory response apoptosis	Homo sapiens interleukin 1, beta (IL-1β)	3.25
Oncoprotein	Stathmin-like 3	7.27
Invasiveness	Rho GDP dissociation 2 inhibitor (Rho GDI2)	3.11

scription factors. AP-1 is a dimeric transcription factor that is enhanced by the MAP kinase pathway in the presence of growth factors, hormones, or other environmental stresses [32,33]. Of the AP-1 components, c-Jun and c-Fos were first identified as viral oncoproteins; thus, their function in tumorigenesis has been established. However, it is also known that some Jun and Fos proteins can suppress tumor formation [34]. Accordingly, we examined the role of Jun B in gastric cancer. In our study, Jun B levels were decreased by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and cell proliferation and invasion were decreased in Jun B knockdown stomach cancer cell lines. Further, Jun B knockdown cells blocked the MMP-9 upregulation induced by HGF. MMP-9 is a matrix metalloproteinase protein that degrades the basement membrane, exposing cryptic sites within the matrix and resulting in cancer cell invasion [35,36]. These data suggest that Jun B expression induced by HGF can activate MMP-9 by the NF-κB pathway and thereby contribute to invasion and cell proliferation in gastric cancer [37].

We recently studied that lipocalin-2 (LCN2) is upregulated by HGF treatment. LCN2 is a member of the lipocalin family, which binds and transports small lipophilic molecules including leukotrienes, retinoic acids, and prostaglandins, and it was first identified as a modulator of the immune system [38]. In addition, LCN2 binds MMP-9, forming a complex comprising LCN2 and MMP-9, promoting MMP-9 activation, and preventing its degradation [35,36]. HGF treatment upregulated the expression of LCN2 in gastric cancer cells, leading to increased activation of MMP-9. Knockdown of LCN2 in these cells decreased MMP-9 activation in response to HGF treatment and treatment of the cells with an NF-κB inhibitor prevented the HGF-mediated upregulation in

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LCN2 expression. Further, HGF-mediated cell proliferation and invasion was decreased in LCN2 knockdown cells compared to control cells [39]. These data suggest that HGF induces the upregulation of LCN2 expression, which activates MMP-9, and HGF may play a role in proliferation and invasion of gastric cancer.

Conclusion

Abberant activation of MET signaling occurs in a subset of advanced cancers, including gastric cancer. The HGF/c-MET axis interacts with several molecules including ECD, uPA, KiSS-9, Jun B, and LCN2. This pathway may affect cell invasion and metastasis or cell apoptosis and is therefore associated with tumorigenesis and metastasis in gastric cancer, which maybe one of the important therapeutic targets. To validate our findings, further experiments are warranted using *in vivo* knockout mouse models.

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Conflicts of interest

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

Author contributions

Conceptualization: SAK, KHL; Data curation: KHL; Formal analysis: SAK; Project administration: KHL; Validation: SAK; Writing–original draft: SAK; Writing–review & editing: SAK, KHL.

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Creativity in medical education: concepts related to creative capacity

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In the 21st-century postmodernism era, which represents diversity and relativity, one of the most essential elements in the field of education is to strengthen individual human values. Accordingly, we must focus on developing capacity in order to adapt to change. It is clear that the medical field maximizes the need for new judgments to solve life-related problems constantly, and this problem-solving capacity is an essential skill for a physician. Problem-solving capacity can be achieved simultaneously with creativity to apply them in an appropriate manner based on standardized expertise and well-trained skills. Creativity is also a key element that medical education is currently pursuing. Many studies on creativity have resulted in confusion and misunderstandings on the concept of creativity due to similar terms and varied definitions, such as creation, innovation, etc. In this study, we attempt to identify the importance of creativity in medical education by comparing and organizing concepts related to creative capacity.

Keywords: Creative thinking; Creativity; Medical education; Problem-solving

Introduction

Medical education is a field where the coldest reason meets the hottest emotion, reality and context are more intertwined than in any other discipline, and it requires constant attention to those who suffer sober judgment and patient care [1]. These efforts have steadily evolved since the inception of medical education in the University of Bologna (Università di Bologna, 1088) and the University of Salerno (Università degli Studi di Salerno, 1231).

Modern medical education has undergone many innovative changes since the commencement of systematic medical education in 1910 under the "Flexner Report." Professor Harden of Dundee University presented the "SPICES" model, outlining innovative educational strategies against traditional methods (Table 1) [2]. He believes that innovative education should change from "teacher-centered" to "student-centered," and learning requires a shift from "information-gathering" to "problem-based," and also from "hospital-based" to "community-based." The model also states that the curriculum should change from "discipline-based" to "integrated/inter-professional," from "uniform standard program" to "elective with a core program" and a pre-planned "systematic approach" is required rather than an "opportunistic approach" during apprenticeship.

The field of medical education in Korea has also grown quantitatively and qualitatively, in line with changes in global medical education, and lately, it has been focusing on transforming into a "capability-oriented curriculum." This trend implies that medical education in Korea has been standardized with a certain level of quantitative foundation for doctor training.

With the advent of the post-modern era, as we enter the Fourth Industrial Revolution, education must be developed in the direction of "rediscovering people's values and maximizing their ability to adapt to change" and "to learn abilities." If we summarize it in one word, it is "creative problem-solving ability."

Table 1. The SPICES model of educational strategies

Innovative strategy	Traditional strategy
Student-centered teaching	Teacher-centered teaching
Problem-based learning	Information gathering learning
Integrated/Inter-professional curricula	Discipline-based curricula
Community-based learning	Hospital-based learning
Electives with a core program	Uniform standard program
Systematic/planned approach	Apprenticeship/opportunistic approach

In the medical field in particular, an emergency situation can develop suddenly and problem-solving ability to apply expertise in such situations without apprehension is one of the most important attributes of doctors. This problem-solving ability is based on standardized expertise and skillful learning, and creativity can be applied at the same time. Sang-Ho Baek's argument, "Education for performable physicians," to implement the 21st-century medical education flow [3] is a representative example of the early emphasis on the importance of creativity in solving problems in various situations.

In this context, the concepts related to creative competencies will be compared and organized to identify its importance in medical education.

Definition and properties of creativity

The etymology of creativity originated in ancient Greece, and its definitions are so diverse that discussions continue to this day. Torrance [4], the master of creative education, expresses the confusion of creative justice by saying: *"The debate over the definition of creativity continues over the last century, but nothing can define it completely..... The definition of creativity will go on constantly, and because of this imperfection, we will know more about creativity."*

Although the etymology of creativity began in ancient Greece, for a long time "create" was regarded as the realm of God, not the human realm. However, with the transition to modern society, creativity has been extended to the human realm, and creativity and creative education discussed in modern education have developed along with the "scientific education of education" of the 20th century modern education. In 1950, Guilford's inaugural address to the American Psychological Association focused on creative education [5], and in the backdrop of the 1957 "Sputnik shock," it brought a new topic of creativity. This triggered vast research and definitions on the issue.

In particular, Rhodes [6], who analyzed the work of many scholars on creativity, rather than defining creativity as a single concept, argued that people, processes, environments, and products overlap each other. It is more productive to define it as working. To summarize the subject of creativity according to the researcher's point of view (Fig. 1).

First, in terms of emphasis on personality, creativity can be defined as human thinking ability and explained as 'spreading thinking' or 'divergent thinking.' Guilford [7], a representative scholar with an emphasis on people, defines creativity as divergent thinking, which involves creating something new. Since Guilford, this perspective has also defined creativity, focusing on the characteristics and dispositions of creative people.

Torrance [8], a representative scholar who emphasizes the creative process, says, "I chose a creative process with a focus on creative thinking." Creativity means a creative thinking process and a creative problem-solving process.

Another position that emphasizes creativity describes it as a psychological, social, and cultural environment that operates in the environment surrounding human beings. In other words, the environment is something that allows creativity to occur [9]. The "press" of the environment is a concept from Murray's personality theory [10], which means a significant environmental factor that influences behavioral decisions [9]. This view has recently evolved into a pluralistic view in which the four elements of creativity interact. Csikszentmihalyi [11] also defined creativity as a field of cultures, bringers of newness, and experts who recognize newness in the environment surrounding individual creative achievement.

From the perspective of emphasizing creative products, it focuses on creativity as a result of original thinking or creativity. Creative output includes both the visible and invisible aspects. [9]. In general, many people seem to use the "newness" and "value" of these outputs as the basis for judgment.

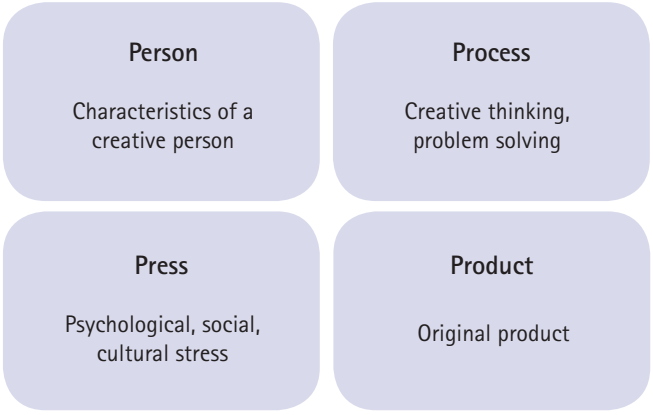

Fig. 1. The attributes of creativity.

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On the numerous definitions and scopes of creativity, Kaufman recently defined the concept of creativity in his book in 2016 [12], and further elucidated the "Four C Model" presented in 2009 [13]. This model is categorized into Big-C and little-c by adding mini-c and pro-c. Big-C suggests genius creativity, such as the likes of Mozart, Einstein, Armstrong, etc. While pro-c is not a genius, but a professional level of creativity, little-c refers to creativity expressed in day-to-day life, and mini-c refers to creative ideas inherent in everyone [12,13].

The volume of studies on creativity in Korean education was insignificant until 1990, and its number has increased since the 2000s. However, in the study of creative education, conceptual studies on creativity have been scarce, and since the emergence of creativity and personality capabilities in the 2009 revised curriculum, the study of creative education commenced. Early creativity focuses on the concept of big creativity that develops something new, but recent research on creativity focuses on small creativity [14].

Creativity and creation

Similar vocabulary is commonly used in terms of "creative" and "creation." According to the Korean dictionary, creation is defined as "the first result of something that never existed," and creativity is defined as "new thoughts." Applying Rhodes' 4P concept mentioned earlier, creativity refers to a person's inclination to seek newness, the idea of pursuing a new perspective based on environmental factors, and the manifestation of such a will. Creation, on the other hand, places a greater emphasis on the end result or output of all these activities, and creation is considered an outcome of creativity. Kaufman's "Four C Model" also indicates that you can start with creativity and go on to creation. In order to resolve the confusion caused by the mixed use of the terms "creative" and "creation," they can be classified into the opinions and etymologies of scholars as follows (Fig. 2).

Creativity means to "create something out of nothing" or create something new from nothing. In Greek, there is a *poiein*, which means make, and is applied to *poiethes*, and only the poet is recognized as the maker of something. Conversely, in the Roman period, "crere," "creating" in addition to "facere" appeared, which implied "creatio ex nihiro" until the Middle Ages. By the 19th century, it was limited to the arts field and applied to poets and artists [15].

Creativity has since been defined to suggest that artists create something new, mainly in art-related activities. Creation is thus used to highlight the process and results of creating something in the absence of experts in the field.

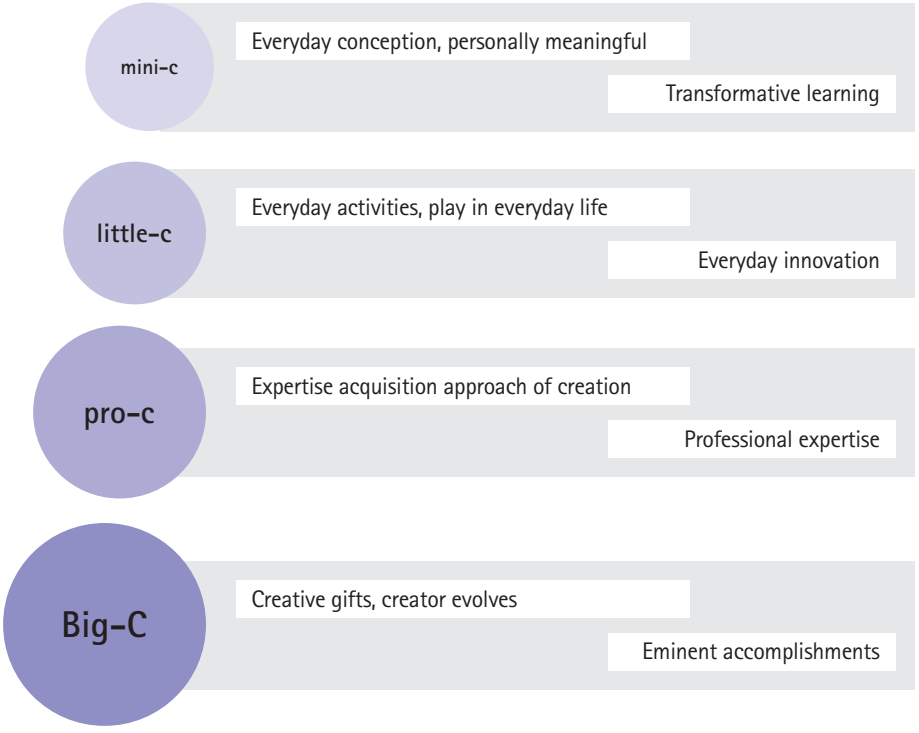

Fig. 2. The Four C Model of creation.

The importance of creativity

Creativity is recognized as a norm in education, and it is a concept that is appropriate not only for education but also for all academic fields and human activities such as literature, art, science and technology [16]. Specifically, activities that are not socially normative or inappropriate are not considered creative. There are some misconceptions about creativity that remind us of new, extraordinary, unusual, and imaginative words [17]. (1) Something magical with only a few great geniuses. (2) Other unusual behavior, unconditional backlash. (3) Mental illness, associated with madness (ex. Gogh's ear cut). (4) Necessary only for persons with special positions in specific departments.

Creativity is based on a high intellectual ability, original thinking, independent judgment, and open thinking. A five-year-old who is not aware of social knowledge and norms depicts a square cow, a neckless mom, and a dad [1]. Knowing the old, adding the new, and having a morally reasonable good value is creativity. It is not known that a child who knows nothing draws a square-necked cow, not so creative, and unrestricted illusions and deviations are not called creativity [18]. On the contrary, children's expressions are considered to be of value only if they fit the established standards, adequacy, truth, and moral right [19]. Creativity is therefore basically an integrated capacity that adds new, good value in addition to standardized knowledge. Elements that define creativity are shown in Fig. 3.

One of the most important aspects of creative education in tertiary institutions is the full acquisition of standardized knowledge in the field of study. For example, when playing a piece of music, when the musician understands the song, memorizes the lyrics, uses the instrument skillfully, and has sufficient practice, he/she can make his/her own new interpretation of the piece. If you play an entirely new piece outside the scope of the song, it can be defined as an activity beyond creativity. Creativity is therefore not limited to any particular field of study but is a factor that must be pursued in all disciplines, beginning with day-to-day life.

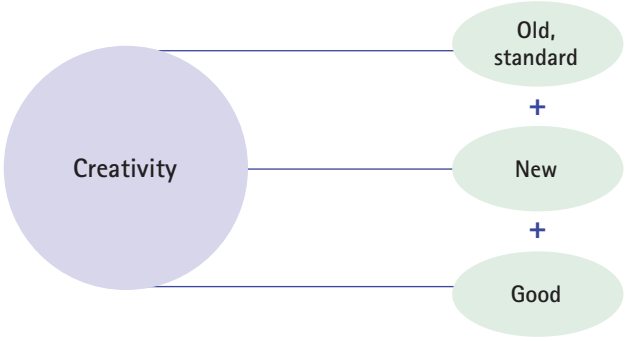

Fig. 3. Elements defining creativity. Creativity is therefore basically an integrated capacity that adds new, good value in addition to standardized knowledge.

Medical education and creativity in Korea

Since Korea's medical education has witnessed a significant growth since the 1990s, it has been striving for qualitative growth by reflecting changes in the medical environment and social needs. In recent years, with the introduction of competency-based and outcome-based curricula, attempts for qualitative growth have become more active, especially with the Korean Institute of Medical Education and Evaluation (KIMEE). Starting this year, medical schools adopted the new "Accreditation Standards of KIMEE 2019" (ASK2019) with the introduction of the World Federation for Medical Education's basic medical education evaluation criteria. The key to this new assessment standard is the shift from traditional quantitative assessments to qualitative assessments that emphasize university autonomy. The necessary and sufficient requirement for a qualitative assessment is the fulfillment of a quantification. The launch of qualitative evaluation through ASK2019 also presupposes that medical education in Korea has already met a certain standardization and quantitative level.

Therefore, it is time to be creative in the field of medical education. First of all, creative individuality needs to work at the university level. Rather than countering the entire medical education flow or creating an entirely new form, it should reflect the changes in individual schools and communities on a standardized basis to form a unique culture of the university. However, it is difficult to accept the demand for new changes in medical education as another process of uniformity.

Instead of eliminating the existing standards, creativity should combine new educational goals and ideas with old values, especially in the field of medical education.

In modern times, the pattern of disease has changed, with new symptoms and diseases emerging, and it has become common to treat patients of various nationalities. Therefore, medical education should once again verify the basics and progress of education that reflects the diversity of the community and students, and at the same time develop the ability of graduates to properly solve problems in various situations in the medical field. Not surprisingly, it is not a threat to the medical field, but it is only natural to have standardized basic knowledge.

It is not possible to respond to the fast-changing modern medical field with average standardized capacity. In addition, human capacity is multidimensional, and an educational environment in

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which one can fully experience and be sure of the ability to be used in different contexts is important. While the primary objective of medical students is to become doctors, ultimately every student may have a different goal. Therefore, in order to realize student-centric medical education, a curriculum that takes into consideration changing times and students' individual competencies should be prepared.

Conclusion

There are also concerns that medical education should be excluded from creative capacity, as the various definitions of creativity seem to involve the risk of considering doctors as creative. But creativity does not just mean something completely new, something completely special, as discussed earlier. Creativity is an ability that can be exercised when there is sufficient expertise in the field of study.

Creative capacity is defined as the ability of a doctor with sufficient standardized knowledge and competence to adapt to a situation based on basic expertise. This is the reason why creative capacity should be viewed anew in the field of medical education. We must go one step further for new growth.

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Conflicts of interest

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

Author contributions

Conceptualization, data curation, formal analysis, project administration, supervision, visualization, writing-original draft, writing-review & editing: YHL, YK.

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Effectiveness of orthoses for treatment in patients with spinal pain

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Spinal pain is a common patient complaint in clinical practice. Conservative treatment methods include oral medication, physical therapy, injections, and spinal orthoses. The clinical application of orthoses is debated because of potential complications associated with long-term use, such as muscle weakness and joint contracture. We reviewed the orthoses most frequently used to manage spinal pain. We review the use of soft cervical and Philadelphia collars, lumbosacral corsets, and thoracolumbosacral orthosis to manage spinal pain. Spinal orthoses can help reduce pain by protecting the muscles and joints of the injured spinal region, preventing or correcting malformations, and limiting trunk flexion, extension, lateral flexion, and rotation. The short-term use of spinal orthoses is known to improve pain and disability during the treatment period without significant adverse effects. Spinal orthoses are expected to alleviate pain and improve patients' lifestyle.

Keywords: Conservative treatment; Orthotic devices; Pain; Spine

Introduction

Spinal pain is a common patient complaint, affecting 80%–90% of individuals at least once in their lifetime [1,2]. There are various causes of spinal pain, such as spinal degeneration, trauma, inflammation, infection, and deformities. In clinical practice, spinal degeneration (herniated disc or spinal stenosis) and trauma are the most common causes of spinal pain [3-5]. To alleviate spinal pain, conservative treatments, including rest, physiotherapy (e.g., heat therapy, traction therapy, and manual therapy), injections, orthoses, and medication, are used before the surgical treatment [6-8]. Although the clinical application of orthoses is debated because of potential complications associated with long-term use, such as muscle weakness and joint contracture, its short-term use is known to improve pain and disability during the treatment period without significant adverse effects [9-11].

In this study, we reviewed the following types of orthoses most frequently used to manage spinal pain: soft cervical and Philadelphia collars, lumbosacral corset, and thoracolumbosacral orthosis (Table 1).

Soft cervical collar

The soft cervical collar is comprised of a soft foam material, a fabric covering the foam, and a Velcro strap (Fig. 1) [12,13]. The strap is mostly fastened at the back but can also be placed at the front, depending on the user's preference. Patients wearing a soft cervical collar can experience feelings of warmth and psychological comfort owing to the fabric sheathing [14]. However, soft cervical collars cannot significantly restrict the cervical spine's range of motion, thus falling short in providing sufficient structural support [12,14]. Therefore, they are used to manage muscle pain and

Table 1. Characteristics of spinal orthoses

	Soft cervical collar	Philadelphia collar	Lumbosacral corset	Thoracolumbosacral orthosis
Material property	Flexible	Rigid	Flexible	Rigid
Application part	Neck	Chin, occiput, neck, upper portion of trunk	Abdomen, under the scapular, upper supra-ilium	Shoulder, thorax, abdomen, medial part of scapula, dorsum, upper supra-ilium
Movement limitation	Slight movement of F, E, L-F, R	F, E, L-F, R	L-F, slight movement of F, E, R	F, E, L-F, R
Indication	Spondylosis or minor trauma, whiplash injuries	Injuries of the bones or ligaments, post-operation	Disc herniation, spinal stenosis, chronic back pain, sprain	Chronic back pain, sprain, fracture, spinal deformities, post-operation

F, flexion; E, extension; L-F, lateral flexion; R, rotation.

Fig. 1. Soft cervical collar. The subject is wearing soft cervical collar.

spasms due to spondylosis or minor trauma and as an initial treatment for whiplash injuries. According to a previous study, the soft cervical collar is recommended to be worn for 2 weeks [11].

Muzin et al. [11] reported no side effects (e.g., muscle weakness) associated with the use of soft cervical collars for fewer than 10 days. Mealy et al. [15] assessed 61 patients with acute cervical whiplash injuries following the use of the soft cervical collar for 2 weeks. The patients were divided into the following two groups: one that progressively combined exercise with use of the soft cervical collar and the other that performed exercise without use of the soft cervical collar. Eight weeks later, the visual analog scale (VAS) score from 0 to 10 (with 10 indicating unsustainable pain and 0 indicating absence of pain) and range of motion of the cervical spine (i.e., flexion, extension, lateral flexion, and rotation) were obtained. The group using the soft cervical collar reported a higher reduction in both the intensity of pain and range of motion of the cervical spine [15]. Furthermore, Rosenfeld et al. [16] investigated 97 patients with whiplash injuries by dividing them into two groups as follows: (1) those who wore soft cervical collars within 96 hours from the injury and were treated after 2 weeks and (2) those who did not use the collar and were treated using the same protocol. In addition, the VAS scores for pain were obtained for both the groups. After 6 months, the VAS scores decreased by 3 points in the group that used the soft cervical collars and only by 1.5 points in the group that did not use the soft cervical collar.

Philadelphia collar

The Philadelphia collar, which usually comprises of a solid plastic sheet, limits a greater range of movements compared to the soft cervical collar (Fig. 2) [12]. It is vertically reinforced from the chin to the manubrium in the front and shaped to cover the area from the external protuberance of the occipital bone to the upper part of the spine of the scapula at the back. The anterior part of the Philadelphia collar has a hole for tracheostomy; therefore, the user's chin has to be aligned with its center [17,18]. Furthermore, the inner side of the Philadelphia collar is lined with a replaceable padding, which permits good hygiene and causes less irritation to the skin. The Philadelphia collar slightly reduces the load on the spine by promoting the correct posture at the cervical spine and plays a role in limiting the cervical flexion/extension, lateral flex-

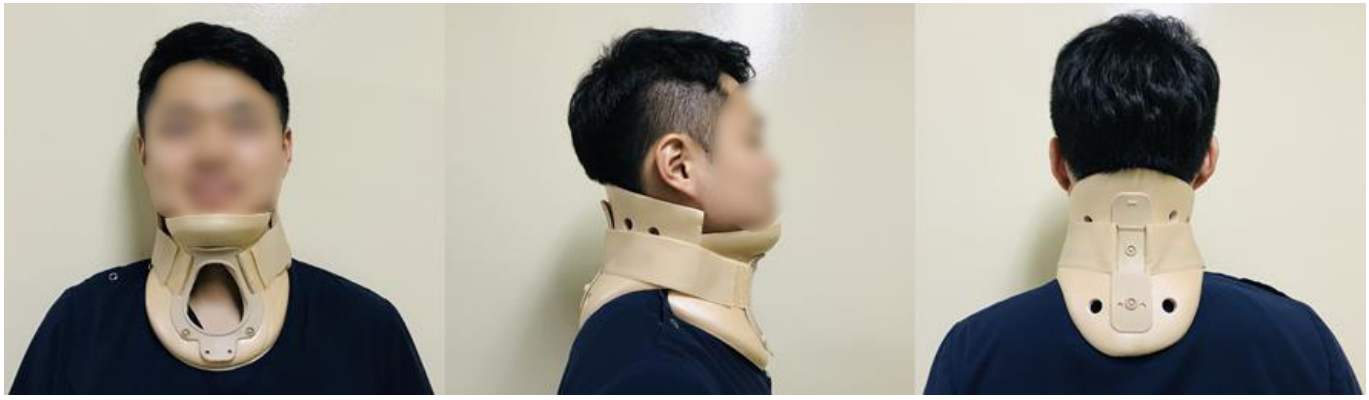

Fig. 2. Philadelphia collar. The subject is wearing Philadelphia collar.

Fig. 3. Lumbosacral corset. The subject is wearing lumbosacral corset.

Fig. 4. Thoracolumbosacral orthosis. The subject is wearing thoracolumbosacral orthosis.

ions and rotation [18,19]. Nonetheless, some pressure may be applied on the clavicle by the Philadelphia collar. Considering that excessive pressure can cause discomfort or pressure sores, special attention is required for users with sensitive skin [18,20]. The Philadelphia collar can be used to treat injuries of the bones and ligaments in the mid-cervical spine region and for postsurgical stabilization. In addition, it can be used instead of the halo orthosis to stabilize upper cervical fractures (Jefferson and hangman's

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fractures) and fractures of the odontoid process [11].

According to a study by Beavis [14], hard cervical collars are effective in limiting the motion of the cervical spine (level of movement reduction: flexion 69%, extension 34%, left lateral flexion 22%, right lateral flexion 34%, leftward rotation 50%, and rightward rotation 48%). Similarly, Muzin et al. [11] suggested that hard cervical collars were effective for the initial management of trauma (i.e., to prevent cervical instability). Finally, Motiei-Langroudi and Sadeghian [21] studied 11 patients with a C2 fracture who used the Philadelphia collar either until the bone completely recovered or until the neck pain disappeared. After a follow-up of 21 months, the patients reported no neurological symptoms or deficits, a mean VAS score of 2, and recovery of their lifestyle before the injury.

Lumbosacral corset

The lumbosacral corset is comprised of soft materials. It encloses the trunk and pelvis and has a string or hook to adjust the circumference. When necessary, a canvas, nylon mesh, or coil spring is used to increase its capability to provide support (Fig. 3). The posterior support column is made of semirigid or soft plastic materials and is molded to the shape of the patient's body. It is inserted into a corset, which confers rigidity to the support, thus limiting hyperextension of the spine and reducing spinal lordosis [22-25]. In the groin region, straps can be attached to prevent the movement of the corset. The upper margin of the anterior surface of the corset is positioned 1.3 cm (1/2 inch) below the xiphoid process, and the lower margin is located 2.5–3 cm (1 inch) above the pubic symphysis. Furthermore, while the upper margin of the posterior surface is 2.5 cm (1 inch) below the inferior angle of the scapula, the lower margin is located at the most prominent part of the hip [18].

The lumbosacral corset limits several movements in the frontal plane. It is less rigid at the pelvis, allowing movements in both the sagittal and transverse planes. Moreover, the corset applies pressure on the abdomen; therefore, the intraabdominal pressure increases, which reduces stress on the spine and load on the spinal disc and extensors. Furthermore, it enhances the user's perception of proprioception. The lumbosacral corset can be used in cases of disc herniation, spinal stenosis, chronic back pain, pelvic fracture, and sprain of the lumbosacral spine [23-27].

Kim [28] investigated 69 patients who used the lumbosacral corset to treat a herniated disc or sprain in the lumbar spine region. Physical examinations (e.g., straight leg raising [SLR] and gait analysis) were performed, and the intensity of pain and clinical outcomes of using the lumbosacral corset were determined based on the criteria suggested by Stauffer and Coventry [29]. While the results of both SLR and gait analysis were "poor" in 63.77% and 59.4% of the patients, respectively, prior to use of the lumbosacral corset, improvements were noticed following its use (i.e., 84.06% and 85.50% of the patients reported a greater than "fair" result). These findings suggest that the use of the lumbosacral corset is effective in reducing pain and improving the activities of daily living. In 2001, Prateepavanich et al. [30] measured the claudication distance and pain score (VAS) in 21 patients with lumbar spinal stenosis without wearing a lumbosacral corset, and a week later with a lumbosacral corset, evaluated again and compared the results. As a result, a significant difference between the two groups, an average claudication distance was 393.2 m when wearing a lumbosacral corset and 314.6 m when not wearing a lumbosacral corset, and a mean value of pain score was 4.7 when wearing a corset and 5.9 when not wearing a lumbosacral corset. This result showed that the effects of lumbosacral corset in lumbar spinal stenosis.

Thoracolumbosacral orthosis

The thoracolumbosacral orthosis (TLSO) can be of the following two types based on the type of material used: soft and hard. In addition, it is classified based on the location and presence of structural elements as flexion adjustable, flexion/extension adjustable, flexion/extension/lateral flexion adjustable, and flexion/extension/lateral flexion/rotation adjustable. It is fabricated on the principle of three-point pressure. TLSO can be used to treat chronic back pain, sprains and fractures of the thoracic or lumbar spine, and spinal deformities, and for postsurgical management of the spine [26,31].

TLSO is widely used in current clinical practice (Fig. 4). Owing to its light and breathable mesh fabric, it provides a comfortable fit. Furthermore, ergonomically designed plastic panels provide high stability through the application of abdominal pressure and insertion of the back panels. In addition, TLSO is adjustable through the connection of two elastic straps so as to fit the shape of the patient's body. It has a shoulder strap to prevent it from sliding out of place.

Jacobs et al. [32] assessed 15 patients with an osteoporotic vertebral compression fracture. Following the use of a semirigid TLSO for 6 weeks, their VAS scores and quality of life (measured using the Quality of Life Questionnaire of the European Foundation for Osteoporosis) were evaluated. The outcomes were decreased mean VAS scores (i.e., from 5 to 2 points) and improvements in pain (38%), physical function (42%), social function (21%), and health perception (16%).

Conclusion

Several patients with spinal pain are encountered in clinical practice. Spinal orthoses are expected to alleviate pain and improve patients' lifestyle. Nevertheless, studies on the clinical efficacy of orthoses are neither quantitatively nor qualitatively sufficient to reach a solid conclusion. Therefore, additional investigations are required to issue guidelines on the appropriate use of spinal orthoses. Our study is limited in that we reviewed only most commonly used orthoses, accordingly more various orthoses should be reviewed in the future study.

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Conflicts of interest

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

Author contributions

Conceptualization: YJC, MCC; Data curation: YJC, MCC; Formal analysis: MCC; Methodology: YJC, MCC; Investigation: YJC; Resources: YJC; Supervision: MCC; Visualization: YJC, MCC; Writing-original draft: YJC, MCC; Writing-review & editing: YJC, MCC.

Additional information

The model provided written informed consent for the use and publication of his photographs.

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Usefulness of subtraction pelvic magnetic resonance imaging for detection of ovarian endometriosis

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Background: To minimize damage to the ovarian reserve, it is necessary to evaluate the follicular density in the ovarian tissue surrounding endometriosis on preoperative imaging. The purpose of the present study was to evaluate the usefulness of subtraction pelvic magnetic resonance imaging (MRI) to detect ovarian reserve.

Methods: A subtracted T1-weighted image (^{sub}T1WI) was obtained by subtracting unenhanced T1WI from contrast-enhanced T1WI (^{ce}T1WI) with similar parameters in 22 patients with ovarian endometriosis. The signal-to-noise ratio (SNR) in ovarian endometriosis, which was classified into the high signal intensity and iso-to-low signal intensity groups on the T2-weighted image, was compared to that in normal ovarian tissue. To evaluate the effect of contrast enhancement, a standardization map was obtained by dividing ^{sub}T1WI by ^{ce}T1WI.

Results: On visual assessment of 22 patients with ovarian endometriosis, 16 patients showed a high signal intensity, and 6 patients showed an iso-to-low signal intensity on T1WI. Although SNR in endometriosis with a high signal intensity was higher than that with an iso-to-low signal intensity, there was no difference in SNR after the subtraction (13.72±77.55 vs. 63.03±43.90, p=0.126). The area of the affected ovary was smaller than that of the normal ovary (121.10±22.48 vs. 380.51±75.87 mm^2, p=0.002), but the mean number of pixels in the viable remaining tissue of the affected ovary was similar to that of the normal ovary (0.53±0.09 vs. 0.47±0.09, p=0.682).

Conclusion: The subtraction technique used with pelvic MRI could reveal the extent of endometrial invasion of the normal ovarian tissue and viable remnant ovarian tissue.

Keywords: Endometriosis; Gadolinium; Magnetic resonance imaging; Subtraction

Introduction

Although pelvic ultrasonography (USG) is the initial method of choice for identifying and characterizing adnexal cystic structures, magnetic resonance imaging (MRI) is performed in patients selected based on the results of USG and severity of symptoms [1-3]. MRI is generally performed to exclude malignancies in cases of intermediate USG features of ovarian masses [4-6]. Recently, an increased number of nulliparous women with ovarian endometriosis and desire to preserve ovarian function have been the main cause of increased MRI examinations. In addition, it is necessary to evaluate the follicular density in the ovarian tissue surrounding the endometrial cyst on preoperative imaging, especially in younger patients scheduled for ovarian cystectomy, to minimize damage to the healthy ovarian tissue and to predict the remnant ovarian function.

Typical MRI features of ovarian endometriosis include a high signal intensity on both T1-weighted images (T1WIs) and T2-weighted images (T2WIs), which persist on subsequent fat-suppressed T1WI [3,6]. However, chronic bleeding with accumulation of high concentrations of iron and protein in the endometriosis could cause gradual variations in the signal intensity [3,7,8]. As data are limited on gadolinium enhancement in the evaluation of endometriosis, the use of gadolinium is recommended as an "option" in the evaluation of indeterminate adnexal endometriosis, such as for distinction from other hemorrhagic adnexal lesions, luteal ovarian cysts, or tubo-ovarian abscesses. In addition, gadolinium enhancement is crucial for depicting strongly enhancing mural nodules if atypical features suggest potential malignancy on USG or T2WI [9,10]. However, the surgeon needs to consider the remnant ovarian tissue and endometriosis involving that area to avoid its destruction with blood coagulation or disruption of the ovarian blood supply while using the appropriate surgical approach [11]. However, it is difficult to determine the degree of invasion of endometriosis from stretching of the surrounding tissues because of the presence of cysts with inflammatory changes due to endometriosis [12]. In such cases, subtraction imaging of the ovary may be useful, in which the differential diagnosis includes displacement of the ovarian tissue and hemorrhagic endometriosis.

After subtraction, native T1 signals disappear, and the remaining signals are due solely to the enhancement associated with shortening of the T1 relaxation time owing to the intravenous contrast administration or flow effect [13,14]. This technique is widely used, and determining the presence/absence of enhancement is critical [15]. Therefore, the purpose of the present study was to evaluate the usefulness of a standardization map of pelvic MRI for patients with ovarian endometriosis.

Materials and methods

Retrospective data collection and analysis were approved by the institutional review board of Kyungpook National University Hospital (IRB No: KNUK 2017-06-012). The need for informed consent was waived due to the retrospective design of the study.

Endometriosis was classified based on the Revised American Society for Reproductive Medicine classification [16]. Twelve patients had stage III endometriosis, and 10 patients had stage IV endometriosis. All patients underwent laparoscopic ovarian cystectomy. The final diagnosis was obtained based on the histopathological/cytological examination of the surgically excised specimen of the lesion. To avoid spontaneous T1 hyperintensity due to menstrual bleeding, MRI was scheduled to be performed after day 8 of the menstrual cycle. Before MRI examination, the patients underwent 6 hours of fasting, followed by an intramuscular administration of a peristaltic inhibitor. MRI examinations were performed on a 3.0T closed-magnet MRI machine (Skyra; Siemens Health Care, Erlangen, Germany). We used a set of 8-channel phased array coils dedicated to different body parts included in the study. Subtraction images were obtained after intravenous contrast injection to assess the presence of enhancement for adequate depiction of these lesions. Contrast-enhanced T1WI (^{ce}T1WI) MRI including subtracted T1WI (^{sub}T1WI) sequences was performed with similar parameters, such as field of view, slice thickness, repetition time, echo time, and fat suppression, for both sequences.

MRI scans were interpreted on a picture archiving and communications system workstation (PiViewStar; Infiniti, Seoul, Korea) to identify endometriosis. An objective visual assessment of MRI scans was used to assess the T1 signal intensity of ovarian cystic lesions. A single author (LHJ) qualitatively analyzed all MRI scans for ovarian endometriosis blinded to any information on clinical details. When the signal intensity of a cyst was higher than that of the adjacent myometrium, the cystic lesion was regarded to show a high signal intensity on T2WI. In contrast, when the signal intensity was similar to or lower than that of the myometrium, the cystic lesion was regarded to show an iso-to-low signal intensity on T2WI [3].

Using the digital image analysis software ImageJ (1.47q, National Institutes of Health, Bethesda, MD, USA), axial pre- and post-contrast T1WIs, T2WIs, and subtraction images were evaluated. To evaluate comparability with the normal ovarian tissue, the signal-to-noise ratio (SNR) of the ovarian endometrial cyst and of the contralateral normal ovarian tissue were measured on all sequences.

To evaluate the effect of contrast enhancement, a standardization map (^{stand}T1WI) was obtained by dividing ^{sub}T1WI with ^{ce}T1WI and T1WI using ImageJ. Consequently, the number of pixels within ^{stand}T1WI was scored from 0 (not perfused) to 1 (totally perfused) (Fig. 1). Each region of interest (ROI) was quantified by outlining it using the measurement tool on the software at the level of the maximal diameter of lesions. The pixel information, including area, mean signal intensity with standard deviation, kurtosis, and skewness, was compared with that of the normal ovary. In addition, we obtained the integrated density, which is the sum of the values of pixels in the image or selection.

Statistical analyses were performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). The Student *t*-test. was employed to examine the difference in numerical variables. Statistical significance was set at a p-value <0.05.

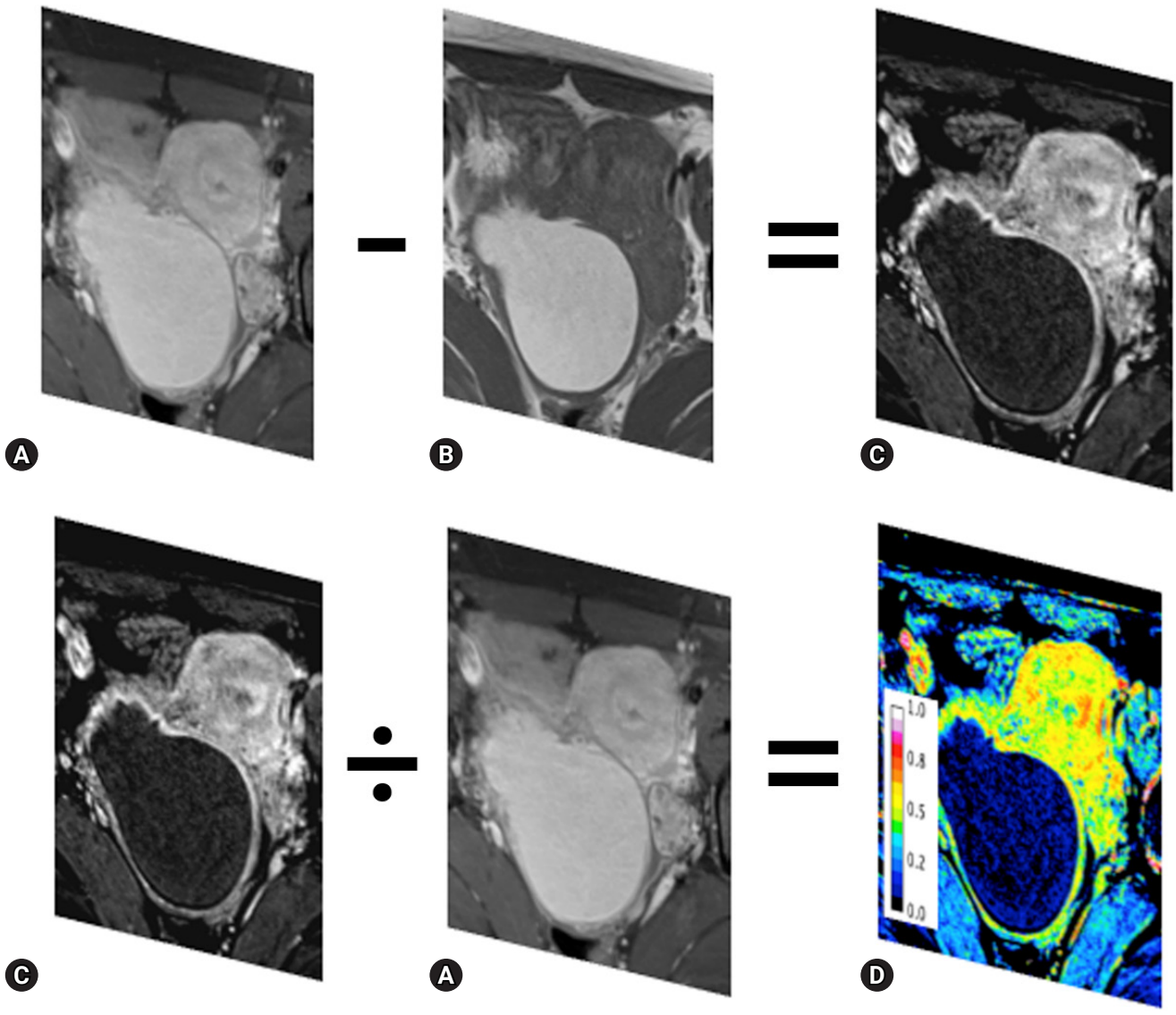

Fig. 1. Subtraction imaging and normalization of the contrast-enhanced effect. The ^{ce}TIWI (A) is subtracted by the unenhanced T1WI (B) to yield the ^{sub}T1WI (C). To normalize the effect of contrast enhancement, the ^{sub}T1WI (C) is divided by the ^{ce}T1WI (A) using ImageJ. The normalized perfusion map (D) is scored 0–1. ^{ce}T1WI, contrast-enhanced T1-weighted image; ^{sub}T1WI, subtracted T1-weighted image.

Results

This study included 22 patients with surgically confirmed ovarian endometriosis who underwent pelvic MRI. The mean age was 31.23 ± 7.21 years. ^{ce}T1WI MRI including ^{sub}T1WI was performed in all patients. On T2WI, the normal ovary showed cysts of varying sizes surrounded by the darker solid ovarian stromal tissue at the level of the maximum ovarian diameter and bright cysts surrounded by the darker solid ovarian stroma. ^{ce}T1WI showed well-enhanced tissue in an area of 380.51 ± 75.87 mm^2. The mean number of pixels in the included ROI in the normal ovary was 0.47 ± 0.09 on ^{stand}T1WI.

The affected ovary showed an area of 56.15 mm^2 at the level of the maximum ovarian diameter. In the visual assessment, 16 ovaries showed a high signal intensity, and 6 ovaries showed an iso-to-low signal intensity on T2WI. However, all cysts showed a low signal intensity on ^{sub}T1WI (Fig. 2). Although SNR of the endometriosis with a high signal intensity was higher than that with an iso-to-low signal intensity, there was no difference in SNR after the subtraction (13.72 ± 77.55 vs. 63.03 ± 43.90, p = 0.126) (Table 1).

The area of the affected ovary was smaller than that of the normal ovary (121.10 ± 22.48 vs. 380.51 ± 75.87 mm^2, p = 0.002), but the mean number of pixels in the remaining viable tissue of the affected ovary was similar to that of the normal ovary

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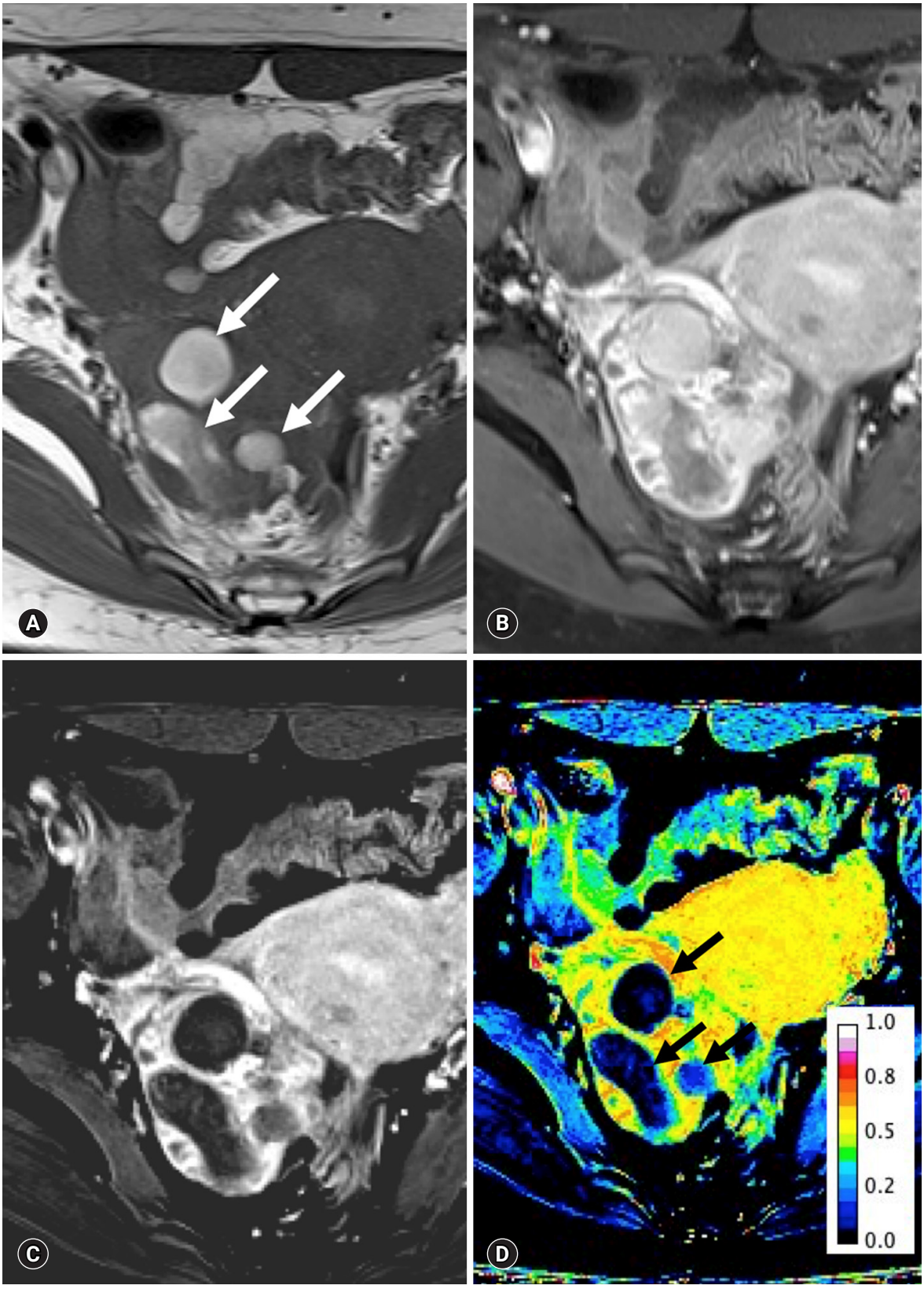

Fig. 2. Multiple hemorrhagic cysts in a 36-year-old woman with endometriosis. The pre-contrast T1WI with fat suppression (A) and post-contrast T1WI in the arterial phase of enhancement with fat suppression (B) show multiple (arrows) high signal intensities. The subtraction image (C) shows low signal intensity, regardless of the pre-contrast imaging. The number of pixels ranges 0.01–0.12 (arrows) (D). T1WI, T1-weighted image.

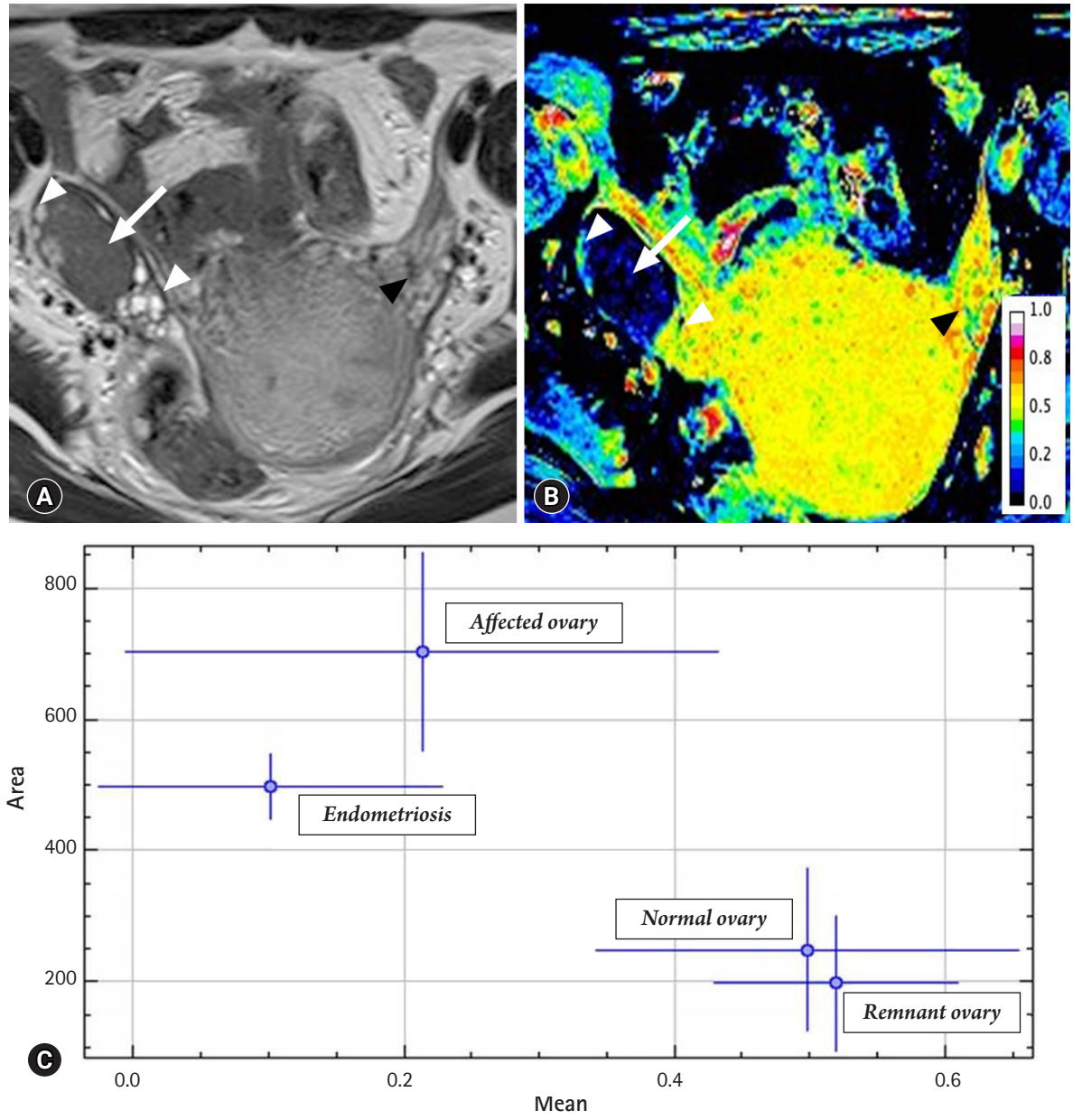

Fig. 3. The T2-weighted image (A) and standardization map of the subtraction image (B) in a woman with endometriosis. The ovary with endometriosis (arrow) displaces the small ovarian follicles (white arrowheads). However, the mean number of pixels in the viable remaining tissue of the ovary with endometriosis is similar to that of the ovary without endometriosis (black arrowheads). Plotting (C) for the uterus, affected ovary, endometriosis, remnant ovary, and normal ovary show similar patterns between the remnant ovary and the normal ovary. The x-axis represents the mean number of pixels (dot) with standard deviation (bar), and the y-axis represents the area (dot) with integral density of the included structure (bar).

(0.53 ± 0.09 vs. 0.47 ± 0.09, $p = 0.682$) (Fig. 3). The integrated density was lower in the affected ovary than in the normal ovary (63.82 ± 6.35 vs. 180.40 ± 17.52, $p < 0.001$) (Table 2).

Discussion

Subtraction imaging is a readily available technique routinely used with MR angiography. It can adequately determine the degree of contrast enhancement in the background of tissues that showed a high signal intensity on unenhanced T1WI MRI, such as hemorrhage or cystic lesions with mucinous or high proteinaceous contents [14,17]. There are many potential applications for this technique, including detection of neoplasms in hemorrhagic masses and complicated cysts and determining the presence/absence of

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Table 1. Comparison of the signal-to-noise ratio between ovaries with and without endometriosis

	Ovarian endometriosis		Control	*p*-value[a]	
	T2 high SI (A)	T2 iso-to-low SI (B)	Normal ovary (C)	A&B	B&C
T2WI	945.31 ± 116.53	557.86 ± 72.18	574.61 ± 155.06	< 0.001	0.824
T1WI	124.98 ± 3.91	505.80 ± 5.76	356.52 ± 32.23	< 0.001	0.001
[ce]T1WI	329.40 ± 17.56	572.25 ± 76.21	697.48 ± 88.97	< 0.001	0.002
Subtraction	13.72 ± 77.55	63.03 ± 43.90	340.97 ± 91.98	0.126	< 0.001

SI, signal intensity; T2WI, T2-weighted image; T1WI, T1-weighted image; [ce]T1WI, contrast enhanced T1WI.
[a]Student *t*-test.

Table 2. Comparison of the standardization map for the subtracted T1-weighted image between ovaries with and without endometriosis

	Affected ovary		Control	*p*-value[a]	
	Endometriosis (A)	Viable ovary (B)	Normal ovary (C)	A&B	B&C
Area	1,240.34 ± 324.50	121.10 ± 22.48	380.51 ± 75.87	< 0.001	0.002
Mean	0.17 ± 0.19	0.53 ± 0.09	0.47 ± 0.09	< 0.001	0.682
Integrated density	214.57 ± 31.20	63.82 ± 6.35	180.40 ± 17.52	< 0.001	< 0.001
Skewness	1.03 ± 20.79	-2.30 ± 0.32	-1.13 ± 0.30	< 0.001	0.453
Kurtosis	-0.451 ± 1.35	3.71 ± 2.26	2.88 ± 1.52	< 0.001	0.326

[a]Student *t*-test.

enhancement. Although a helpful tool, subtraction MRI is still underused for non-vascular cases. It can unambiguously evaluate contrast enhancement in lesions that showed initial T1 high signal intensity, thereby characterizing their nature. Complex ovarian cysts often show a high signal intensity on T1WI owing to the presence of intracystic hemorrhage.

Qualitative detection of enhancement, such as visual assessment of such lesions, is often difficult because of hemorrhagic or proteinaceous contents producing a high signal intensity on T1WI. Subtraction imaging is highly sensitive for detection of enhancement within these lesions and for accurate classification of benign hemorrhagic cysts or cystic ovarian malignancies. Although subtraction MRI could help evaluate ovarian lesions, its use has not been widely discussed in the radiological literature [14,17-19]. In the present study, the possibility of endometriosis suggested with the subtraction technique was confirmed after the surgery in all 22 patients. Six patients in our study presented with an iso-to-low signal intensity on T2WI. In all of them, subtraction images showed the absence of enhancement within the lesions, regardless of the shading effect, confirming the diagnosis of endometriosis after the surgery. [sub]T1WI can be useful in differentiating complex cystic lesions with T1 high signal intensity. In ectopic pregnancy, contrast enhancement may be mild, but on subtraction imaging, the differentiation is clearer [20]. The role of [sub]T1WI is crucial in unusual subtypes of endometriosis, including scar endometriosis, infiltrating endometriosis, endometriosis with infection, or endometriosis in the adenomyotic uterus [3,21,22].

Contrast enhancement depends on many variables. Therefore, standardization is required of the signal intensity scale for the effect of contrast enhancement [23]. [stand]T1WI was obtained by dividing subtraction images with non-enhanced images in the current study to analyze images performed in different environments. [stand]T1WI showed no enhancement of the lesions in the six patients with a chocolate cyst. Subtraction of high-resolution images can aid in evaluation of the remnant ovarian tissue. Endometrial invasion of the ovarian tissue is associated with the ovarian function. Moreover, bilateral invasion of the ovarian tissue is associated with infertility. Therefore, preoperative evaluation of the viable ovarian tissue is important. [stand]T1WI could be used to quantitatively analyze enhancement within this subset of cystic ovarian masses to prevent false-negative results. In addition, assessment of the extent of ovarian involvement is mandatory to determine the preoperative grade [24,25]. However, there are no definite MRI findings suggestive of deep invasion of the ovary. In this study, we regarded integrated density as the sum of pixel densities modified by area instead of the sum of the number of pixels. Although further clinical studies are required, the value could be a marker for remnant viable ovarian tissue. The presented technique could be useful in determination of the surgical approach for ovarian endometriosis.

However, this technique has some disadvantages. Although subtraction MRI adds only a few extra minutes in the process after contrast-enhanced MRI ([ce]MRI), it requires strict adherence to a specific protocol [26,27]. The radiology staff should be trained to ensure that correct images are obtained, and the post-acquisition

analysis is appropriate, including matching the exact pre- and post-contrast images to generate the subtracted image, which can be hampered by patient movement [28]. As a result, many images in our study were not suitable for analyses. These issues have not been highlighted by the previous studies on subtraction MRI. The utility of contrast MRI with the subtraction technique is rarely discussed.

This study highlighted the role of subtraction imaging with MRI. Pelvic MRI with subtraction imaging revealed ovarian endometriosis invasion of the adjacent healthy ovarian tissue. Subtraction images showed the absence of enhancement within the lesions, confirming the diagnosis of hemorrhage due to endometriosis. The normalized perfusion index map could be helpful for evaluating the remnant ovarian tissue. The application of ^{ce}MRI with the subtraction technique has rarely been discussed; however, it could be promising for the preoperative evaluation in patients who desire ovarian preservation during the surgical treatment. In conclusion, the subtraction technique used with pelvic MRI could reveal the extent of the endometrial invasion and viable remnant ovarian tissue.

Acknowledgments

Conflicts of interest

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

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Comparison of small bowel findings using capsule endoscopy between Crohn's disease and intestinal tuberculosis in Korea

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Background: Little is known about capsule endoscopy (CE) findings in patients with intestinal tuberculosis who exhibit small bowel lesions. The aim of the present study was to distinguish between Crohn's disease (CD) and intestinal tuberculosis based on CE findings.
Methods: Findings from 55 patients, who underwent CE using PillCam SB CE (Given Imaging, Yoqneam, Israel) between February 2003 and June 2015, were retrospectively analyzed.
Results: CE revealed small bowel lesions in 35 of the 55 patients: 19 with CD and 16 with intestinal tuberculosis. The median age at diagnosis for patients with CD was 26 years and 36 years for those with intestinal tuberculosis. On CE, three parameters, ≥10 ulcers, >3 involved segments and aphthous ulcers, were more common in patients with CD than in those intestinal tuberculosis. Cobblestoning was observed in five patients with CD and in none with intestinal tuberculosis. The authors hypothesized that a diagnosis of small bowel CD could be made when the number of parameters in CD patients was higher than that for intestinal tuberculosis. The authors calculated that the diagnosis of either CD or intestinal tuberculosis would have been made in 34 of the 35 patients (97%).
Conclusion: The number of ulcers and involved segments, and the presence of aphthous ulcers, were significantly higher and more common, respectively, in patients with CD than in those with intestinal tuberculosis. Cobblestoning in the small bowel may highly favor a diagnosis of CD on CE.

Keywords: Capsule endoscopy; Crohn disease; Small intestine; Tuberculosis

Introduction

Crohn's disease (CD) and intestinal tuberculosis are chronic granulomatous diseases that can involve any part of the gastrointestinal tract but have a predilection for the terminal ileum and cecum [1]. Although intestinal tuberculosis has long been a common problem in developing countries, it has resurged in Western countries due to human immunodeficiency virus (HIV) infection and immigration from developing countries [2-4]. At the same time, the incidence of CD in areas endemic for intestinal tuberculosis has increased [5,6]. Thus, differentiation between the two diseases has become more important. Ileocolonoscopy is the primary diagnostic modality for both CD and intestinal tuberculosis [7], and colonoscopic findings differentiating intestinal tuberculosis from CD have been well described [8]. Small bowel lesions, however, are common in patients with CD. For example, in Korea,

21% of patients with CD were found to have small bowel disease [5]. Intestinal tuberculosis also primarily involves the distal ileum and cecum, followed by the small bowel [9].

Capsule endoscopy (CE), which can directly visualize the mucosa of the small bowel [10], is an effective modality for the diagnosis of CD undetected using conventional diagnostic techniques [11]. Less is known, however, about CE findings in patients with intestinal tuberculosis [12]. Misdiagnosing intestinal tuberculosis as CD may be harmful to patients in areas endemic for intestinal tuberculosis because CD is treated with intensive immunomodulator therapy and surgery. Therefore, we assessed the utility of CE in the differential diagnosis of CD and intestinal tuberculosis.

Materials and methods

1. Ethics statement

The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB No: 2010-0894).

2. Patient selection

This was a retrospective study of information housed in the CE database of the Asan Medical Center (Seoul, Korea). CD was diagnosed based on conventional clinical, radiological, endoscopic, and histopathological criteria [6]. Between February 26, 2003 and June 12, 2015, 23 patients with CD underwent CE. Indications for CE included determination of the extent of small bowel disease in patients with established CD (n = 19) and workup of suspected CD (n = 4). The latter four patients were excluded because they were classified with probable CD based on clinical and histopathological criteria. Thus, only the 19 patients with established CD were enrolled [8,13].

During the same time period, 32 patients who underwent CE and diagnosed with intestinal tuberculosis, defined as meeting one of the following diagnostic criteria, were identified: histological evidence of caseating granulomas (n = 14) on colonoscopic biopsy; histological demonstration of acid-fast bacilli (n = 2) on colonoscopic biopsy; growth of *Mycobacterium tuberculosis* on tissue culture (n = 8) of colonoscopic biopsy specimens; and colonoscopic evidence of intestinal tuberculosis and resolution after anti-tuberculous medication (n = 8) [8,14]. CE for evaluation of the small bowel was performed in patients with confirmed intestinal tuberculosis immediately before starting anti-tuberculous medication. All patients provided written informed consent before the procedure. Patients taking nonsteroidal anti-inflammatory medications or aspirin were excluded.

3. Capsule endoscopy methods and imaging analysis

All patients ingested a polyethylene glycol electrolyte lavage solution for bowel preparation before CE, which was performed using the PillCam SB CE system (Given Imaging, Yoqneam, Israel). The CE parameters evaluated in this study included the number of ulcers, number of segments involved, aphthous ulcers, linear ulcers, a "cobblestone" appearance, focal lymphangiectasia, and stricture. The number of ulcers was dichotomized as ≥ 10 or < 10. The presence or absence of lesions was assessed separately in four segments. The four segments were evenly divided throughout the entire small bowel passage time except the duodenum. If transient CE retention in the small bowel occurred, the delay time was not included in assessing the four segments. A stricture was defined as the presence of luminal narrowing that restricted passage of the capsule in the small bowel. Two endoscopists retrospectively reviewed all CE findings on a workstation and were blinded to the diagnoses. Discrepancies were resolved by consensus discussion after review.

4. Statistical analysis

Data are expressed as median and range, and were compared between the CD and intestinal tuberculosis groups using the Pearson chi-squared test or Fisher exact test; differences with $p < 0.05$ were considered to be statistically significant. All statistical evaluations were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Study population

A total of 55 patients were assessed: 23 with CD and 32 with intestinal tuberculosis. CE revealed small bowel involvement in 19 of 23 CD (83%) and 16 of 32 intestinal tuberculosis (50%) patients. Analysis of these 35 patients (19 with CD and 16 with intestinal tuberculosis), revealed a male-to-female ratio of 14:5 and 3:5, respectively. Median age at diagnosis was 26 years (range, 12–47 years) in patients with CD, and 36 years (range, 16–46 years) in those with intestinal tuberculosis. All patients were Asian, primarily Korean. Abdominal pain was the most common symptom in both groups, and there were no significant between-group differences in weight loss and the incidences of abdominal pain and diarrhea. The median duration between symptom onset and undergoing CE was 5.5 months (range, 1–36 months) in patients with CD, and 6 months (range, 2–12 months) in those with intestinal tuberculosis. There were also no significant differences in hemoglobin and C-reactive protein concentrations, and erythrocyte sedimentation rate. Patient char-

Table 1. Clinical characteristics of patients

Characteristic	Crohn's disease (n = 19)	Intestinal tuberculosis (n = 16)	*p*-value
Age, yr (median, range)	26 (12–47)	36 (16–46)	NA
Symptom to diagnosis (median, range)	6 (1–36)	6 (2–12)	NA
Sex (male:female)	14:5	3:5	NS
Symptom			
Weight loss	14	7	NS
Abdominal pain	17	9	NS
Diarrhea	7	0	0.009
Laboratory abnormality			
Hemoglobin (g/dL)	12.6	12.4	NA
Erythrocyte sedimentation rate (mm/hr)	30	24	NA
C-reactive protein (mg/dL)	1.86	0.83	NA

NA, not available; NS, non-specific.

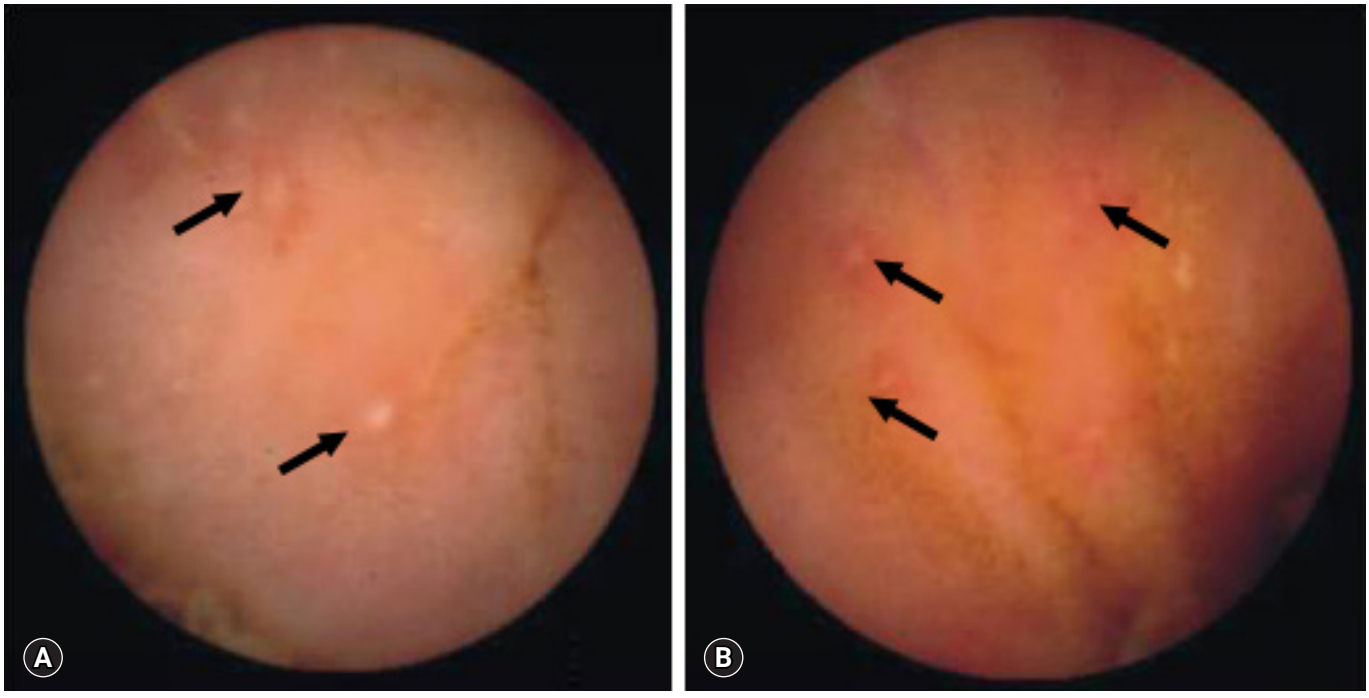

Fig. 1. Capsule endoscopy reveals multiple aphthous ulcers (arrows) in patients with Crohn's disease (A) and intestinal tuberculosis (B).

acteristics are summarized in Table 1.

Among patients with CD, only 2 (10.5%) exhibited the stricturing type, the others were non-stricturing, non-penetrating type. The mean duration between symptom onset to diagnosis was 6.9 ± 7.8 months. Among these, 11 patients (57.9%) had colonic lesions (L3) and 7 (36.8%) had concomitant perianal disease.

2. Capsule endoscopic findings

All 18 patients with CD had ≥ 10 ulcers in the small bowel, compared with only 2 of the 16 with intestinal tuberculosis ($p < 0.001$). Moreover, all 17 CD patients had ulcers in > 3 segments of the small bowel, compared with 1 of the 16 with intestinal tuberculosis ($p < 0.001$). Aphthous ulcers in the small bowel were observed in all patients with CD and in 4 of 16 patients with intestinal tuberculosis ($p < 0.001$) (Fig. 1). Linear ulcer of the small bowel was found in 10 of 19 with CD (52.6%) and in 4 of 16 with intestinal tuberculosis (25.0%) (Fig. 2). Cobblestoning was found in 5 of 19 CD (26.3%) and 0 of 16 intestinal tuberculosis patients ($p < 0.001$) (Fig. 3), and strictures in 2 of 19 (10.5%) and 1 of 16 CD (6.3%) and intestinal tuberculosis patients, respectively (Fig. 4). CE findings in the two groups are summarized in Table 2. Overall, three parameters, ≥ 10 ulcers in the small bowel, involvement of > 3 seg-

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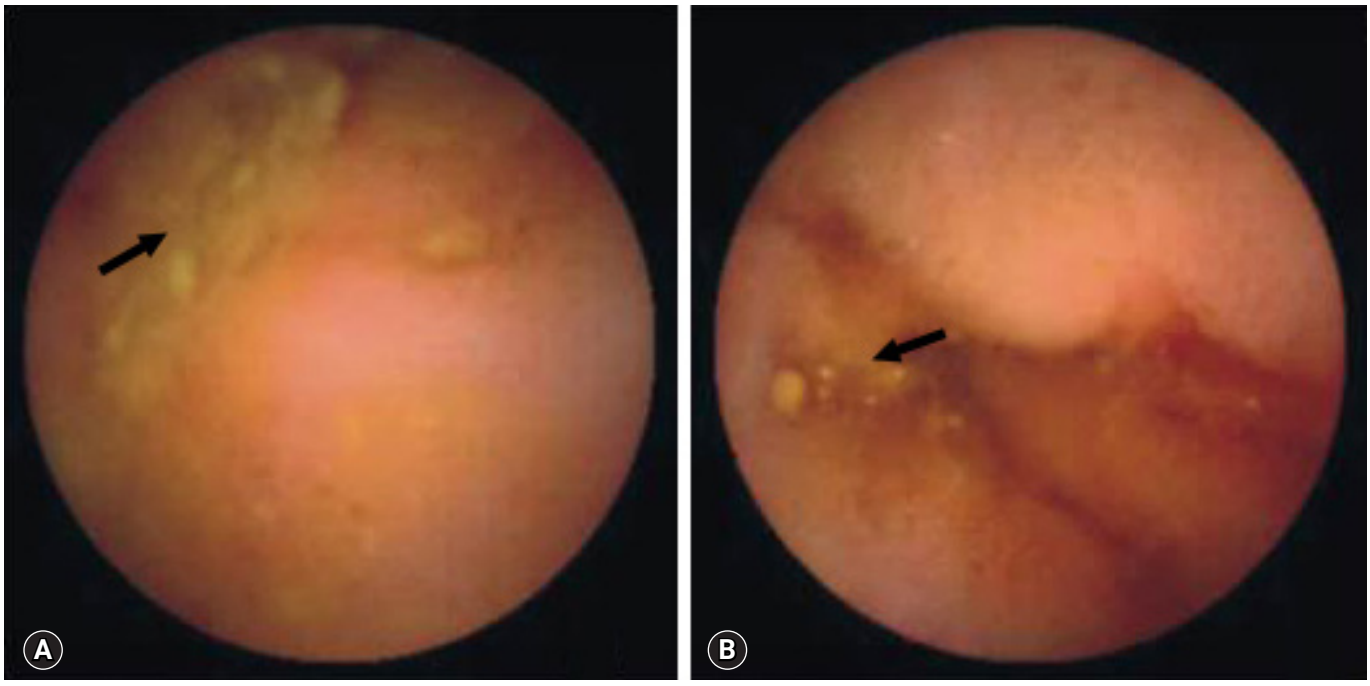

Fig. 2. Capsule endoscopy reveals linear ulcers (arrow) in patients with Crohn's disease (A) and intestinal tuberculosis (B).

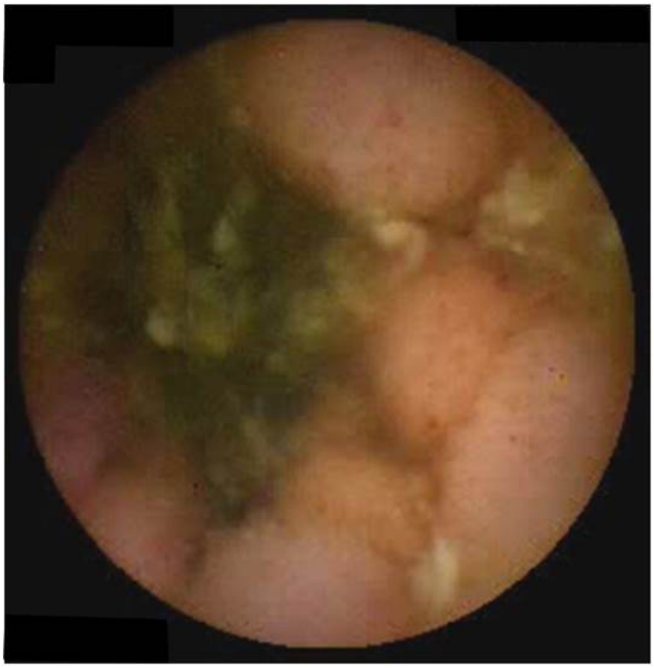

Fig. 3. Capsule endoscopy reveals cobblestone features in patients with Crohn's disease.

ments, and aphthous ulcers and cobblestoning, were significantly more common in patients with CD than in those with intestinal tuberculosis.

Discussion

To our knowledge, this study is the first in Korea, to report CE findings that distinguished CD from intestinal tuberculosis. We found that CD was more commonly characterized by the presence of ≥ 10 ulcers, > 3 involved segments, and aphthous ulcers. All of these criteria differed significantly between patients with CD and intestinal tuberculosis, and all were highly diagnostic.

CD and intestinal tuberculosis present with similar clinical manifestations, including weight loss, anemia, abdominal pain, and diarrhea [15]. We found that these clinical manifestations, including symptoms and laboratory findings, were similar in the two groups, although age at diagnosis was greater in patients with intestinal tuberculosis. Although colonoscopy can distinguish between ileocolic involvement in patients with intestinal tuberculosis and CD [6,13-15], one-fifth to one-third of patients with CD present with only small bowel involvement. Small bowel involvement is also common in patients with intestinal tuberculosis. In fact, we found that 50% of patients with intestinal tuberculosis exhibited small bowel involvement. Establishing a correct diagnosis is critical for choosing the appropriate therapy and for predicting prognosis, especially in areas in which intestinal tuberculosis is highly endemic. Although radiological examination, including small bowel follow-through, may be helpful in differential diagnosis, its diagnostic yield is not satisfactory.

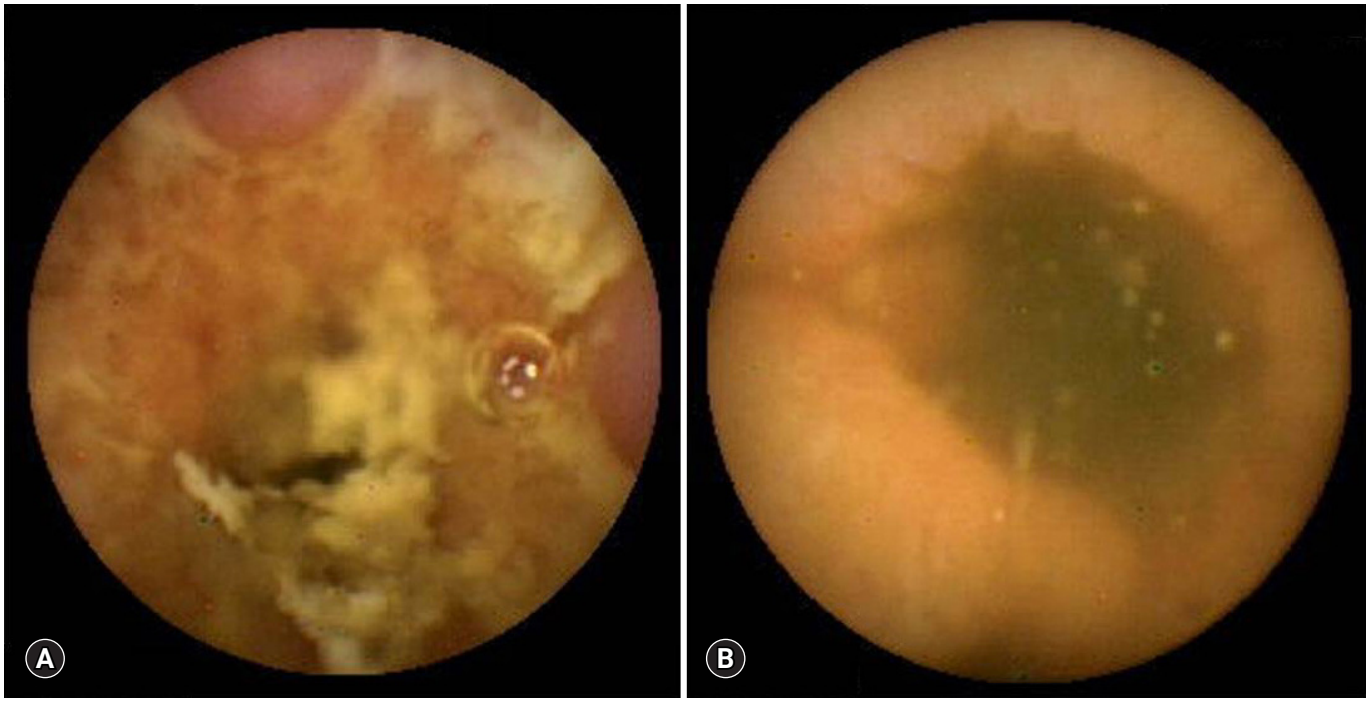

Fig. 4. Capsule endoscopy reveals strictures in patients with Crohn's disease (A) and intestinal tuberculosis (B).

Table 2. Comparison of capsule endoscopic findings between Crohn's disease and intestinal tuberculosis

Variable	Crohn's disease (n = 19)	Intestinal tuberculosis (n = 16)	*p*-value
Numbers of ulcer			< 0.001
≥ 10	18 (94.7)	2 (12.5)	
< 10	1 (5.3)	14 (87.5)	
Numbers of involved segment			
1	0	13	
2	2	2	
3	4	1	
4	13	0	
Numbers of more than half of involved segment			< 0.001
≥ 3	17 (89.5)	1 (6.3)	
< 3	2 (10.5)	15 (93.7)	
Upper gastrointestinal lesion	4 (21.1)	4 (25.0)	NS
Aphthous ulcer	19 (100)	4 (25.0)	< 0.001
Linear ulcer	10 (52.6)	4 (25.0)	NS
Cobblestoning	5 (26.3)	0	0.027
Focal lymphangiectasia	6 (31.6)	1 (6.3)	NS
Stricture	2 (10.5)	1 (6.3)	NS

Values are presented as number (%).
NS, non-specific.

Although CE may be useful in diagnosing CD in western countries [16,17], to date, there are no established criteria or guidelines for diagnosing CD. Studies have suggested that > 3 or 10 small bowel ulcers are diagnostic for CD [16-18]. Those studies, however, involved patients in western countries, which have a low prevalence of intestinal tuberculosis. Distinguishing CD from intestinal tuberculosis, especially in areas highly endemic for tuberculosis, is more challenging.

In comparing CE findings in patients with established CD and intestinal tuberculosis, we assessed the number of ulcers, the

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number of segments involved, the presence of aphthous ulcers, linear ulcers, cobblestoning, focal lymphangiectasia, and strictures. However, we did not include ileocecal valve involvement because we believe that ileocecal valve involvement is a colonic or colonoscopic finding [19]. We found that CD involved more segments, with more ulcers and with aphthous ulcers, than intestinal tuberculosis. We did not detect cobblestoning in any of our patients with intestinal tuberculosis, and cobblestoning of the small bowel was highly significant in our study. Linear ulcers were more common in patients with CD than in those with intestinal tuberculosis; however, the difference was not significant. Cobblestoning and linear ulcer of the small bowel may not be specific to small bowel CD because both have been reported in patients with other conditions such as intestinal tuberculosis [8]. Larger-scale studies, however, may reveal significant differences in these two endoscopic findings.

The main concern in performing CE in these patients is capsule retention due to an unpredicted stricture in the small bowel. The leading cause of capsule retention is stricturing CD [20,21]. Capsule retention was more common in patients with confirmed CD than in those with suspected CD [22,23]. For predicting CE retention, two methods have been attempted: dedicated small bowel cross-sectional techniques; and patency capsules. However, cross-sectional techniques and patency capsules are both effective in decreasing the retention rate, although neither able to completely eliminate the risk for retention [24]. We found that passage of the capsule was delayed in 10% of CD patients and 12.5% of intestinal tuberculosis patients. Fortunately, all capsules passed spontaneously during follow-up without mechanical obstruction. Although capsule retention did not occur among our patients, physicians should be aware of the risk for capsule retention in patients with both intestinal tuberculosis and CD.

The main strength of the present study was the exclusion of patients with suspected CD (i.e., CE was performed only in patients with established CD or intestinal tuberculosis); as such, we avoided misclassification of CE findings. An important result of this study was our finding of potential diagnostic criteria distinguishing between CD and intestinal tuberculosis in tuberculosis endemic areas. In addition, we demonstrated that CE was diagnostically accurate in patients with these two diseases. Previous studies demonstrated that CE has a higher diagnostic yield for lesions associated with CD when compared with small bowel X-rays, ileocolonoscopy, computed tomographic enterography, push enteroscopy, or magnetic resonance imaging [11,16,23,25].

Some may argue that our study population was inappropriate for the comparison of CE findings because the male-to-female ratio, age at diagnosis, and extensive small bowel involvement in CD patients. Age at presentation can be a characteristic that differentiates CD from intestinal tuberculosis [26]. A male predominance in CD has been reported in Asian countries, including Japan, Hong Kong, and Korea [27,28]. Despite the relatively short duration between symptom onset to performing CE in patients with CD (5.5 months), compared with a western study (11 months) [29], our patients exhibited extensive lesions in their small bowel. Extensive small bowel lesions in CD patients with small bowel involvement are probably another characteristic of CD in Asians or, perhaps the use of CE enables the detection of previously undetected small bowel lesions [30].

This study had several limitations, including its retrospective design, which is prone to bias from unrecognized or unmeasured factors. However, we assessed CE results in patients with confirmed intestinal tuberculosis to avoid diagnostic misclassification. Second, our findings may not apply to HIV-infected patients because all of our subjects were HIV-negative. Third, our findings require validation in populations with different prevalences of CD and intestinal tuberculosis. Finally, we enrolled only CD patients who were not undergoing non-steroidal anti-inflammatory drug (NSAID) therapy. Thus, our diagnostic criteria cannot be applied to other ulcerative lesions such as NSAID-induced ulcers.

In conclusion, we found that three parameters—umber of ulcers, number of involved segments, and the presence of aphthous ulcers—were significantly more common in patients with CD than in those with intestinal tuberculosis. Cobblestoning in the small bowel may highly favor a diagnosis of CD on CE. Our results should, nevertheless, be confirmed in a larger, prospective study.

Acknowledgments

Conflicts of interest

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

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Predictive value of C-reactive protein for the diagnosis of meningitis in febrile infants under 3 months of age in the emergency department

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Background: Fever is a common cause of pediatric consultation in the emergency department. However, identifying the source of infection in many febrile infants is challenging because of insufficient presentation of signs and symptoms. Meningitis is a critical cause of fever in infants, and its diagnosis is confirmed invasively by lumbar puncture. This study aimed to evaluate potential laboratory markers for meningitis in febrile infants.

Methods: We retrospectively analyzed infants aged <3 months who visited the emergency department of our hospital between May 2012 and May 2017 because of fever of unknown etiology. Clinical information and laboratory data were evaluated. Receiver operating characteristic (ROC) curves were constructed.

Results: In total, 145 febrile infants aged <3 months who underwent lumbar punctures were evaluated retrospectively. The mean C-reactive protein (CRP) level was significantly higher in the meningitis group than in the non-meningitis group, whereas the mean white blood cell count or absolute neutrophil count (ANC) did not significantly differ between groups. The area under the ROC curve (AUC) for CRP was 0.779 (95% confidence interval [CI], 0.701–0.858). The AUC for the leukocyte count was 0.455 (95% CI, 0.360–0.550) and that for ANC was 0.453 (95% CI, 0.359–0.547). The CRP cut-off value of 10 mg/L was optimal for identifying possible meningitis.

Conclusion: CRP has an intrinsic predictive value for meningitis in febrile infants aged <3 months. Despite its invasiveness, a lumbar puncture may be recommended to diagnose meningitis in young, febrile infants with a CRP level >10 mg/L.

Keywords: C-reactive protein; Fever; Infants; Meningitis; Spinal puncture

Introduction

Fever is a common cause of patient visits in pediatric practice [1]. In many patients, the main cause of infection cannot be identified based solely on the clinician's physical examination, especially in pediatric patients [2]. When infants who visit the emergency department exhibit fever without a clear source of infection, doctors must differentially diagnose various diseases from a simple viral infection to a serious bacterial infection [3]. The management of febrile infants aged < 3 months is especially challenging because of the relatively high prevalence of serious bacterial infections such as bacteremia, meningitis, and urinary tract infection, and the lack of specific signs or symptoms to differentiate these infections from a simple viral infection [4,5]. A combination of medical history and physical and laboratory findings has been widely accepted as an approach to identify the source of infection in fe-

brile patients [6].

Meningitis is one of the causes of fever, and lumbar puncture (LP) is required to determine the presence of meningitis by obtaining a cerebrospinal fluid (CSF) sample. Making a decision of when to perform an LP to differentiate meningitis from other diseases can be difficult [7]. In early-onset sepsis in the neonatal period, the American Academy of Pediatrics (AAP) recommends performing an LP in the case of positive blood culture results, if the "clinical course or laboratory data strongly suspect bacterial sepsis," or if the infant does not respond to antimicrobial therapy [8]. However, even with meningitis, young infant patients often do not present symptoms such as fever, vomiting, or headache, and blood culture examinations normally take a couple of days. Therefore, many clinicians rely on laboratory findings, including the level of C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to tissue injury or inflammation, which is a sensitive marker for infection [9,10]. The National Institute for Health and Care Excellence (NICE) published clinical guideline 149 (CG149) that suggests considering LP if the blood culture result is positive, the patient does not respond to antimicrobial therapy, or if the patient has a CRP level > 10 mg/L [11]. Many studies have analyzed the diagnostic markers for serious bacterial infections in febrile infants, but markers indicating meningitis and the cut-off values for the diagnosis of meningitis have rarely been evaluated.

Therefore, the aim of this study was to retrospectively assess several laboratory markers, such as CRP, white blood cell (WBC) and absolute neutrophil count (ANC), as markers of meningitis in febrile infants in the emergency department and to identify predictive values using receiver operating characteristic (ROC) curves for meningitis.

Materials and methods

1. Ethics statement

Ethical approval for this study was obtained from the Institutional Review Board of Wonkwang University Hospital (IRB No: WKUH 2019-04-045). The requirement to obtain informed consent was waived given the retrospective nature of the study.

2. Data collection, study setting, and definitions

This retrospective study included all infants aged < 3 months who visited the emergency department of our hospital from May 2012 to May 2017 for fever with no clear source of infection. Electronic medical records of 610 infant patients whose history and physical examination could not reveal the source of infection and who underwent a blood test were analyzed. The exclusion criteria were lack of blood test results and antibiotic therapy prior to the visit.

All patients underwent a full physical examination to localize the source of the fever, including the evaluation of their overall physical appearance as well as assessment of the heart, lungs, pharynges, fontanel, and ears. We collected the following clinical data from the electronic medical records: patient's age, sex, duration of fever before the hospital visit, final diagnosis, CRP level, WBC count, ANC, platelet (PLT) count, and results of the CSF analysis when LP was performed according to the ward's policy. Meningitis was defined as meningism without altered consciousness, with CSF WBC count ≥ 5/μL in infants older than 28 days and ≥ 30/μL in neonates [12]. Bacterial meningitis was confirmed based on the culture results of the CSF, Wellcogen (Remel Europe Ltd., Dartford, Kent, UK) bacterial antigen rapid latex agglutination test, or polymerase chain reaction (PCR) using dual priming oligonucleotide, Seeplex (MT Promedt Consulting GmbH, St. Ingbert, Germany). Viral meningitis was confirmed based on positive viral multiplex PCR results in the CSF. Aseptic meningitis was confirmed by negative bacterial growth in the CSF. For comparative analysis, we distinguished aseptic meningitis from viral meningitis. We confirmed that no bacterial pathogens were found in all investigated specimens from the aseptic or the viral meningitis groups. Undetermined fever was defined when the cause of fever was not revealed after 7 days of hospitalization. Urinary tract infection was diagnosed with pyuria (WBC > 5/high power field) and the isolation of > 100,000 colony-forming units per milliliter of a single pathogen from the urine collected in a urine bag. Cultures with more than one isolate were considered contaminated. Fever was defined as a tympanic membrane temperature of 38°C or higher.

3. Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were expressed as a number (%) using the cross analysis. The independent t-test was used when comparing the meningitis and non-meningitis group. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curves (AUCs) for laboratory biomarkers with respect to the diagnosis of meningitis were calculated and compared. Data were analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Results

During the study period, 610 febrile infants aged < 3 months were evaluated at the emergency department or outpatient pedi-

atric department of our hospital due to fever with no clear source of infection. Of these, three patients did not undergo laboratory tests, and 36 patients were treated with antibiotic therapy prior to the visit. Thus, a total of 571 infants who met the inclusion criteria were enrolled in the study. Among the 571 patients, LP was performed in 145 patients and 57 patients were definitively diagnosed with meningitis. The meningitis group was comprised three patients with bacterial meningitis and 54 patients with aseptic or viral meningitis. Among the viral meningitis group, 50 patients were diagnosed with enteroviral meningitis, and 4 patients were diagnosed with herpes simplex virus type 2 meningitis. Moreover, 88 patients comprised the non-meningitis group (Fig. 1). Febrile illness without a source of infection was the most common final diagnosis in all studied infants, accounting for 54.3% of all diagnoses (Table 1). Urinary tract infection was the next most common diagnosis, accounting for 157 patients (27.5%). Respiratory tract infection accounted for 33 patients (5.8%). Human rhinovirus was the most common pathogen accounting for 14 patients (2.5%). Respiratory syncytial virus, parainfluenza virus, enterovirus, coronavirus, human bocavirus, and influenza virus were the pathogens detected in the respiratory tract. Gastrointestinal tract infection accounted for 14 patients (2.5%). Rotavirus was the most commonly identified pathogen and astrovirus was also detected in the stool multiplex PCR.

The demographic characteristics and laboratory findings of infants with and without meningitis were evaluated. A total of 61.4% of the non-meningitis group were male infants (n=54), and 64.9% of the meningitis group were also male infants (n=37). The mean age was 40.9±23.7 days in the non-meningitis group and 40.6±25.3 days in the meningitis group. The mean duration of fever at the time of visit was 1.9±1.9 and 1.8±1.3 days in the non-meningitis group and meningitis group, respectively. Moreover, no significant difference in sex, age, fever duration, and mean time required for improvement of fever was found. A statistically significant difference was found in terms of CRP level between the meningitis and non-meningitis groups ($p<0.05$). The mean CRP level was 24.32±33.66 mg/L in the meningitis group and 7.44±6.50 mg/L in the non-meningitis group. Other laboratory variables showed no statistically significant differences (Table 2).

For predicting meningitis, the AUC was 0.779 for CRP (95% confidence interval [CI], 0.701–0.858), 0.455 for WBC (95% CI, 0.360–0.550), and 0.453 for ANC (95% CI, 0.359–0.547) (Fig. 2). The AUC for CRP was significantly higher than that for WBC and ANC. The ROC curve was used to select optimal cut-off values of laboratory factors for predicting whether LP is needed to detect meningitis. CRP was the only laboratory parameter found to be associated with meningitis. According to the data in this study, a CRP cut-off of 10 mg/L showed both relatively high sensitivity and specificity. At that threshold, a sensitivity of 73.7%, specificity of 77.3%, and NPV of 81.9% for possible meningitis were noted in febrile infants (Table 3).

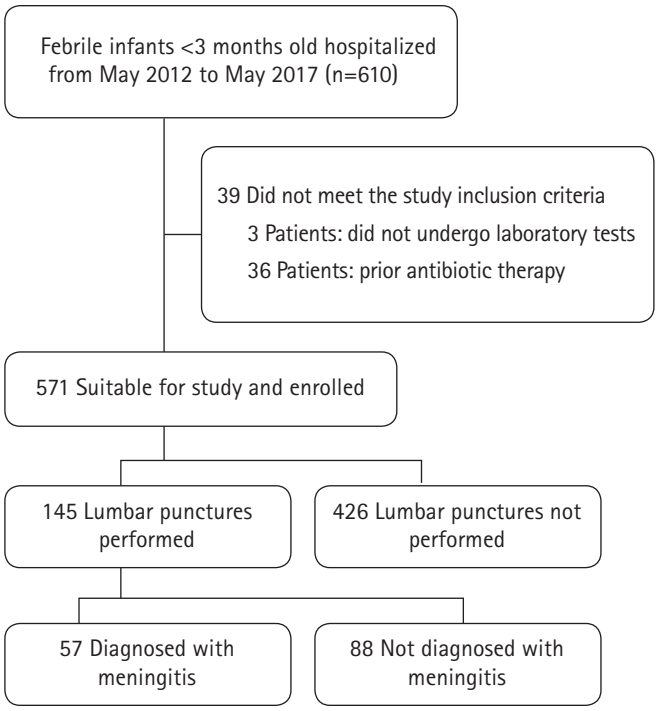

Fig. 1. Subject enrollment flow chart shows the number of patients in each classified group.

Table 1. Final diagnosis of febrile infants aged <3 months (n=571)

Final diagnosis	No. (%)
Undetermined fever	310 (54.3)
Urinary tract infection	157 (27.5)
Respiratory tract infection	33 (5.8)
Viral meningitis	28 (4.9)
Aseptic meningitis	26 (4.6)
Gastrointestinal tract infection	14 (2.5)
Bacterial meningitis	3 (0.5)

Discussion

In this study, we analyzed febrile infants with an unknown source of infection who met the inclusion criteria in the study period and compared the predictive values of commonly used laboratory data to establish effective markers for predicting meningitis.

When febrile infants without a clear source of infection seek treatment in a hospital, deciding the management approach is

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Table 2. Comparison of clinical and laboratory characteristics between the meningitis group and non-meningitis group

Variable	Meningitis (n = 57)	Non-meningitis (n = 88)	*p*-value
Male sex	37 (64.91)	54 (61.36)	0.699
Age (day)	40.6 ± 25.3	40.9 ± 23.7	0.944
Fever duration (day)	1.8 ± 1.3	1.9 ± 1.9	0.511
Fever improvement (day)	3.0 ± 1.4	2.6 ± 2.0	0.201
Hemoglobin (g/dL)	11.27 ± 2.43	11.14 ± 2.18	0.739
White blood cell count × 10^3 (/μL)	9.58 ± 5.12	10.39 ± 5.40	0.370
Absolute neutrophil count × 10^3 (/μL)	5.04 ± 3.74	5.63 ± 3.69	0.350
Neutrophil (%)	51.76 ± 15.73	52.58 ± 15.19	0.757
Lymphocyte (%)	37.80 ± 15.22	35.39 ± 13.87	0.329
Platelet count × 10^3 (/μL)	364.47 ± 126.49	344.89 ± 114.62	0.337
C-reactive protein (mg/L)	24.32 ± 33.66	7.44 ± 6.50	0.001

Values are presented as number (%) or mean±standard deviation.

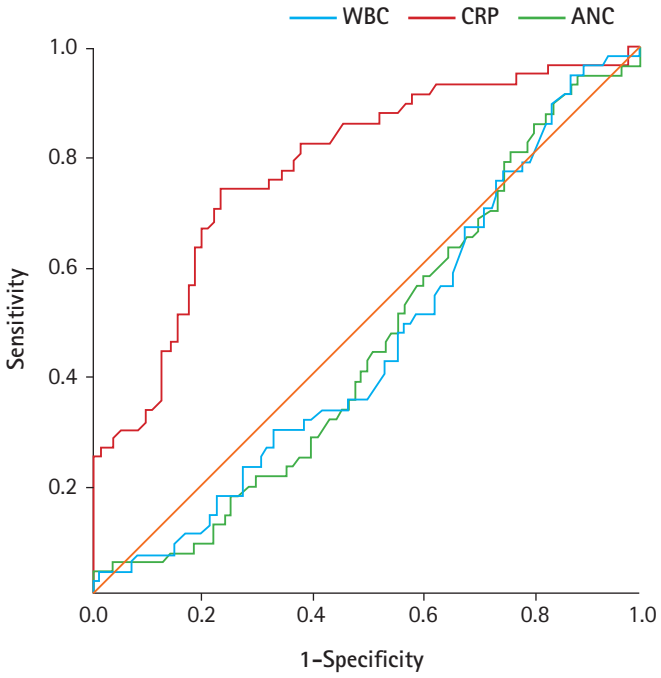

Fig. 2. Receiver operating characteristic curves for CRP (p<0.05), WBC (p=0.36), and ANC (p=0.34) for predicting meningitis shows that CRP has the most valuable predictive value indicating meningitis compared to WBC and ANC. CRP, C-reactive protein; WBC, white blood cell count; ANC, absolute neutrophil count.

Table 3. C-reactive protein decision thresholds as an indicating marker of meningitis

Threshold (mg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5	86.0	47.7	51.6	84.0
10	73.7	77.3	67.7	81.9
15	50.9	84.1	67.4	72.5
20	31.6	90.9	69.2	67.2

PPV, positive predictive value; NPV, negative predictive value.

quite challenging for clinicians. Particularly, febrile infants aged < 3 months are frequently evaluated for the risk of invasive bacterial infections such as bacteremia or bacterial meningitis in the pediatric department [13,14]. The probability of serious bacterial infection without a definitive etiology is reported to be approximately 12% in the neonatal period and up to 9% between 1 and 3 months of age [15]. Diagnostic tests for differentiating severe bacterial infections from viral infections have long been the focus of several investigations [16]. Chest radiography has been used for diagnosing pneumonia. Urine and CSF samples have been used for the diagnosis of urinary tract infection and meningitis, respectively [17]. However, deciding the timing of LP for CSF sampling has been challenging [7]. For neonates with early-onset sepsis, the AAP recommends performing LP if the blood culture result is positive with clinical or laboratory findings strongly indicating bacterial sepsis or if the patients do not respond to antibiotic therapy [8]. Gajdos et al. [18] analyzed predictive factors of bacterial infection in febrile infants aged < 3 months and found that only an elevation in WBC with > 50% of neutrophils and an elevation in CRP levels > 20 mg/L could predict serious bacterial infection, with a negative predictive value of 93%. Pulliam et al. [1] demonstrated that CRP level was a better diagnostic tool than WBC and ANC for predicting serious bacterial infection in a group of febrile children aged between 1 and 36 months.

During infection or inflammation, the plasma pro-calcitonin (PCT) concentration is known to both increase and return to normal concentration more rapidly than the CRP level [19]. The PCT level was also observed to increase faster than the CRP level 6 hours after the onset of severe infection or inflammation [20]. Therefore, the PCT test has been considered a useful tool for early diagnosis of infection [21]. In other studies, PCT was found to be

a useful biomarker to distinguish between bacterial and viral meningitis [22]. Moreover, in Korea, several published studies have focused on the value of laboratory markers in discriminating serious bacterial infections, and Hur et al. [23] studied the diagnostic value of PCT and CRP simultaneously using blood samples from 1,270 patients with blood culture-positive sepsis. According to their report, the diagnostic utility of the PCT was better than that of CRP. However, in the case of diagnosing neonatal bacterial infection, the PCT test was found to be more expensive, with similar or better sensitivity than CRP and acceptable specificity [24]. Kim et al. [25] also reported that in febrile infants aged ≤6 months, there is no diagnostic value of measuring serum PCT concentration for determining bacterial infection. Since a PCT assay is more expensive than CRP level analysis and is not readily available in all facilities, only a few infants are analyzed for changes in the PCT level. In contrast, CRP can be determined in less than an hour using a small amount of blood and the CRP level test is not cost intensive. Hence, we determined a cut-off level for CRP for better diagnostic accuracy and ease of access to all patients.

Sturgeon et al. [7] suggested that it does not appear prudent to assign CRP cut-off values for consideration in LP for neonates because of its low sensitivity and specificity. They emphasized the importance of a multi-faceted decision-making process based on clinical assessment, microbiology results, as well as any blood test findings such as CRP level [7].

In this study, sex and age at diagnosis in the meningitis group did not significantly differ from those in the non-meningitis group. The main finding of this retrospective study was that CRP is a relatively valuable laboratory factor in the assessment of meningitis in febrile infants aged <3 months. As shown in Fig. 2, various cut-off levels of CRP had better sensitivity, specificity, PPV, and NPV than those of WBC or ANC. Our data also showed that different cut-off values of CRP levels had different diagnostic values (Table 3). We found that with assuming a cut-off CRP level of 10 mg/L, the sensitivity and specificity for predicting meningitis were both >70%, with a relatively high NPV >80%.

This study has some limitations that need to be considered while interpreting the results. First, this study was conducted using medical records from a single hospital; thus, our study population does not represent the whole population of infants in Korea. Second, we collected urine samples using urine bags rather than catheterization or bladder puncture, which could have increased the likelihood of contamination. Finally, a comparison between the bacterial meningitis group and the aseptic meningitis group could not be performed because there were only 3 cases of bacterial meningitis in this study cohort. Even with these limitations, this comparative analysis of laboratory markers for predicting meningitis in infants is significant in terms of its contribution to the literature.

In summary, this study showed that in the evaluation of young, febrile infants in the emergency department, CRP was a stronger independent predictor for meningitis than WBC or ANC. We suggest the use of CRP levels as a part of the evaluation for every febrile infant aged <3 months. CRP levels >10 mg/L suggest the presence of meningitis in febrile infants with greater accuracy. However, clinicians should keep in mind that a single laboratory marker indicates only the probability but never the certainty of the presence or absence of meningitis.

Acknowledgments

Conflicts of interest

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

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Does oral doxycycline treatment affect eradication of urine vancomycin-resistant *Enterococcus*? A tertiary hospital study

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Background: Vancomycin-resistant *Enterococcus* (VRE) has become more common in nosocomial infections, especially in urine samples. However, until now, no treatment regimen has been proven to effectively eradicate urine VRE colonization. Therefore, to evaluate the efficacy of doxycycline in eradicating urine VRE and shortening VRE isolation period, we compared VRE colony detection period between doxycycline-treated and untreated patients.
Methods: A retrospective cohort study of 83 patients with VRE colonization in urine cultures was conducted at a tertiary academic hospital from January 2011 to February 2018. Kaplan-Meier survival analysis was used to evaluate eradication rates in the treatment and non-treatment groups. Factors affecting urine VRE colonization persistence were analyzed by multiple logistic regression analysis.
Results: The overall rate of VRE eradication during the entire hospital stay was higher in the doxycycline treatment group (90.5%) than in the non-treatment group (58.1%, p=0.014). Survival analysis showed that the 5-, 10-, and 20-day cumulative eradication rates were 78.3%, 100%, and 100% in the doxycycline treatment group, and 18.5%, 45.7%, and 67.8% in the non-treatment group, respectively, thereby indicating that eradication rates were higher in the doxycycline treatment group than in the non-treatment group (p<0.001). Only doxycycline treatment was shown to affect urine VRE colonization persistence in multivariate logistic regression analysis.
Conclusion: Doxycycline treatment enhanced the eradication rate of urine VRE colonization and appeared to be useful in shortening VRE isolation period.

Keywords: Affect; Doxycycline; Tetracycline; Vancomycin-resistant Enterococci

Introduction

Vancomycin-resistant *Enterococcus* (VRE) has emerged as an important nosocomial pathogen worldwide. VRE infections have been shown to account for approximately 30% of total enterococcal infections at hospitals [1], and nosocomial VRE infections can significantly increase hospital costs [2]. Antibiotic guidelines and restrictions help reduce the selective pressure that allows VRE to flourish in the gastrointestinal tract, but they are still difficult to implement, especially in severely ill patients in which empiric antibiotic use is common and needs to be continued [3].

Currently, the demand for an isolation facility in South Korea is

increasing owing to the emergence of VRE and carbapenem-resistant Enterobacteriaceae. This problem is not only limited to South Korea; it is also considered a significant economic burden in other countries [2,4]. Prolonged asymptomatic carriage of VRE in the gastrointestinal tract and lack of an effective decolonization regimen perpetuate the endemicity of VRE in healthcare settings [5]. When VRE is detected in any cultures, hospitals should isolate and quarantine patients until three consecutive negative VRE surveillance cultures are confirmed. However, the management of beds is a challenge at hospitals with limited quarantine space. It has been known that reduction in colonization rate may translate to reduced infection rates [6]. Several pharmacological treatments for VRE eradication in the gastrointestinal tract have been attempted, as spontaneous decolonization occurs infrequently. Among the treatments, a combined treatment with doxycycline showed 100% gastrointestinal VRE decolonization [7]. To verify whether eradication of urine VRE can reduce hospital isolation period, we investigated the efficacy of oral doxycycline treatment in eradicating urine VRE colonization.

Materials and methods

1. Ethics statement

The Institutional Review Board of Kyungpook National University Hospital approved the study protocol (IRB No: 2018-08-028).

2. Identification of subjects and data collection

A retrospective analysis was performed at Kyungpook National University Hospital, a 920-bed teaching hospital, between January 2011 and February 2018. All medical records were reviewed for patients who were subjected to a urine culture test. The medical records were reviewed from the date of the initial VRE isolation to the clearance of colonization or to the last urine culture test during the same hospital admission period. A total of 319 patients were found to be VRE-positive during the admission period. Among these, 87 patients were excluded because the first urine culture follow-up was not conducted. Among the remaining 232 patients, we excluded 59 patients who were under 8 years of age or pregnant at diagnosis, and another 20 patients who did not meet the VRE minimum inhibitory concentration (MIC) diagnostic criteria (MIC, <32 μg/mL). From the remaining total of 153 VRE-positive patients, we excluded six patients positive for urine VRE colonization at outpatient clinics, three patients treated with minocycline, seven patients treated with tigecycline, and two patients receiving concomitant doxycycline and tigecycline treatment. Four patients who were confirmed to be VRE-negative before drug administration and 42 patients who were not confirmed to have VRE clearance after three consecutive cultures were also excluded.

A total of 83 patients were eligible for this study. The number of study participants is shown (Fig. 1). We evaluated VRE eradication rate following doxycycline treatment. Doxycycline (100 mg) was administered orally every 12 hours according to the current standardized treatment dosage. Doxycycline was randomly administered to patients according to the clinical physician's decision after urine VRE identification. The duration of doxycycline treatment was also determined by the physician. In the doxycycline treatment group, the mean duration of drug administration was 3 days (range, 2–5 days). The mean duration from urine culture collection to obtaining of VRE results was 5 days (range, 4–6 days). The following information was collected:

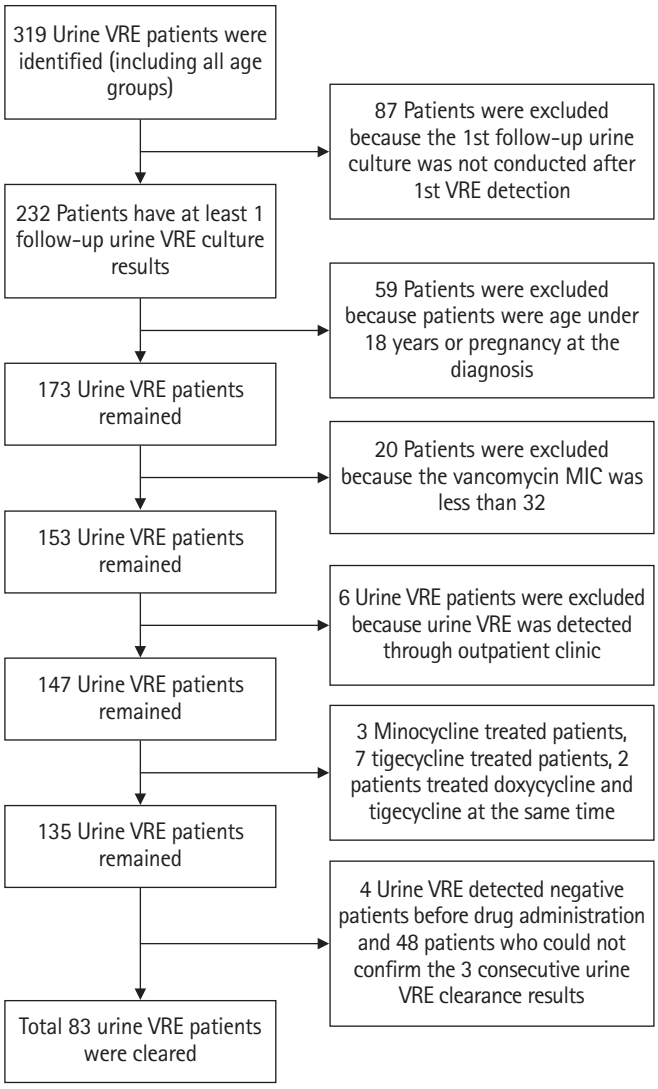

Fig. 1. Number of patients in the study. VRE, vancomycin-resistant *Enterococcus*; MIC, minimum inhibitory concentration.

age at admission; sex; *Enterococcus* species; MIC; department by which urine VRE was detected; infection location; presence of indwelling urinary catheter, double J catheter, and percutaneous drainage (PCD) or percutaneous nephrostomy (PCN) catheter; nearby urinary symptoms when urine VRE was detected; presence of pyuria; death during admission period; presence of bacteremia before urine VRE detection; VRE bacteremia after urine VRE detection; VRE recurrence event; underlying diseases, including hemato-oncologic malignancy, diabetes mellitus (DM), chronic kidney disease with hemodialysis or peritoneal dialysis, cerebrovascular accident (CVA), and degenerative brain diseases (dementia or Parkinson's disease) (Table 1); and information of antibiotics from the initial collection date of VRE-containing urine culture to the confirmation date of urine VRE eradication or the last date of continued urine VRE confirmation (Table 2). Antibiotics administered at least over 2 days were included in the antibiotic use category.

3. Definitions

Sampling was conducted at least once a week, with a median interval of 4 days (range, 3–5 days). The date of urine sample collection was used as the first urine VRE detection date. If the urine culture was positive for vancomycin-sensitive *Enterococcus* or any bacteria or fungi other than VRE, it was considered negative. If VRE was detected after the culture was verified to be VRE-negative at least one time during the same admission period, it was indicative of VRE recurrence. The presence of ≥10 white blood cells per high-power field was indicative of pyuria. The urogenital abnormality group included patients who showed the presence of PCD, PCN, or double J catheter owing to obstructive hydronephrosis.

4. Statistical analysis

All data are presented as median and range. Comparisons between groups were performed using the Kaplan-Meier survival analysis and chi-square test. Factors affecting urine VRE colonization persistence were determined using univariate and multivariate logistic regression analyses. Although the *p*-value (<0.2) was not significant in univariate analysis, clinical factors that could affect VRE persistence were considered simultaneously. In the final regression model, potential confounding variables were simultaneously entered. For all analyses, a *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using R statistics version 3.1 (The R Foundation; https://www.r-project.org).

Results

1. Demographic and clinical characteristics of urine VRE-positive patients

Among 83 patients with a median age of 72 years (interquartile range, 60–79 years), 22 were males (26.5%) and 61 were females (73.5%). Twenty-one patients (25.3%) were included in the doxycycline treatment group. During the same admission period, urine VRE eradication was observed in 55 patients (66.3%), whereas VRE colonization continued in 28 patients (33.7%). The mean duration of urine VRE eradication was 8 days (range, 6–10.5 days). However, after doxycycline treatment, VRE colonization was lower in the treatment group than in the non-treatment group. Among the 55 urine VRE-eradicated patients, 19 patients (90.5%) were in the treatment group and 36 patients (58.1%) in the non-treatment group. Eradication rate was significantly higher in the doxycycline treatment group than in the non-treatment group ($p=0.014$).

E. faecium was identified in 81 cases (97.6%) and *E. faecalis* was identified in two cases (2.4%). The predominantly identified *Enterococcus* species was *E. faecium*. Tetracycline-resistant *Enterococcus* species were found in 15 patients (18.1% of the total enrolled patients): one patient in the doxycycline treatment group (4.8%) and 14 patients in the non-treatment group (22.6%, $p=0.132$). The identified *Enterococcus* species were all susceptible to tigecycline.

Among the total 83 patients, urine VRE was identified in 96.4% and 3.6% of the patients in the general ward and intensive care unit (ICU), respectively ($p=0.726$). Pyuria during hospitalization was observed in eight patients (38.1%) in the doxycycline treatment group and nine patients (14.5%) in the non-treatment group. Statistical significance was confirmed ($p=0.045$).

There were no significant differences between the treatment and non-treatment groups in terms of age, sex, species, infected locations (ward or ICU), underlying diseases, death during hospitalization, VRE recurrence during same admission period, status of hemodialysis, presence or absence dysuria ($p=0.565$), presence or absence of Foley catheter ($p=1.000$), and presence or absence of PCD or PCN ($p=0.207$). During the time from the first urine VRE culture collection to the confirmation of urine VRE-negative result, the use rate of antibiotics other than tetracycline and linezolid was 82.3% (51/62) in the non-treatment group and 71.4% (15/21) in the doxycycline treatment group; however, there was no significant difference between the two groups. In addition, no significant difference in the use of carbapenems, glycopeptides, piperacillin/tazobactam, third-generation cephalosporins, fluoroquinolones, metronidazole, and ampicillin/

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Table 1. Demographic and clinical characteristics of urine VRE-positive patients

Characteristic	Doxycycline treatment (n = 21)	Non-treatment (n = 62)	Total (n = 83)	*p*-value
Age (yr)	73 (63–79)	71.5 (59–79)	72 (60–79)	0.814
Sex				0.970
Male	5 (23.8)	17 (27.4)	22 (26.5)	
Female	16 (76.2)	45 (72.6)	61 (73.5)	
Eradication				0.014
No	2 (9.5)	26 (41.9)	28 (33.7)	
Yes	19 (90.5)	36 (58.1)	55 (66.3)	
VRE recurrence				0.452
No	17 (81.0)	56 (90.3)	73 (88.0)	
Yes	4 (19.0)	6 (9.7)	10 (12.0)	
Total admission days	52.0 (25.0–79.0)	41.5 (24.0–62.0)	43.0 (24.5–68.0)	0.274
Admission days after VRE detection	31.0 (19.0–44.0)	23.5 (12.0–42.0)	26.0 (14.0–42.0)	0.175
Culture follow-up days after VRE detection	4 (3–5)	4 (3–5)	4 (3–5)	0.548
Species				0.992
Enterococcus faecalis	0	2 (3.2)	2 (2.4)	
Enterococcus faecium	21 (100)	60 (96.8)	81 (97.6)	
Tetracycline (MIC)				0.132
R (≥16)	1 (4.8)	14 (22.6)	15 (18.1)	
S (≤2)	20 (95.2)	48 (77.4)	68 (81.9)	
Tigecycline (MIC)				NA
R (≥4)	0	0	0	
S (≤0.25)	21 (100)	60 (100)	81 (100)	
Indwelling catheter at diagnosis				1.000
No	9 (42.9)	26 (41.9)	35 (42.2)	
Yes	12 (57.1)	36 (58.1)	48 (57.8)	
Urogenital abnormality[a]				0.207
No	17 (81.0)	58 (93.5)	75 (90.4)	
Yes	4 (19.0)	4 (6.5)	8 (9.6)	
Pyuria				0.045
No	13 (61.9)	53 (85.5)	66 (79.5)	
Yes	8 (38.1)	9 (14.5)	17 (20.5)	
Dysuria				0.565
No	19 (90.5)	60 (96.8)	79 (95.2)	
Yes	2 (9.5)	2 (3.2)	4 (4.8)	
Hematologic malignancy				0.528
No	20 (95.2)	54 (87.1)	74 (89.2)	
Yes	1 (4.8)	8 (12.9)	9 (10.8)	
Solid tumor				1.000
No	18 (85.7)	55 (88.7)	73 (88.0)	
Yes	3 (14.3)	7 (11.3)	10 (12.0)	
Diabetes mellitus				0.252
No	11 (52.4)	43 (69.4)	54 (65.1)	
Yes	10 (47.6)	19 (30.6)	29 (34.9)	
Chronic kidney disease (HD, PD)				0.491
No	14 (66.7)	48 (77.4)	62 (74.7)	
Yes	7 (33.3)	14 (22.6)	21 (25.3)	
Cerebrovascular accident				1.000
No	15 (71.4)	45 (72.6)	60 (72.3)	
Yes	6 (28.6)	17 (27.4)	23 (27.7)	
Degenerative brain disease				1.000
No	20 (95.2)	58 (93.5)	78 (94.0)	
Yes	1 (4.8)	4 (6.5)	5 (6.0)	

Univariate analysis following doxycycline administration. Values are presented as median (interquartile range), number (%) or mean (range).
VRE, vancomycin-resistant *Enterococcus*; MIC, minimum inhibitory concentration; R, resistant; S, sensitive; HD, hemodialysis; PD, peritoneal dialysis; NA, not available.
[a]Urogenital abnormality group included patients who showed the presence of percutaneous drainage, percutaneous nephrostomy, or double J catheter owing to obstructive hydronephrosis.

Table 2. Comparison of antibiotic use between doxycycline treatment and non-treatment groups

Characteristic	Doxycycline treatment (n = 21)	Non-treatment (n = 62)	Total (n = 83)	*p*-value
Antibiotic use				0.453
Yes	15 (71.4)	51 (82.3)	66 (79.5)	
No	6 (28.6)	11 (17.7)	17 (20.5)	
Carbapenems				1.000
Yes	5 (23.8)	16 (25.8)	21 (25.3)	
No	16 (76.2)	46 (74.2)	62 (74.7)	
Glycopeptides				1.000
Yes	2 (9.5)	7 (11.3)	9 (10.8)	
No	19 (90.5)	55 (88.7)	74 (89.2)	
Piperacillin/tazobactam				0.120
Yes	3 (14.3)	22 (35.5)	25 (30.1)	
No	18 (85.7)	40 (64.5)	58 (69.9)	
Third-generation cephalosporins				0.080
Yes	1 (4.8)	16 (25.8)	17 (20.5)	
No	20 (95.2)	46 (74.2)	66 (79.5)	
Fluoroquinolones[a]				1.000
Yes	4 (19.0)	12 (19.4)	16 (19.3)	
No	17 (81.0)	50 (80.6)	67 (80.7)	
Metronidazole				1.000
Yes	3 (14.3)	7 (11.3)	10 (12.0)	
No	18 (85.7)	55 (88.7)	73 (88.0)	
Ampicillin/sulbactam				0.338
Yes	3 (14.3)	3 (4.8)	6 (7.2)	
No	18 (85.7)	59 (95.2)	77 (92.8)	

Values are presented as number (%).
[a]Fluoroquinolones include ciprofloxacin and levofloxacin.

sulbactam, as well as urine in VRE detection department was observed between the treatment and non-treatment groups. However, urine VRE colonization was the most commonly detected at the neurosurgery department (13/83, 15.7%), followed by the nephrology (11/83, 13.3%), infectious diseases (10/83, 12%), general surgery (9/83, 10.8%), and hemato-oncology (8/83, 9.6%) departments (Supplementary Table 1).

2. Effectiveness of doxycycline treatment in urine VRE-positive patients

The cumulative eradication rates at 5, 10, and 20 days after VRE isolation were determined by the Kaplan-Meier survival curves. Based on the survival period from drug administration day to confirmed eradication day or to the last detection day of continued VRE, the survival of VRE was found to be statistically different between the treatment and non-treatment groups ($p < 0.001$) (Fig. 2). Considering the natural VRE clearance effect due to time lag, we measured the average time (5 days) taken from the urine culture test to the identification of urine VRE colonization. The survival of VRE was found to be significantly different between the two groups ($p = 0.024$). The results showed that the 5-, 10-, and 20-day cumulative eradication rates were 78.3%, 100%, and 100% in the doxycycline treatment group, and 18.5%, 45.7%, and 67.8% in the non-treatment group, respectively, thereby indicating that eradication rates were higher in the treatment group than in the non-treatment group.

Mortality due to VRE infection was not observed in both groups. In the non-treatment group, VRE bacteremia was found in one patient (5%), whereas in the doxycycline treatment group, VRE bacteremia was not detected in any patient. Statistical significance was not confirmed between these two groups ($p = 1.000$) (Table 3).

3. Factors associated with colonization persistence of VRE in urine

Based on the above results, factors affecting the colonization persistence of VRE in urine, including underlying diseases depending on the VRE detection department were analyzed. Results

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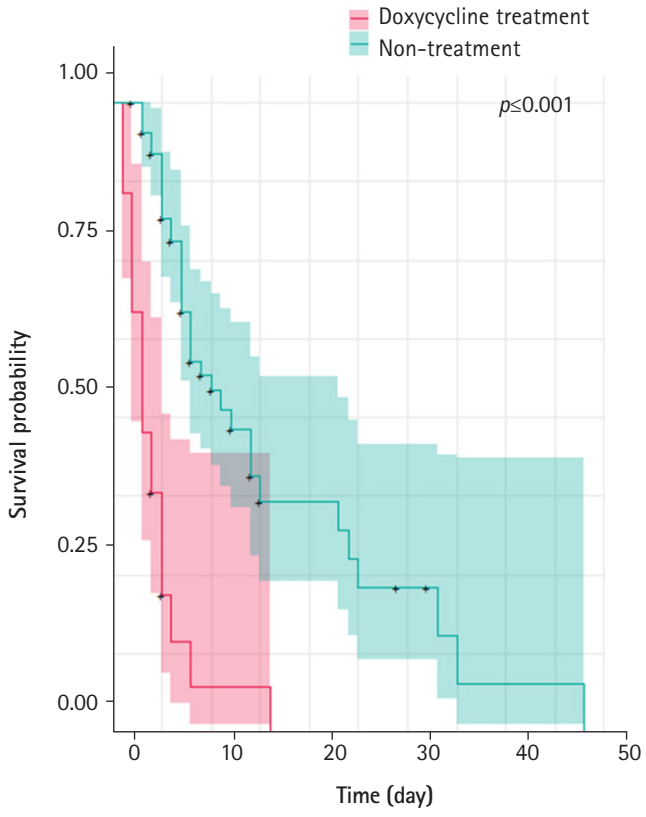

Fig. 2. Survival period from drug administration day to confirmed vancomycin-resistant *Enterococcus* eradication day ($p<0.001$).

showed that the presence of pyuria; indwelling catheter (Foley catheter), PCD, PCN, or double J catheter; bacteremia during admission period; DM; and CVA had no significant effect on urine VRE colonization persistence. Multivariate analysis with *p*-values less than 0.5 revealed that patients over the age of 80 years (odds ratio [OR], 2.42; confidence interval [CI], 0.74–8.25) and patients with underlying solid tumors (OR, 2.46; CI, 0.53–12.25) or hematologic disease (OR, 1.76; CI, 0.36–8.31) showed relatively high odds ratio, although there was no statistical significance. Only the non-treatment group showed an OR of 6.04 (CI, 1.46–41.99), and statistical significance was confirmed ($p=0.028$) (Table 4).

Discussion

This was the first study to show that oral doxycycline treatment affected urine VRE colonization. In our study, oral doxycycline treatment increased the overall eradication rate of urine VRE and enhanced the eradication process. In particular, taking into account the possibility of natural VRE decolonization, our results showed that doxycycline increased the eradication rate regardless of the other antibiotics administered during the same period.

Preservation of antibiotic effectiveness and prevention of adverse effects associated with unnecessary antibiotic use are of utmost importance in all healthcare systems [8]. However, with the emergence of multidrug-resistant pathogens, there are difficulties in the selection of suitable antibiotics.

Eradication of VRE colonization remains a great challenge for infection-control professionals. To reduce or eradicate VRE colonization, various approaches, such as pharmacological treatments, use of bacteriophages, and fecal transplantation, have been previously assessed. However, there are several limitations to the clinical commercialization of these treatment options, and additional studies are needed.

Doxycycline is a bacteriostatic agent that reversibly binds to ribosomal units and inhibits bacterial protein synthesis. Approximately 90%–100% of this drug is absorbed after oral administration [9]. Doxycycline concentration is the highest in the liver, kidney, and digestive tract, which are excretory organs. Doxycycline is eliminated unchanged via both the renal and biliary routes. Approximately 35%–60% of this drug is excreted via urine and the remainder via feces [10]. Peak levels of doxycycline are reached at approximately 2–4 hours after administration. Its plasma half-life is 18–22 hours in adults with normal renal function, and 20–30 hours in patients with severe renal impairment [11].

In the past years, decolonization of the gastrointestinal tract has been investigated as a method for the prevention of VRE infection in vulnerable patient groups. Various oral antimicrobial regimens have been evaluated for gastrointestinal VRE decolonization. Single agents and combinations of several antimicrobial agents have been used [3]. In one prospective observational cohort study, patients were treated with bacitracin solution (75,000 units daily) and doxycycline capsules (100 mg daily) for 14 days. At the end of the 14-day treatment period, all 15 treated patients (100%) showed stool VRE clearance, with only eight of the untreated patients (33%) were VRE-free. However, there was no difference in the frequency of intermittent or persistent VRE colonization at 4 months between the two groups, suggesting that oral bacitracin and doxycycline treatments were not effective in reducing the carriage of VRE beyond the 2-week interval and did not exert a long-term effect on VRE colonization [7]. In our study, 100 mg doxycycline was administered orally twice a day, which was double the dose administered in previous studies. In addition, the median time for urine VRE eradication was identified to be 8 days, which was shorter compared with that in former rectal swab VRE studies. Moreover, we could not identify the persistence or eradication

Table 3. Comparison between mortality rates and bacteremia state in urine VRE patients

Characteristic	Doxycycline treatment (n = 21)	Non-treatment (n = 62)	Total (n = 83)	*p*-value
Infection location				0.726
Ward	21 (100)	59 (95.2)	80 (96.4)	
ICU	0	3 (4.8)	3 (3.6)	
VRE detection department[a]				1.000
Surgery[b]	7 (33.3)	21 (33.9)	28 (33.7)	
Non-surgery[c]	14 (66.7)	41 (66.1)	55 (66.3)	
In-hospital mortality				1.000
No	19 (90.5)	56 (91.9)	75 (90.4)	
Yes	2 (9.5)	6 (9.7)	8 (9.6)	
Mortality within 6 months after urine VRE detection				1.000
No	17 (81.0)	52 (83.9)	69 (83.1)	
Yes	4 (19.0)	10 (16.1)	14 (16.9)	
Mortality due to VRE infection				NA
No	21 (100)	62 (100)	83 (100)	
Yes	0	0	0	
VRE bacteremia				1.000
Yes	0	1 (1.6)	1 (1.2)	
No	21 (100)	61 (98.4)	82 (98.8)	
Bacteremia[d] during admission				0.191
Yes	3 (14.3)	20 (32.3)	23 (27.7)	
No	18 (85.7)	42 (67.7)	60 (72.3)	
Bacteremia[d] identified after urine VRE detection				0.361
Yes	1 (4.8)	6 (9.7)	7 (8.4)	
No	20 (95.2)	52 (83.9)	72 (86.7)	
Same time	0	4 (6.5)	4 (4.8)	

Values are presented as number (%).
VRE, vancomycin-resistant *Enterococcus*; ICU, intensive care unit.
[a]Supplementary Table 1. [b]Surgery departments include colorectal surgery, urology, plastic surgery, neurosurgery, general surgery, breast and thyroid surgery, and vascular surgery departments. [c]Non-surgery departments include endocrinology, rheumatology, gastroenterology, cardiology, nephrology, infection, emergency, rehabilitation, and neurology departments. [d]Bacteremia regardless of bacterial species, including VRE.

Table 4. Univariate and multivariate logistic regression analyses of risk factors for urine VRE colonization persistency

Risk factor	Urine VRE colonization (n = 83)			
	Univariate OR		Multivariate OR	
	95% CI	*p*-value	95% CI	*p*-value
Age (>80 yr)	2.42 (0.83–7.15)	0.105	2.42 (0.74–8.25)	0.1463
Doxycycline non-treatment	6.86 (1.78–45.45)	0.014	6.04 (1.46–41.99)	0.0279
Presence of pyuria	0.54 (0.14–1.72)	0.323	-	-
Presence of indwelling catheter (Foley catheter)	0.77 (0.31–1.94)	0.575	-	-
Presence of PCD, PCN, or double J catheter	0.25 (0.01–1.54)	0.211	-	-
Bacteremia[a] during admission period	0.94 (0.35–2.67)	0.901	-	-
Solid tumor	2.17 (0.56–8.55)	0.254	2.46 (0.53–12.25)	0.2496
Hematologic malignancy	1.67 (0.38–6.86)	0.475	1.76 (0.36–8.31)	0.4692
Diabetes mellitus	0.83 (0.31–2.15)	0.703	-	-
Chronic kidney disease (HD, PD)	0.77 (0.28–2.17)	0.625	-	-
Cerebrovascular accident	0.81 (0.28–2.23)	0.694	-	-

VRE, vancomycin-resistant *Enterococcus*; OR, odds ratio; CI, confidence interval; PCD, percutaneous drainage catheter; PCN, percutaneous nephrostomy catheter; HD, hemodialysis; PD, peritoneal dialysis.
[a]Bacteremia regardless of bacterial species, including VRE. Results from the finally selected model were presented in multivariate OR column.

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of gastrointestinal VRE. Because our study was conducted retrospectively, a rectal swab culture was not routinely performed during the study period. However, our study presented the possibility of reducing the propagation of surrounding contaminations caused by urine VRE.

It is challenging to assess the clinical significance of VRE in routine cultures or to differentiate colonization from infection, especially when VRE is detected in urine as part of a polymicrobial infection, as it is a colonizer of the genitourinary tract and often results in asymptomatic bacteriuria [12]. A previous retrospective study showed that most patients with VRE bacteriuria were classified as colonization and asymptomatic bacteriuria, and only 25% of patients with VRE bacteriuria required antibiotic therapy. Moreover, among urine VRE strains, *E. faecium* was identified in the urine culture of 99 patients (68.8%), whereas *E. faecalis* was identified in 45 patients (31.2%) [13]. In our study, *E. faecium* was identified in the urine culture of 81 patients (97.6%), whereas *E. faecalis* was identified only in two patients (2.4%). Pyuria was identified in 17 patients (20.5%). The accuracy of this result might have been affected by previous use of other antibiotics. However, most of the patients did not have urinary symptoms, indicating that the risk of VRE urinary tract infection (UTI) is low, and most of the urine VRE-positive patients in hospitals can be considered positive for VRE colonization.

When VRE is detected in urine culture samples, if there are no signs of UTI; thus, waiting for natural decolonization or discontinuation of antibiotics within a short time can be considered. However, in certain clinical situations, such as when the cause of the infection is unclear, when persistent long-term antibiotic treatment is required, or when VRE is continuously identified in severely ill patients with immunocompromised diseases in a hospital setting, the need for antibiotic administration might arise. Environmental contamination can increase the risk of VRE acquisition [14]. VRE can be transmitted from patient to patient any time; therefore, careful contact precautions must be taken. Our study showed that doxycycline treatment for urine VRE colonization was effective in shortening the urine VRE isolation period; however, considering the natural urine VRE decolonization period, decolonization treatment must be administered to carefully selected patients who need it.

A previous study showed that 4% (31/768) of all VRE-colonized patients developed VRE blood stream infection (BSI), and the independent risk factors for death included immunosuppression and VRE BSI [15]. VRE infections tend to occur in more debilitated or seriously ill hospitalized patients. Mortality rate in patients with VRE BSI can reach up to 70% [16-18]. In our study, VRE BSI was detected in 0.012% of the patients (1/83). VRE BSI was not detected in the doxycycline treatment group, but was detected in one patient with myelodysplastic syndrome who did not receive doxycycline treatment. Furthermore, no deaths were observed in all patients regardless of doxycycline administration. However, previous studies have reported that patients with neutropenia, organ transplants, dialysis, or hematologic malignancy are at a high risk of experiencing prolonged bacteremia or death due to VRE infection [19,20]. Doxycycline treatment for urine VRE decolonization might have protective effects against severe bacteremia in certain high-risk patients, but further prospective studies are needed for verification. According to a recent study, stool VRE colonization appears to be an independent risk factor for *Clostridioides difficile* infection recurrence [21]. Therefore, decolonization of the gastrointestinal tract, the primary reservoir for VRE, might be useful in certain immunocompromised patients with hematologic diseases or those who have undergone organ transplantation. In our study, a rectal swab study was not performed. However, if urine VRE is detected in patients positive for rectal swab VRE, doxycycline treatment can be considered, as doxycycline is also excreted via feces.

As our results did not allow us to conclude whether doxycycline treatment prevented sepsis development, further prospective studies with a larger number of patients should be performed to validate this relationship and the pathophysiology between VRE eradication and doxycycline. We hypothesize that, by reducing urine VRE colonization, doxycycline treatment may reduce the number of deaths due to VRE bacteremia.

Cephalosporin antibiotics have become a major part of the antibiotic formulary of hospitals, and are prescribed for various infections, including UTI. Prior use of cephalosporin antibiotics is a major risk factor for enterococcal infections [22,23]. The most common infections caused by VRE are UTIs, bacteremia, and wound infections [24]. Risk factors for VRE acquisition include colonization pressure, use of antimicrobials, old age, diabetes, installation of a urinary catheter, severe illness (especially end-stage renal diseases requiring dialysis), cancer, and previous transplants [25]. In our study, once urine VRE was acquired, among the modifiable factors, Foley catheter change did not lower urine VRE persistence rate, whereas doxycycline administration decreased VRE colonization and persistency rate. Hence, for patients requiring continuous immunosuppressive therapy and continued use of restriction antibiotics, urine VRE can be considered as a therapeutic target. Current guidelines regarding asymptomatic bacteriuria or VRE-associated urinary colonization are observation without any pharmacological treatment. Specific management guidelines for urine VRE for various population groups have not been published. This study provided information that might help elucidate

the pharmacological treatments needed for certain patient groups.

However, this study had several limitations. First, this was a single-center study with a relatively small study population. Second, as this was a retrospective study, we could not perform rectal swab cultures. When urine VRE was detected, stool samples were not collected at the same time. Hence, further studies are required for simultaneous stool and urine VRE screening. Third, the follow-up urine culture time was not consistent. We followed the revised guidelines of the Korea Centers for Disease Control and Prevention on VRE management [26]. According to the guidelines, culture follow-up intervals range from 3 days to 1 week, but in our study, culture follow-up time showed an irregular tendency. If the culture follow-up interval is long, there may be a difference in VRE eradication rate due to the longer duration taken to obtain negative culture results. However, no significant difference in the average culture interval was observed between the doxycycline treatment and non-treatment groups. Additional prospective studies are needed to further validate our results.

The current VRE isolation criterion is the confirmation of three consecutive negative VRE surveillance cultures conducted at least once a week. To date, VRE decolonization studies are usually conducted at 1-week intervals. However, in a typical clinical setting where isolation rooms are limited, culture trials are often implemented at least twice a week on average after VRE confirmation. Here, we established a model that mimicked an actual clinical setting. Our study included severely ill patients who were subjected to continued antibiotic use, and our results showed that additional doxycycline treatment significantly increased urine VRE eradication rate.

In conclusion, doxycycline treatment for urine VRE colonization appeared to be useful in shortening the urine VRE isolation period, reducing the risk for further nosocomial spread of VRE, and lowering the need for prolonged isolation. Achieving a high eradication rate can shift the treatment paradigm and offer clinicians an alternative to the traditional anti-VRE agents for the management of urine VRE colonization. Moreover, identifying appropriate antibiotic therapies for urine VRE colonization might play an important role in improving antimicrobial stewardship.

Acknowledgments

Conflicts of interest

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

Author contributions

Conceptualization: YK, HHC, KTK, SWK; Data curation: YK, SB, SH, SJK, HKP, JML; Formal analysis: YK, KTK, SWK; Methodology: YK, KTK, SWK; Project administration: YK, HHC, SJK, HKP, JML, SWK; Visualization: YK, KTK, SWK; Writing–original draft: YK; Writing–review & editing: YK, HHC, KTK, SB, SH, SJK, HKP, JML, SWK

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Supplementary materials

Supplementary Table 1. Distribution of departments in urine VRE diagnosis

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Fatal progressive right heart failure in a pancreatic cancer patient

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Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare but fatal complication of cancer and causes pulmonary hypertension and acute/subacute right heart failure. PTTM is most commonly associated with gastric cancer and more rarely associated with pancreatic cancer. We report a case of progressive right heart failure associated with clinically diagnosed pancreatic cancer, suggesting PTTM.

Keywords: Pancreatic cancer; Pulmonary hypertension; Right sided heart failure; Thrombotic microangiopathy

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare but fatal complication of cancer [1]. PTTM appears to be caused by unexplained pulmonary hypertension (PH) and acute/subacute right heart failure. PTTM is histo-pathologically diagnosed by pulmonary vascular tumor microembolic nests with activated coagulation and obliterative intimal proliferation [2]. Almost all cases of PTTM, die within a few days or weeks of the onset of dyspnea. Hence, until recently, antemortem diagnosis has been very difficult [3]. In this study, we report a case of clinically diagnosed PTTM complicated with pancreatic cancer.

Case

This study was approved by the Institutional Review Board of Wonkwang University Hospital (IRB No: 2020-03-041).

A 72-year-old female was referred to our hospital with unresolved dyspnea. She had a history of hypertension, diabetes, asthma, and cerebral infarction. Two weeks before admission, dyspnea and cough developed. She was admitted to the local hospital for 10 days and was on antibiotics, including a third generation cephalosporin (ceftriaxone) and carbapenem (meropenem), resulting from suspected pneumonia.

At admission, she had resting dyspnea. Her body temperature was 37.1°C, heart rate 108 beats/min, blood pressure 140/80 mmHg, respiratory rate 24 breaths/min, and oxygen saturation 84% while receiving oxygen via a nasal cannula at a rate of 5 L/min. Physical examination was notable for crackles without wheezing in the lungs and pitting edema in both lower legs. Arterial blood gas analysis showed pH 7.33, PCO_2 52 mmHg, PO_2 56 mmHg, HCO_3^- 20.6 mM/L, and O_2 saturation 84.6%. Laboratory tests revealed the following values: white blood cell count 8,840/μL, hemoglobin 11.2 g/μL, platelet count 393 K/μL, total bilirubin 0.17 mg/dL, aspartate aminotransferase 20 IU/L, alanine aminotransferase 14 IU/L, alkaline phosphatase 97 IU/L (range, 30–120 IU/L), gamma glutamyl transferase 46 IU/L (range, 5–39 IU/L), blood urea nitrogen 29.9 mg/dL, creatinine 0.69 mg/dL,

C-reactive protein 27.57 mg/L (range, 0–5 mg/L), activated partial thrombin time 25.8 sec (range, 23–35 sec), and international normalized ratio 1.15. The level of brain natriuretic peptide and D-dimer were 1,921 pg/mL (range, 0–150 pg/mL) and 5.8 μg/mL (range, 0–0.5 μg/mL), respectively; other laboratory results were unremarkable. Electrocardiogram showed sinus tachycardia at a rate of 110 beats/min, T wave inversion in V1-4, poor R-wave progression, and rightward axis deviation, known as 'right ventricle (RV) strain.'

Transthoracic echocardiography (TTE) (Fig. 1) showed RV dilatation with reduced systolic function, moderate tricuspid valve regurgitation (proximal isovelocity surface area radius, 5.1 mm; jet area, 7.5 cm^2), left ventricle septal flattening during the systolic phase, inferior vena cava plethora, and moderate PH (pulmonary artery systolic pressure [PASP], 65.7 mmHg; mean pulmonary arterial pressure, 44 mmHg) without obvious atrial or ventricular septal defect. Left ventricular systolic function was preserved with an ejection fraction of 71%. Contrast–enhanced chest computed tomography (CT) with pulmonary arteriography was performed. CT showed the presence of multiple small consolidative lesions in both lung fields without evidence of pulmonary thromboembolism. A pulmonary function test showed moderate obstructive lung defect with good response to bronchodilator (forced expiratory volume in 1 sec [FEV_1]/forced vital capacity [FVC] 78%, pre-FEV_1 0.79 L, 43%→post-FEV_1 0.99 L, 58%). A 15% decrease in the diffusing capacity of the lung for carbon monoxide was noted.

Given these findings, right-sided heart failure originating from untreated asthma and acute decompensation caused by community-acquired pneumonia was suggested as the initial diagnosis. However, despite antibiotics and proper diuretic-based heart failure therapy, her dyspnea gradually worsened. On the 12th hospital day (HD), oxygen was supplied using a high flow nasal cannula (FiO_2, 0.4; flow, 40 L/min), and oxygen saturation was maintained within the range of 90%–95%.

On the 14th HD, contrast-enhanced whole-body CT and ventilation/perfusion lung scans were performed to determine the cause of clinical deterioration. Chest CT showed numerous centrilobular nodules with "tree-in-bud" sign and pleural- enhancing nodules (Fig. 2A). Abdominopelvic CT showed a 3-cm less enhancing mass with ill-defined margins located at the pancreatic head and neck region, in addition to upstream pancreatic duct dilatation (Fig. 2B). A ventilation lung scan showed no significant decreased activity while a perfusion lung scan revealed multifocal peripherally distributed small perfusion defects in the bilateral lung fields (Fig. 3). Moreover, serum carbohydrate antigen 19-9 level was elevated 77.9 U/mL (range, 0–35 U/mL); therefore, an endoscopic ultrasonographic-guided biopsy was needed for histopathological confirmation of pancreatic cancer. However, it was impossible to obtain the biopsy due to the unbearable severe dyspnea and opposition of the patient's family. ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography integrated with computed tomography (FDG-PET/CT) was performed for diagnosis and staging of pancreatic cancer after discussion with the Pancreatobiliary Department (Fig. 4). This test showed an intensive hypermetabolic mass at the pancreatic head and neck portion with multiple common hepatic, portocaval, aortocaval, hepatoduodenal, para-aortic, left common iliac, mediastinum, right lower paratracheal, and right interlobar lymph node metastases in addition to numerous tiny bilateral lung and both pleural metastases.

According to these clinical and radiologic findings, PTTM sec-

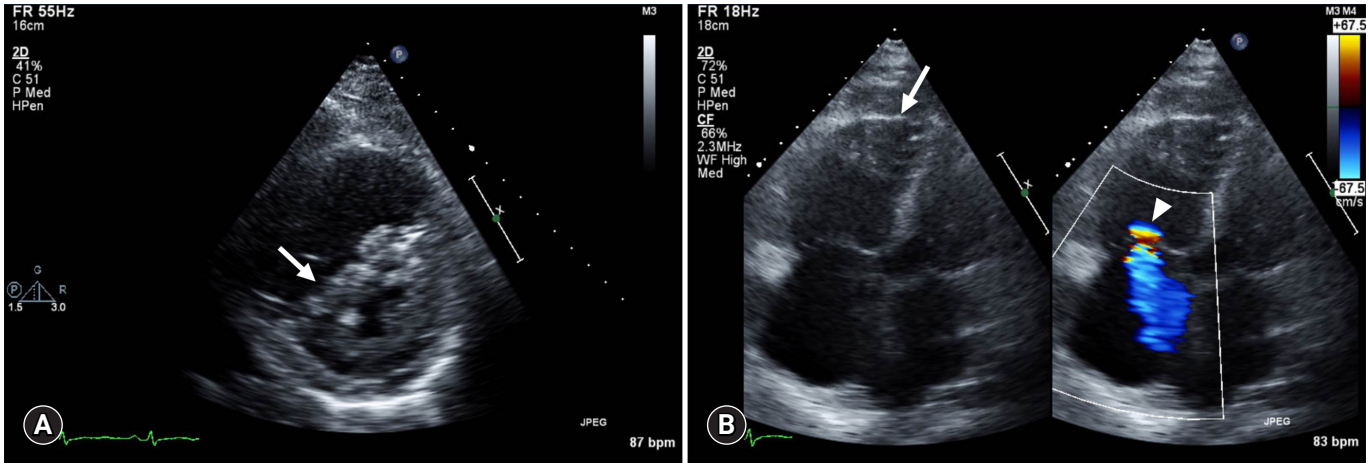

Fig. 1. Transthoracic echocardiography. (A) Parasternal short-axis view shows LV systolic septal flattening (arrow) with RV enlargement. (B) Apical 4 chamber view with color Doppler of the tricuspid valve shows RV enlargement (arrow) and moderate tricuspid regurgitation (arrowhead). LV, left ventricle; RV, right ventricle.

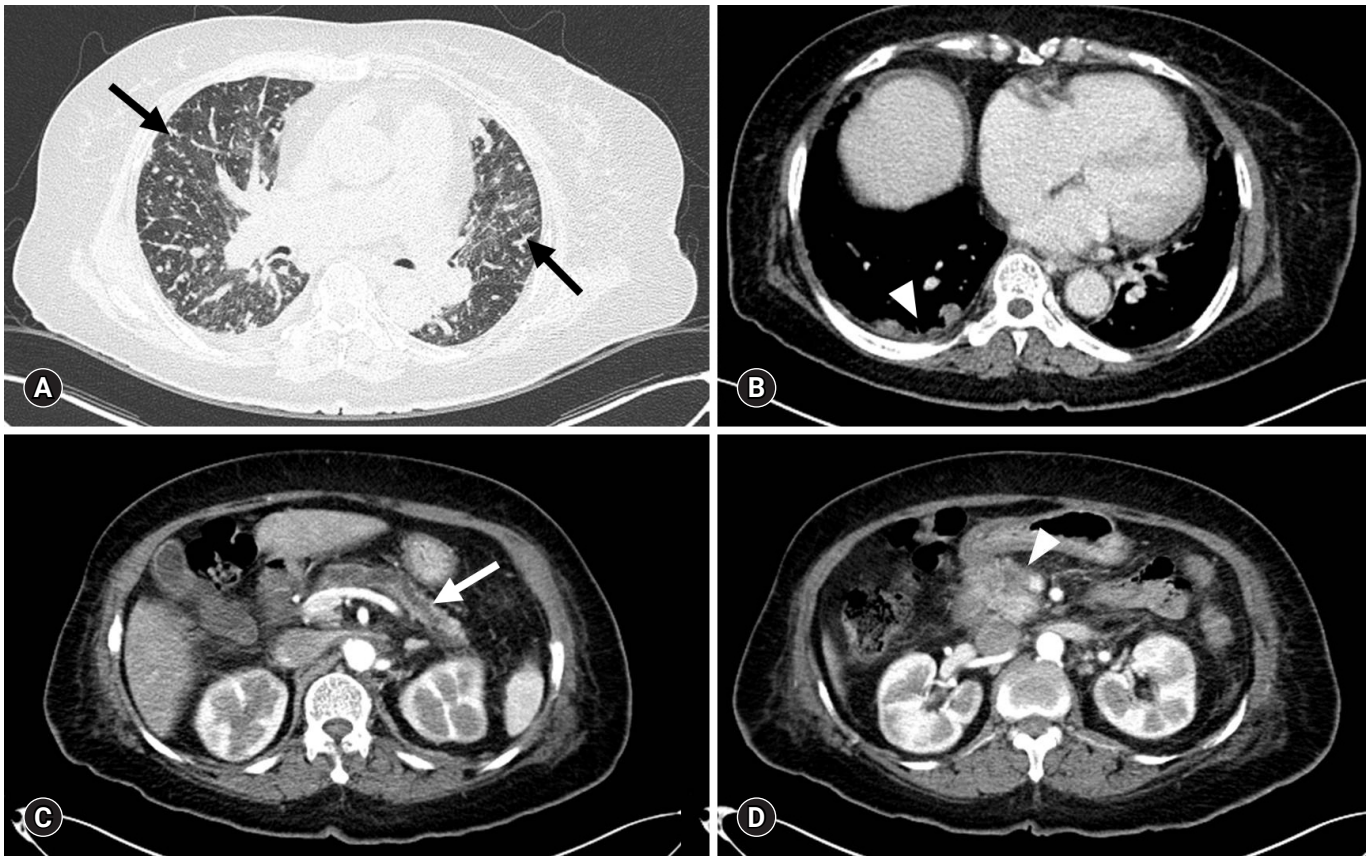

Fig. 2. Contrast-enhanced CT. (A) Chest CT (lung window) with centrilobular nodules with "tree-in-bud" sign (arrows). (B) Chest CT (mediastinal window) with pleural-enhancing nodules (arrowhead). (C) Abdominopelvic CT show upstream pancreatic duct dilatation (arrow). (D) Abdominopelvic CT with pancreatic head neoplasm (arrowhead). CT, computed tomography.

ondary to advanced pancreatic cancer was suggested as the final diagnosis. The clinical stage was TxN2M1, stage IV according to the 8th edition of the American Joint Committee on Cancer staging system [4]. Since the disease continuously progressed to multi-organ failure, including respiratory failure and acute kidney injury, only supportive care could be provided, and the patient died on the 27th day after diagnosis.

Discussion

PTTM, a rare complication associated with cancer, which can cause PH and right heart failure, was first described in 1990 by von Herbay et al. [1]. PTTM is histopathologically characterized by the presence of pulmonary vascular tumor microembolic nests with evidence of activation of the coagulation cascade, obstructive fibrointimal proliferation, and ultimately PH [2]. The most common primary malignancy associated with PTTM is gastric cancer, especially histologically mucinous, signet ring cells, and poorly differentiated subtypes [3]. It is known to be associated with a variety of carcinomas such as lung, breast, ovarian, and bladder cancers, in that order [5,6]. However, cases with pancreatic cancer are relatively rare. Including our case, there have only been four reported cases associated with pancreatic cancer [6].

Clinical manifestations of PTTM are vague and may include a dry cough, dyspnea, and hypoxemia which are common symptoms in various cardiopulmonary diseases. Clinical suspicion is crucial because these can interfere with accurate diagnosis of PTTM. Most cases of PTTM were diagnosed postmortem with ~79% of reported PTTM due to rapidly aggravating clinical course and fatal prognosis. PTTM tends to be under-diagnosed as most patients' families do not request an autopsy [7].

In laboratory tests, elevations of D-dimer, anemia, thrombocytopenia, and elevation of serum lactate dehydrogenase are the most common elevations but are non-specific [7]. In radiologic studies, centrilobular nodularity, ground glass opacity, and interlobular septal thickening have been reported in high resolution CT as in this case, but these findings may be seen in other lung diseases such as interstitial pneumonia [2]. On lung perfusion scans, perfusion defects distributed bilaterally may be observed unlike pulmonary thromboembolism which is limited by the vas-

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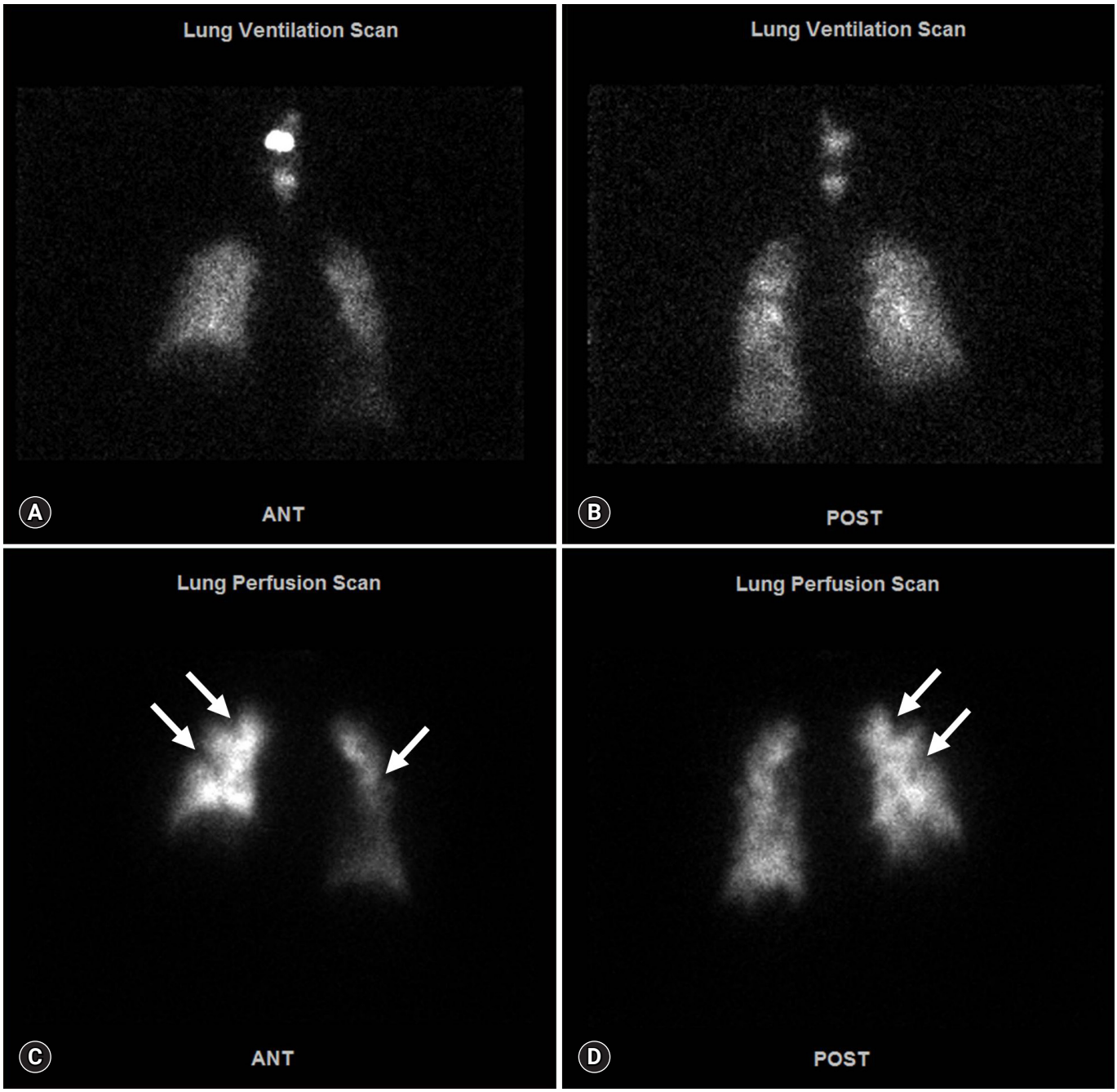

Fig. 3. Ventilation/perfusion lung scan. Anterior view (A) and posterior view (B) of ventilation lung scan present no significant decreased ventilation activity. Anterior view (C) and posterior view (D) of perfusion lung scan show multifocal peripherally distributed small perfusion defects in bilateral lung fields (arrows).

cular distribution. FDG-PET/CT can be effective for the diagnosis of primary malignancy. In PTTM, hypermetabolism of the area which can be confirmed as PTTM via biopsy was observed in FDG-PET/CT, but negative findings may be seen in small lesions or some subtypes such as the signet ring cell type [2]. TTE should be performed as soon as possible to determine the extent of PH and RV dysfunction; however, there is no evidence based on TTE to distinguish PTTM from other causes of PH. In the present case, the patient was also initially misdiagnosed with pneumonia accompanied by cor pulmonale which delayed PTTM diagnosis since there were no clinical indications of malignancy. Although contrast-enhanced whole-body CT and ventilation/perfusion lung scans were done almost concurrently and malignancy in addition to PTTM was diagnosed in a short inter-

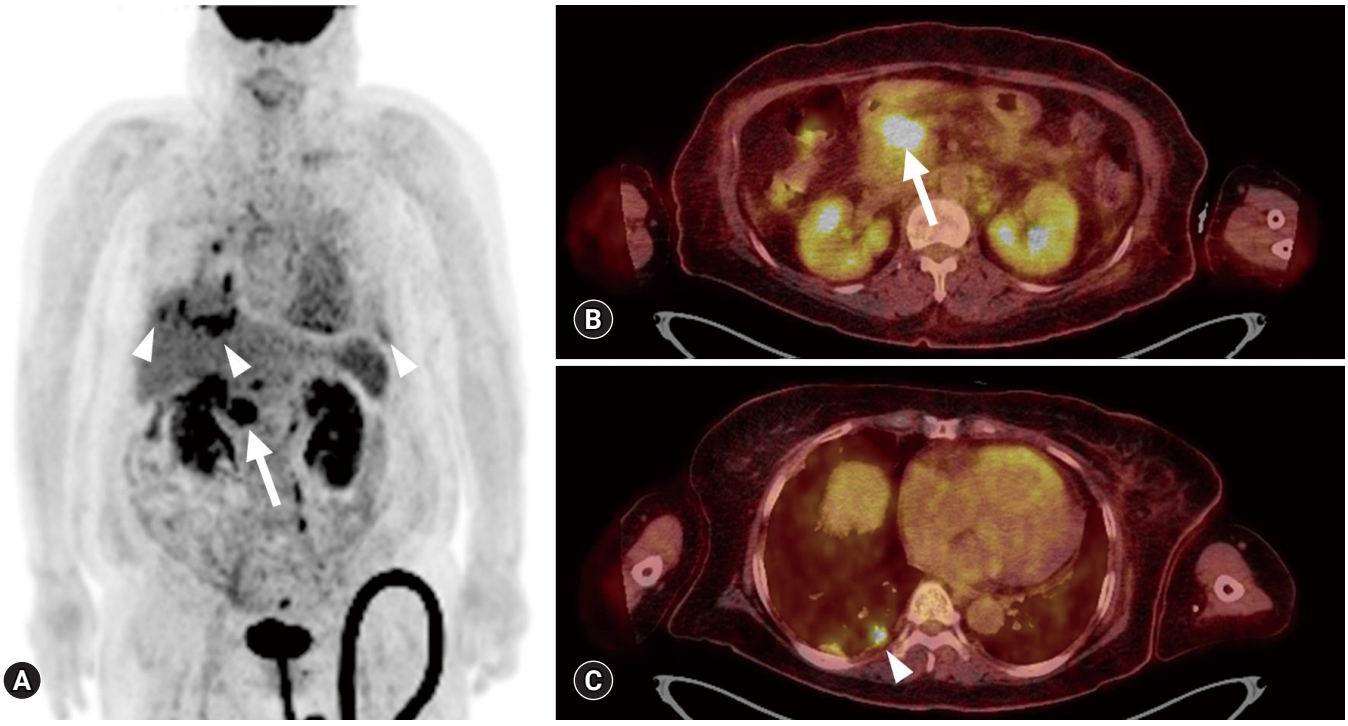

Fig. 4. ^{18}F-2-fluoro-2-deoxy-D-glucose-positron emission tomography integrated with computed tomography. Maximum intensity projection image (A) and fusion axial views (B, C) show a hypermetabolic mass at the pancreatic head and neck region (arrow) with systemic lymph nodes, bilateral lung and both pleural metastases (arrowhead).

val, this case identified the need for the thorough evaluation of PH including cancer. This is especially important if a patient with high PASP presents with progressive dyspnea. Prompt diagnosis of the systemic malignancy underlying PTTM should be done so at least it provides an opportunity for treatment with appropriate chemotherapy.

CT-guided lung biopsy, video-assisted thoracoscopic surgery, or bronchoscopy is necessary for histological confirmation of PTTM diagnosis because of the diagnostic limitations of these noninvasive tests. However, the risk of surgery or procedure is very high if accompanied by advanced PH and right heart failure. Alternatively, cytological examination of aspirated blood using a wedged pulmonary artery catheter with a sensitivity of 80%–88% and specificity of 82%–94% can be done. Additionally, if the TTE results are ambiguous, right heart catheterization may be useful for a more accurate assessment of PH [2,7].

To date, all cases reported as PTTM have died, and the average duration from symptom onset to death has been reported to be about 9.5 weeks. Furthermore, the mean duration of death after dyspnea was reported to be 16.2 days. Once the dyspnea occurs, the patient appears to experience rapid deterioration [7,8]. Various therapeutic methods including medical and oxygen therapy have been attempted, but no consensus has been established. It is thought that chemotherapy for primary malignancy reduces fibrointimal proliferation by reducing the number of cancer cells [2]. Thrombolysis is known to have no benefit. Anticoagulation appears to improve prognosis, but the evidence for its efficacy is weak [7]. There is no evidence that endothelin receptor antagonists, such as bosentan and ambrisentan, reduce pulmonary vascular remodeling but can be used to reduce pulmonary vasoconstriction [3]. Dexamethasone has been reported to improve the natural course in a few cases in combination with anticoagulation and chemotherapy [3]. Imatinib, a tyrosine kinase inhibitor that blocks the phosphorylation of the platelet-derived growth factor receptor, may be beneficial for survival. Bevacizumab, a vascular endothelial growth factor inhibitor, may be more effective when combined with imatinib than when used alone [2]. However, since most of these treatments are based on case reports, systematic research will be needed in the future.

In a patient presenting with progressive right heart failure of unknown origin, PTTM should be considered regardless of the presence or absence of known cancer upon high index of suspicion. Although prognosis remains very poor, prompt antemortem diagnosis of PTTM will allow specific and aggressive therapies, such as chemotherapy, to be used and may improve the prognosis in limited cases.

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Conflicts of interest

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

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Extramedullary tanycytic ependymoma of the lumbar spinal cord

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Tanycytic ependymoma is a rare variant of ependymoma that commonly affects the cervical and thoracic spinal cord. It usually arises as intramedullary lesions, and extramedullary cases are extremely rare. We report a case of a 44-year-old woman who was diagnosed with tanycytic ependymoma in her lumbar spine at level 2-3. The tumor mass developed in an intradural extramedullary location. Histopathologically, tanycytic ependymoma can be misdiagnosed as schwannoma or pilocytic astrocytoma. Immunohistochemical findings such as strong positivity for glial fibrillary acidic protein, perinuclear dot-like positive patterns for epithelial membrane antigen, and focal positivity for S100 protein are helpful in diagnosing tanycytic ependymoma. It is important to be aware of this rare tumor to ensure appropriate patient management and accurate prognosis.

Keywords: Ependymoma; Glial fibrillary acidic protein; Lumbar vertebrae; Spinal cord neoplasms

Introduction

Tanycytic ependymoma is a histologically distinct rare subtype of ependymoma and is recognized as a grade II tumor in the latest World Health Organization classification in 2016 [1]. This tumor is usually found in the cervical and thoracic spine as an intramedullary mass but can also rarely present as an extramedullary mass in the lower spine [2]. Diagnosis in this location is difficult because the pathologic features resemble the findings of schwannoma and pilocytic astrocytoma. We present a case of tanycytic ependymoma in the lumbar spine and a brief literature review.

Case

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

A 44-year-old woman with complaints of a 4-year history of progressively worsening low back pain and sensory loss in her lower extremities visited our neurosurgery clinic. Four years prior, she had visited another hospital during which magnetic resonance imaging (MRI) revealed a 6-mm-sized intradural extramedullary mass in her lumbar spinal cord at level 2-3 (L2-3). The well-demarcated solid mass showed high signal intensity on T1-weighted imaging and low-to-intermediate signal intensity on T2-weighted imaging (Fig. 1). Surgery was recommended, but the patient refused. She had been intermittently treated with conservative therapy. However, recently, the pain in her low back, right buttock, and posterior aspect of her calf had aggravated. No muscle weakness or movement impairment was observed. Follow-up MRI showed that the mass had increased to 10 mm at L2-3. Her past medical history was unremarkable. The results of laboratory tests, including complete blood counts and liver and renal function tests, were within normal ranges. Under the preoperative diagno-

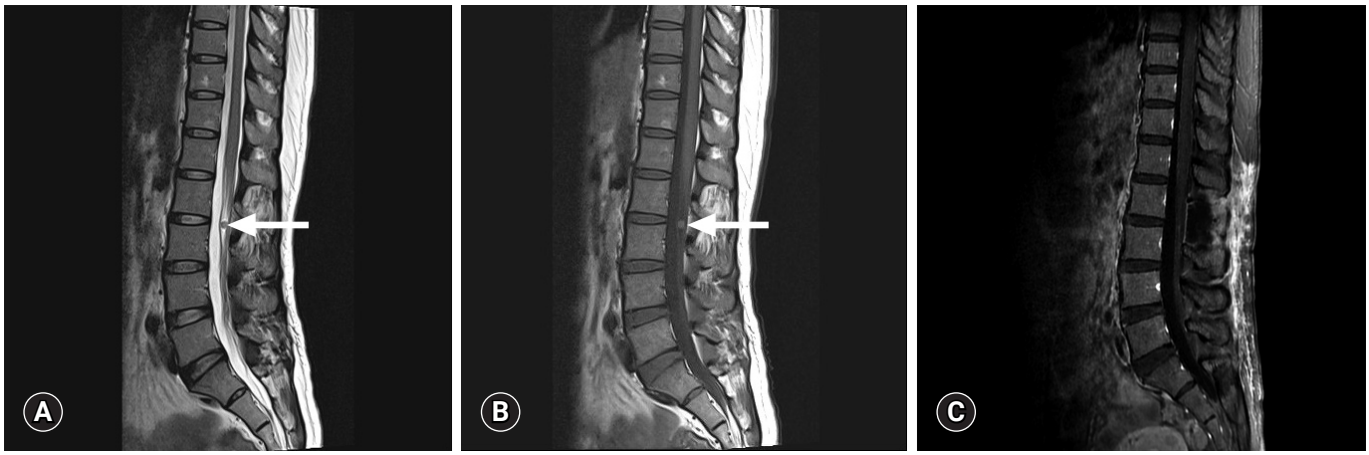

Fig. 1. Magnetic resonance imaging (MRI) findings. (A) Sagittal T2-weighted MR image of the lumbar spine showing a well-demarcated low-to-intermediate signal mass at lumbar level 2-3 spine (arrow). (B) Sagittal T1-weighted image showing high signal intensity (arrow). (C) No evidence of recurrence is visible in follow-up T1-weighted enhanced MRI.

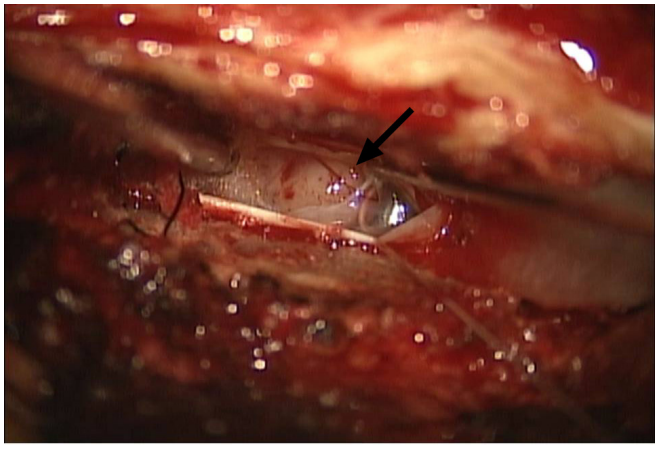

Fig. 2. Intraoperative findings. A well-demarcated tumor mass is visible upon opening of the dura (arrow). The nerve root is close to the mass but can be separated from the tumor surface.

sis of schwannoma, the patient underwent L2 hemilaminectomy. The opening of the dura revealed a well-demarcated tumor mass at the L2-3 spinal cord, which was not attached to the nerve root (Fig. 2). The gross total excision of the mass was performed.

Histopathologic analysis of the tumor mass revealed a non-encapsulated cellular neoplasm comprising short, vaguely intertwining fascicles of spindle cells. The tumor cells had oval or elongated nuclei with rich fibrillary processes resembling pilocytic astrocytoma. The nuclei displayed speckled chromatin and mitotic activity was inconspicuous. Hyalinized blood vessels and occasional perivascular pseudorosettes of elongated tumor cells were also observed (Fig. 3). However, true ependymal rosettes were absent. These histopathologic features resulted in a differential diagnosis including schwannoma, pilocytic astrocytoma, or other spindle cell neoplasm of the spinal cord. Immunohistochemical analyses, including those for glial fibrillary acidic protein (GFAP), vimentin, epithelial membrane antigen (EMA), S100 protein, CD34, and calretinin, showed tumor cells diffusely positive for GFAP and vimentin. S100 protein was focally positive, and EMA showed positive perinuclear dot-like or ring-like patterns consistent with ependymal differentiation (Fig. 4). The tumor cells were negative for CD34 and calretinin. Thus, a definitive diagnosis of tanycytic ependymoma was established. The postoperative results were uneventful, and the patient's symptoms improved.

Discussion

Ependymomas of the spinal cord usually arise within the cervicothoracic segment and are the most common intramedullary neoplasms of adulthood. The typical histopathologic features include a dense meshwork of fibrillary cytoplasmic processes forming perivascular pseudorosettes. Tanycytic ependymoma exhibits distinctive histologic features and was initially described by Friede and Pollak [3] in 1978. The term "tanycytic" refers to the spindle elongated cell morphology and the origin of the tumor cells from tanycytes, which are special and unique ependymal cells. Tanycytes are most commonly located in the wall of the third ventricle, in the circumventricular organs, and in the spinal cord [4]. In the spinal cord, they surround the spinal canal and radiate toward the grey matter. They are considered to participate in the communication between the cerebrospinal fluid, brain parenchyma, and vasculature [5].

Tanycytic ependymomas are commonly found in the cervical

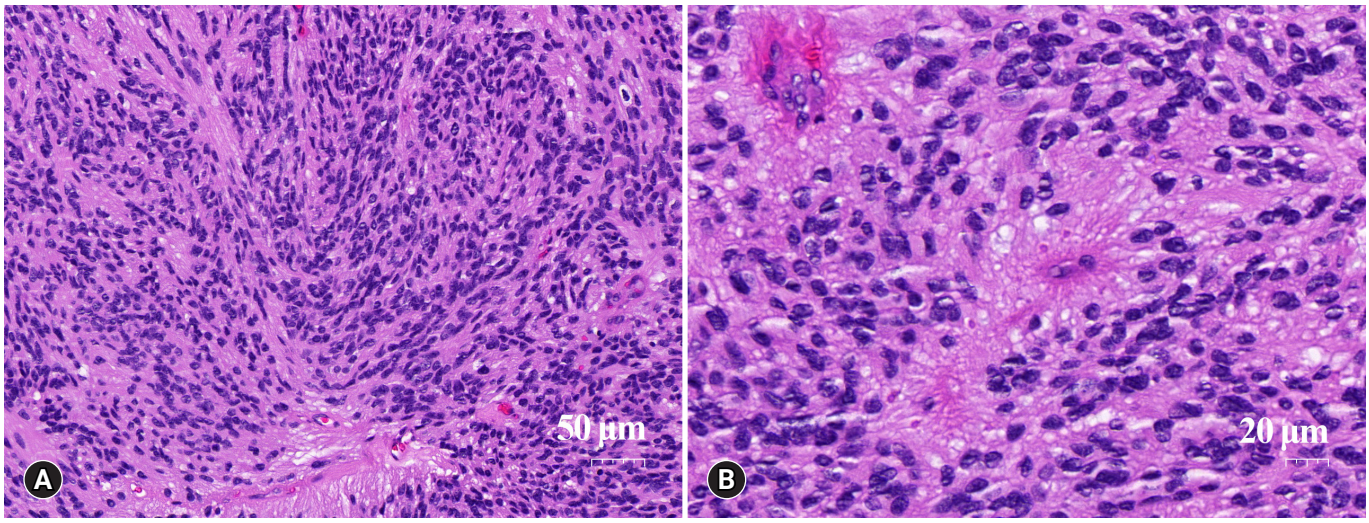

Fig. 3. Microscopic features. (A) Histopathologic analysis showing a moderately cellular neoplasm composed of short fascicles of elongated cells. The tumor cells have bland nuclei with no mitotic figures. The elongated cells are rich fibrillary processes (hemtoxylin and eosin stain, x200). (B) Hyalinized blood vessels and pseudorosettes are seen (hemtoxylin and eosin stain, x400).

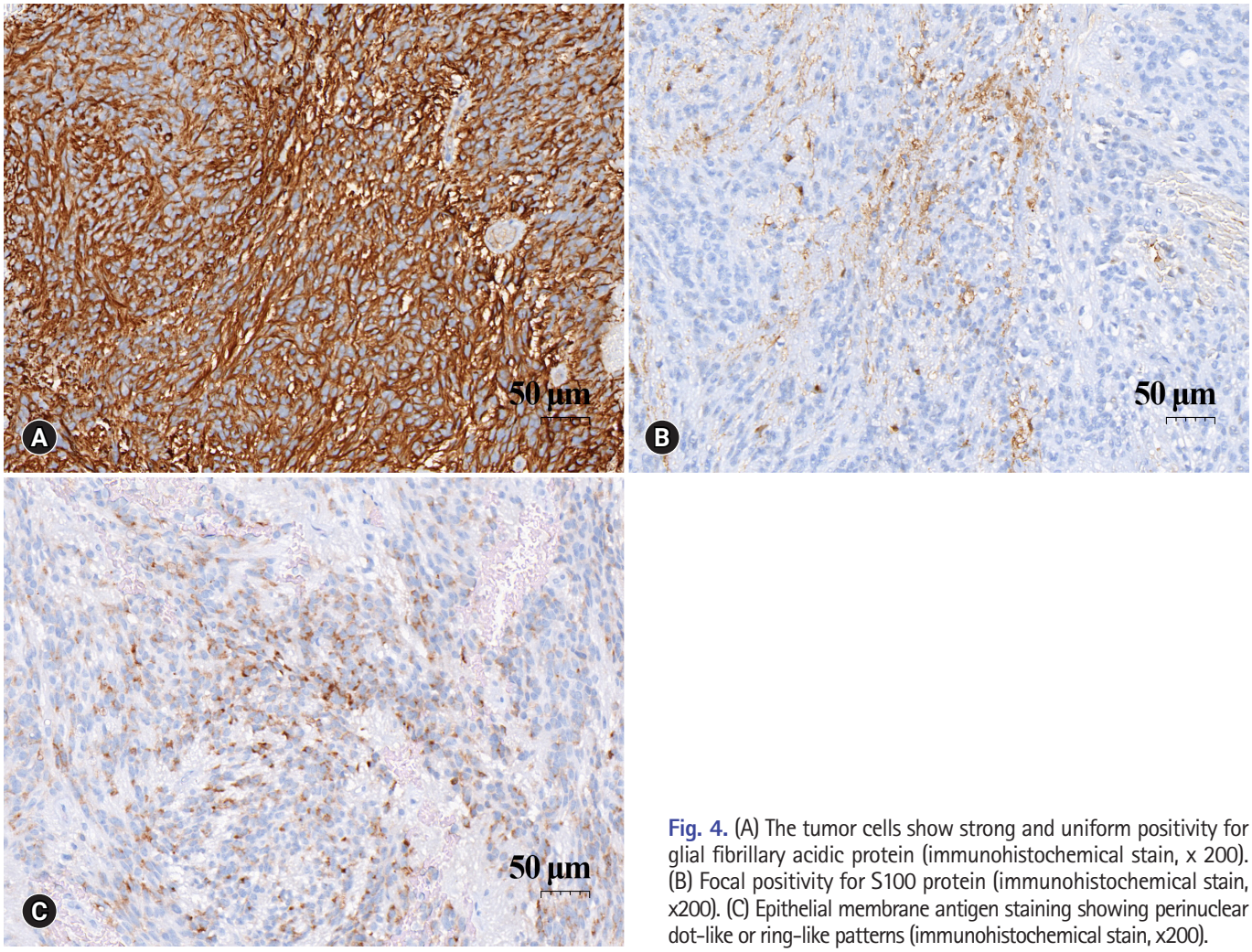

Fig. 4. (A) The tumor cells show strong and uniform positivity for glial fibrillary acidic protein (immunohistochemical stain, x 200). (B) Focal positivity for S100 protein (immunohistochemical stain, x200). (C) Epithelial membrane antigen staining showing perinuclear dot-like or ring-like patterns (immunohistochemical stain, x200).

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and thoracic spinal cord [2,6]. Tumors arising in the lumbar or thoracolumbar regions are very rare [2,4,7-9]. Extramedullary tanycytic ependymomas in the filum terminale are rarely reported [7-9]. According to the 40 cases of spinal cord tanycytic ependymoma reported by Tao et al. [2], only one and four cases were lumbar lesion and in extramedullary locations, respectively. Extramedullary tumors were found in the lower thoracic or lumbar spine. Tanycytic ependymoma accounted for approximately 1% of spinal cord tumors (40 of an estimated 4,000) and one patient had tumor recurrence after surgery. Thus, patients are usually expected to show long-term survival with a low rate of recurrence. Rare cases of tanycytic ependymoma associated with multiple endocrine neoplasia type 1 or neurofibromatosis type 2 have been also reported [7,10,11]. We found only one published case of tanycytic ependymoma in Korea in a Medline search of the English literature [10]. In that case, the patient had neurofibromatosis type 2 and was diagnosed with tanycytic ependymoma of the cervical spine.

The differential diagnosis on radiologic imaging features included schwannoma, neurofibroma, or myxopapillary ependymoma. In this case, the preoperative diagnosis was schwannoma. However, schwannoma may demonstrate more heterogeneous T2 signal hyperintensity. Most of the MRI features in previously reported cases of tanycytic ependymoma were T1-isointense and T2-hyperintense; however, the findings can be variable and non-specific. Therefore, the radiologic diagnosis of tanycytic ependymoma remains challenging. While tanycytic ependymoma is typically solid, cystic components were reported in half of the cases [12].

The histologic features show fascicles of spindle fibrillary tumor cells with low to moderate cellularity that can be misinterpreted as schwannoma, pilocytic astrocytoma, meningioma, or neurofibroma [2,6,12,13]. Myxopapillary ependymoma can be differentiated from tanycytic ependymoma because there are no pathological findings of a papillary arrangement of the tumor cells or deposition of basophilic mucinous materials. Immunohistochemical staining shows strong positivity for GFAP and focal reactivity for S100 protein in tanycytic ependymoma. The perinuclear dot-like or ring-like positive patterns of EMA are a peculiar feature in ependymoma. In contrast, schwannoma is negative for GFAP and EMA and uniformly positive for S100 protein. Moreover, schwannoma tends to be more cellular and has typical Antoni A and B patterns. Pilocytic astrocytoma can resemble tanycytic ependymoma. A pilocytic astrocytoma is strongly positive for GFAP but negative for vimentin. The findings of Rosenthal fibers and eosinophilic granular bodies are helpful in the diagnosis of pilocytic astrocytoma.

A case series of ependymoma reported that the Ki-67 labeling index appeared to be an important prognostic factor [14]. While Ki-67 labeling index values of less than 4.0 have been associated with long survival times, a predictive threshold has not been established [15]. In our case, the Ki-67 labeling index was estimated to be less than 2%. Radiotherapy can be considered for cases with incomplete resection and aggressive treatment such as chemotherapy is usually not indicated. There has been no evidence of tumor recurrence during the 1-year follow-up period after gross total resection (Fig. 1C).

The present case is a rare intradural extramedullary tanycytic ependymoma that developed in the L2-3 spine with slow tumor growth over 4 years. The histopathologic features were unique but accurate diagnosis was challenging and difficult due to unusual location and rarity. The precise diagnosis of tanycytic ependymoma is important because local recurrence is possible.

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Conflicts of interest

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

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Rectus abdominis muscle atrophy after thoracotomy

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Intercostal nerve injury is known to occur during thoracotomy; however, rectus abdominis muscle atrophy has rarely been reported. We describe a 52-year-old man who underwent primary closure of esophageal perforation and lung decortication via left thoracotomy. He was discharged 40 days postoperatively without any complications. He noticed an abdominal bulge 2 months later, and computed tomography revealed left rectus abdominis muscle atrophy. We report thoracotomy induced denervation causing rectus abdominis muscle atrophy.

Keywords: Intercostal nerves; Muscle denervation; Muscular atrophy; Rectus abdominis; Thoracotomy

Introduction

Muscle atrophy observed after abdominal surgery is often attributable to direct muscle injury caused by incisions and sutures, as well as denervation of and reduced blood supply to the affected muscle [1,2]. However, abdominal muscle atrophy is uncommon after thoracotomy. We report a case of rectus abdominis muscle atrophy after left thoracotomy via the 9th intercostal space (ICS).

Case

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

A 52-year-old man was referred to our hospital with acute mediastinitis, empyema, and thoracotomy incision site infection. The patient underwent surgical treatment for esophageal rupture at another hospital, 9 days prior to presentation. On admission, the patient was in a state of septic shock; therefore, we performed emergency left thoracotomy via the previous incision site in the 9th ICS, and primary repair was performed. Three chest tubes were inserted into the 9th and 10th ICS for drainage. The patient's postoperative recovery was uneventful without esophageal leakage and/or wound complications. Owing to turbidity of the drained pleural fluid, we performed saline irrigation of the pleural

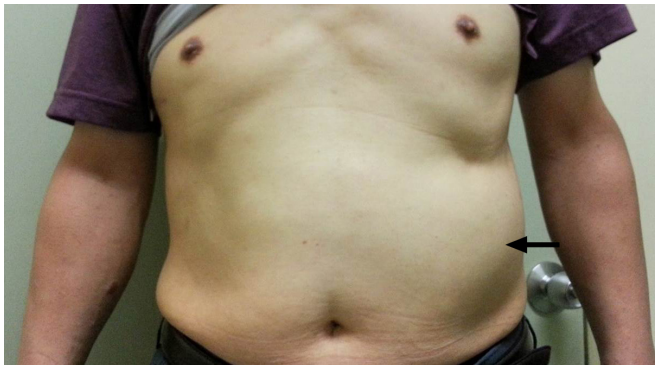

Fig. 1. Photograph of the left rectus abdominis muscle atrophy. The left lateral abdominal wall bulging is present (arrow).

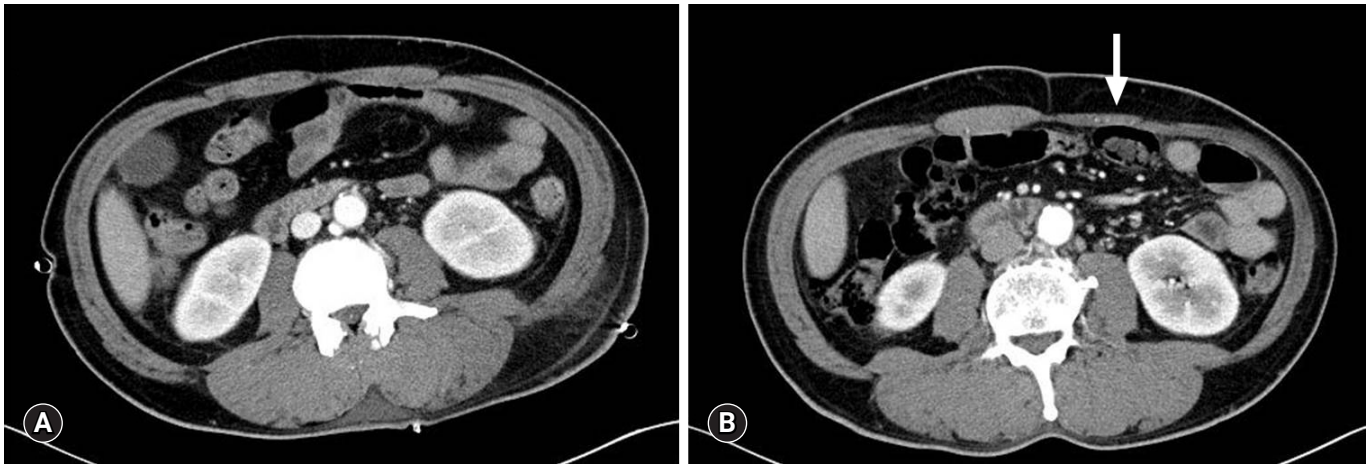

Fig. 2. (A) Preoperative abdominal computed tomography (CT) scan shows normal symmetric rectus abdominis. (B) Follow-up CT scan reveals a flattening of the left side rectus abdominis (arrow).

cavity through the chest tubes over several weeks. He was discharged in a good condition 6 weeks postoperatively. The patient returned 2 months later with a lump in the left anterior abdominal wall (Fig. 1), and we performed abdominal computed tomography (CT) at his follow-up visit. His preoperative CT revealed a normal symmetric rectus abdominis muscle (Fig. 2A); however, follow-up CT revealed flattening of the left rectus abdominis (Fig. 2B). CT confirmed left rectus abdominis muscle atrophy, which was presumably due to intercostal nerve injury during thoracotomy. The degree of intercostal nerve impairment is usually evaluated using electromyography, somatosensory evoked potentials, and assessment of tactile and pain thresholds to electrical stimulation [3]. However, in the present case, we diagnosed this condition based on the patient's clinical presentation and did not perform any other evaluation to assess nerve injury. Anatomically, lower thoracotomy is associated with a risk of rectus muscle paralysis because the rectus abdominis is innervated by the 7th through 12th intercostal nerves [2,4]. Thoracotomy may cause direct or indirect injury to intercostal nerves. Intercostal nerves that are not transected show axonal regeneration at a rate of 1–3 mm/day [5]. However, such nerve regeneration is usually asymmetrical and is associated with unaesthetic outcomes. Therefore, we expect that the nerve regeneration and recover the weakened rectus abdominis.

Discussion

The rectus abdominis muscle originates from the costal cartilages of the 5th, 6th, and 7th ribs and is inserted into the symphysis pubis and pubic crest. This muscle is innervated by anterior branches from the 7th through 12th intercostal nerves [2,4]. The incision made in the chest wall or rib spreading during thoracotomy may cause intercostal nerve injury [6], and such nerve injury can cause muscle paralysis [7]. In our case, left thoracotomy was performed via the 9th ICS and spreading two times; therefore, we conclude that rectus abdominis muscle atrophy was attributable to intercostal nerve injury.

Acknowledgments

Conflicts of interest

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

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Anti-nuclear antibody-negative immunoglobulin G4-associated autoimmune hepatitis mimicking lymphoproliferative disorders

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Immunoglobulin G4 (IgG4)-associated autoimmune hepatitis (AIH) is a very rare subtype of autoimmune hepatitis and characterized by marked elevated serum IgG and hepatic infiltration of IgG4-expressing plasma cells. Pathologic confirmation of hepatic IgG4-expressing plasma cells is usually required for the final diagnosis of IgG4-associated AIH. Herein, we report the case of a 47-year-old female diagnosed with autoantibody-negative IgG4-associated AIH mimicking lymphoproliferative disorders.

Keywords: Autoimmune hepatitis; Immunoglobulin G; Immunoglobulin G4-related disease; Plasma cells; Prednisolone

Introduction

Autoimmune hepatitis (AIH) is an autoimmune liver disease characterized by hypergammaglobulinemia, the presence of serum autoimmune antibodies, and interface hepatitis. AIH is treated with immunosuppressants, including glucocorticoids, with or without azathioprine [1-3]. The diagnosis of AIH is usually made according to a scoring system, such as the Revised International Autoimmune Hepatitis Group (IAIHG) scoring system, due to heterogeneous clinical manifestations [4]. Recently, a new disease entity called Immunoglobulin G4 (IgG4)-associated AIH, which is different from classic AIH, has been described [5]. IgG4-associated AIH, as a subtype of AIH, is a rare disease characterized by the hepatic accumulation of IgG4-expressing plasma cells with markedly elevated serum IgG4 levels [6].

Differential diagnosis involves observation of markedly elevated serum IgG levels, presence of rouleaux formation in the peripheral smear, and low albumin/globulin ratios expressed in mono or polyclonal gammopathy in order to differentiate the condition from lymphoproliferative disorders such as multiple myeloma [7]. We report on a 47-year-old female with autoantibody-negative IgG4-related AIH that mimicked a lymphoproliferative disorder.

Case

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images. This study was approved by the Institutional Review Board of the Yeungnam University Hospital (IRB No: 2020-03-026).

A 47-year-old female visited our clinic for evaluation of abnormal liver function tests on a health-check examination. She had a previous history of a contrast allergy. She did not have any significant symptoms. There were no abnormal findings on physical ex-

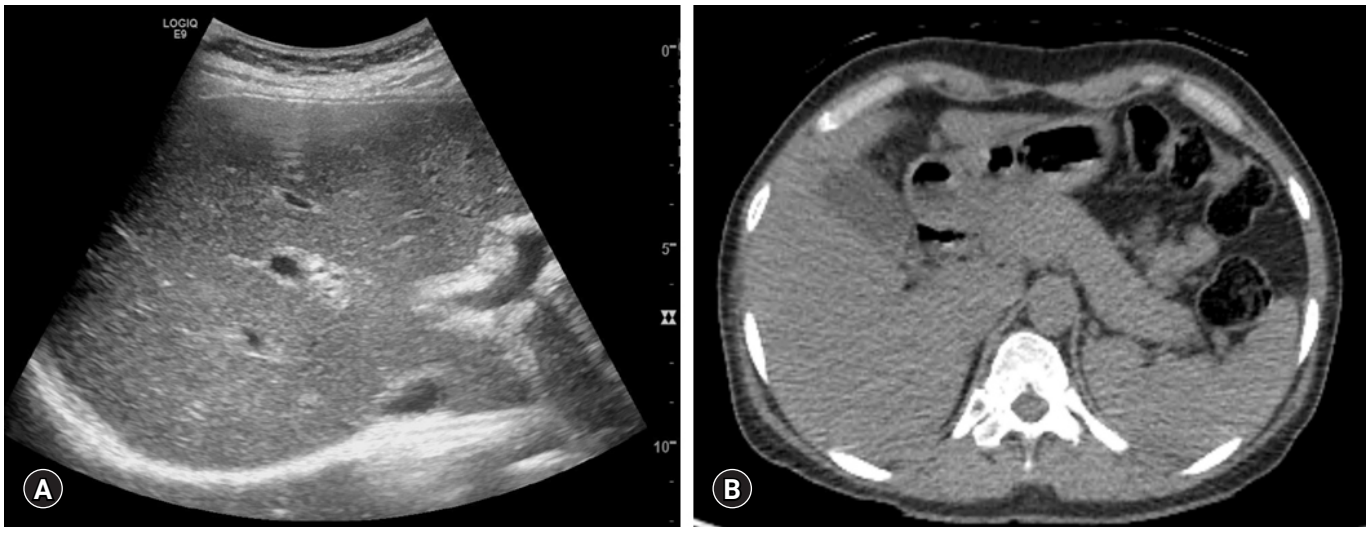

Fig. 1. Abdominal sonography and computed tomography showing (A) increased echogenicity of the liver parenchyma with heterogeneous echotexture and (B) normal pancreas without significant evidence of autoimmune pancreatitis.

amination. Abdominal ultrasound and non-contrast computed tomography revealed coarsened hepatic echotexture, without any biliary duct abnormalities, and no evidence of pancreatitis such as peripancreatic swelling or a sausage-like lesion (Fig. 1). Blood chemistry revealed the following: white blood cells, 3,650/μL; hemoglobin, 12 g/dL; platelets, 294×10^3/μL; serum total protein, 11.03 g/dL; serum albumin, 3.63 g/dL; total bilirubin, 1.02 mg/dL; serum aspartate aminotransferase (AST), 610 IU/L; alanine aminotransferase (ALT), 221 IU/L; alkaline phosphatase (ALP), 102 IU/L; gamma-glutamyl transferase (GGT), 176 IU/L; amylase, 65 IU/L; lipase, 54 IU/L; and prothrombin time-international normalized ratio, 1.12.

Additional serologic tests, including serum hepatitis B surface antigen, hepatitis C antibody, anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-mitochondria antibody, anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal type 1 antibody, and other viral tests—including Epstein-Barr virus and cytomegalovirus—were all negative. However, she exhibited a markedly elevated serum IgG level at 6,614 mg/dL (range, 700–1,600 mg/dL). Peripheral blood smear revealed the rouleaux formation of the red blood cells (RBC).

The patient was referred to the Department of Hematology to evaluate the possibility of a lymphoproliferative disorder, such as multiple myeloma (MM). Serum and urine protein electrophoresis, free light chain ratio, skeletal survey, and bone marrow aspiration were performed. All were normal with the exception of an elevated serum IgG4 subclass level, which was 221.3 mg/dL (range, 6–120 mg/dL).

A percutaneous ultrasound-guided liver biopsy was performed. The pathologic results revealed moderate spotty necrosis and interface hepatitis with highly elevated IgG4-positive plasma cells (10–15/high power field [HPF]), consistent with AIH (Fig. 2). The pretreatment revised IAIHG scoring was 17, consistent with a definite diagnosis of AIH. Detailed IAIHG scoring was as follows: histological feature, 4; no drug and alcohol history, 3; negative findings of viral markers, 3; hypergammaglobulinemia, 3; ALP/AST ratio < 1.5, 2; and female, 2.

Initially, she was treated with 60 mg prednisolone daily, which was tapered by 10 mg prednisolone weekly for 3 weeks. After 3 weeks, her laboratory test results were much improved as follows: AST, 25 IU/L; ALT, 23 IU/L; GGT, 67 IU/L; and IgG, 2,067 mg/dL. Subsequently, 50 mg azathioprine was added for maintenance treatment, and 30 mg prednisolone was tapered by 5 mg weekly for 4 weeks. After 4 weeks, her laboratory test results were slightly worsened as follows: AST, 57 IU/L; ALT, 65 IU/L; GGT, 103 IU/L; and IgG, 1,367 mg/dL. Considering the risk of possible worsening after early prednisone withdrawal, we increased the dose of prednisolone up to 20 mg and then slowly tapered every 2 weeks. After 1 month, all laboratory test results normalized (Fig. 3).

Discussion

In our case, the initial presumptive diagnosis was monoclonal or polyclonal gammopathy, such as MM or other lymphoproliferative diseases, based on the initial serological results including those for inverted albumin/globulin ratio (A/G) ratio (0.33), elevated serum IgG, rouleaux formation of RBC, and negative serologic autoimmune markers. However, based on the results of the

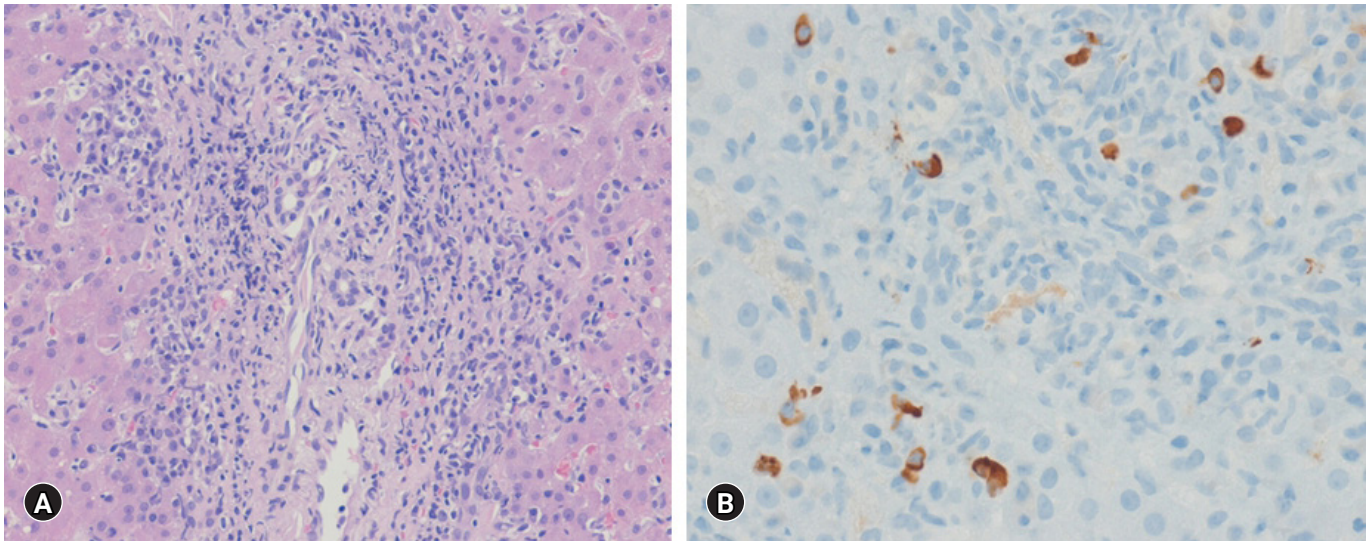

Fig. 2. Histologic findings of liver. (A) Moderate interface hepatitis with lymphocytes and plasma cells infiltration in the portal tract is present (hematoxylin-eosin stain, x200). (B) Immunoglobulin G4-positive plasma cells are seen (immunohistochemical stain, x400).

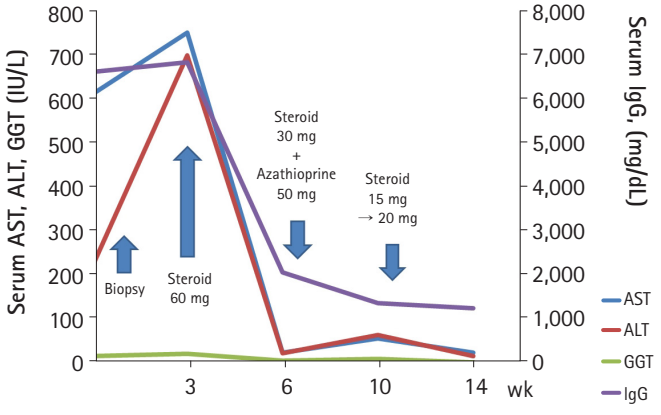

Fig. 3. The clinical course of the patient. AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G.

liver biopsy and elevated serum IgG4 levels, the final diagnosis was IgG4-associated AIH which was treated with prednisolone and azathioprine.

Previous studies of IgG4-associated AIH are summarized in Table 1 [6,8-11]. Recently, a new disease entity called IgG4-associated AIH, which is different from classic AIH, has emerged [5]. Umemura et al. [5,6] had proposed that IgG4-AIH, as a subtype of AIH, is a rare disease characterized by the hepatic accumulation of IgG4-expressing plasma cells (≥ 10 IgG4 plasma cells per HPF) with markedly elevated serum IgG levels (≥ 135 mg/dL). Of the 60 patients with AIH in Japan, only two (3%) were diagnosed with IgG4-associated AIH [6]. The median values of IgG and IgG4 levels were 4,015 mg/dL and 560 mg/dL, respectively. These levels were higher than those of classic AIH (IgG, 2,940 mg/dL and IgG4, 22 mg/dL, respectively) [6]. Also, two patients were diagnosed with IgG4-associated AIH, with positive ANA and SMA (1 of 2 patients), which was defined as a subtype of AIH [6]. In a Western study, based on Umemura's histologic criterion, the prevalence of IgG4-associated AIH was 25% (7 patients). The presence of the autoimmune antibodies was not significantly different from IgG4-associated AIH and classic AIH [8].

In our case, serum IgG and IgG4 levels were 6,614 mg/dL and 221.3 mg/dL, respectively. These markedly elevated IgG levels were four times greater than the normal upper level, which satisfied Umemura's serologic criterion. In the liver, IgG4-bearing plasma cells of 10–15 HPF also met Umemura's histologic criterion for diagnosis of IgG4-associated AIH. Owing to the initially all-negative autoimmune antibody serology, marked elevated hypergammaglobulinemia, and inverted A/G ratio in our case, we preferentially considered a lymphoproliferative disorder such as MM. Though most IgG4-associated AIH had positive ANA or SMA [6,8], the frequency of autoantibody-negative AIH in patients with acute and acute-severe clinical features reached 7% in one study [12]. Therefore, though patients show negative ANA, hypergammaglobulinemia, and elevated liver enzymes, additional serum IgG4 tests would be needed for differential diagnosis of IgG4-associated AIH. Then, when IgG4 is elevated, a subsequent liver biopsy is required for the definite diagnosis of IgG4-associ-

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Table 1. Autoantibody-negative immunoglobulin G4-associated autoimmune hepatitis

Study	Country	IgG4-AIH/autoantibody negative IgG4-AIH (no.)	Diagnostic criteria for IgG4-AIH (IgG4-positive plasma cells/HPF)	IgG/IgG4 levels (median, mg/dL)	IAIHG score (median)	Combination therapy (PD+azathioprine)
Uemmura et al. [6]	Japan	2/0	> 10	4,015/560	17	Yes
Chung et al. [10]	Japan	9/0	> 5	NA	NA	Only PD
Amarapurkar et al. [9]	India	10/NA	> 5	1,600/300 (3 patients)	NA	Yes
Canivet et al. [8]	France	7/NA	> 10	2,500/NA	NA	Yes
Aydemir et al. [11]	Turkey	6/NA	> 10	2,636/NA	17.8	Yes
This case	Korea	1/1	> 10	6,614/560	17	Yes

IgG4-AIH, immunoglobulin G4-associated autoimmune hepatitis; HPF, high power field (x400); IAIHG, International Autoimmune Hepatitis Group; PD, prednisolone; NA, not applicable.

ated AIH, as with our case.

There can be some conflicts regarding IgG4-related disease (IgG4-RD) and IgG4-associated AIH, as noted by several studies [6,8-10]. The clinical features of IgG4-RD, which are similar to elevated IgG and IgG4 levels, include multiple organ involvement with storiform fibrosis. IgG4-RD preferentially affects the pancreas, bile duct, kidneys, and salivary glands, but rarely involves the liver [13,14]. However, it is still uncertain whether IgG4-associated AIH is a subtype of AIH or hepatic involvement of IgG4-RD. In our opinion, when evidence of multiple organ involvement and pathologic storiform fibrosis are not seen, the possibility of IgG4-associated AIH is higher than IgG4-RD.

Complete normalization of ALT and IgG levels is the clinical target for the treatment of AIH [15]. The treatment of IgG4-AIH is not much different from that of AIH, and involves glucocorticoids with or without azathioprine [16]. The efficacy of these treatments could be predicted by the accumulation of plasma cells in the liver [16]. However, some studies reported that the time to return to ALT normalization after administration of glucocorticoids is shorter in patients with IgG4-associated AIH than in those with classic AIH (3.7 months vs. 6.7 months, respectively) [10,11]. In our study, mild flare-up while switching from a glucocorticoid to combination therapy was observed, which may have resulted from rapid tapering of the glucocorticoid dose by 5 mg weekly. The early withdrawal of immunosuppressants could be a risk factor for flares of AIH, which require increased doses of glucocorticoids [15]. Therefore, monitoring intervals should be adjusted according to the individual clinical response, which could be extended to 1–3 months with combination treatment [15].

In conclusion, IgG4-associated AIH should be contemplated in patients with marked hypergammaglobulinemia and abnormal liver function test results, even when the autoimmune test is negative. Liver biopsy should be required for the diagnosis of IgG4-associated AIH in these patients with elevated serum IgG4.

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Conflicts of interest

Joon Hyuk Choi serves as an editor-in-chief of the Yeungnam University Journal of Medicine, but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: MKK, JGP, JHC; Data curation: MKK; Methodology: MKK, JGP; Investigation: MKK, JHC; Resources: JHC; Project administration: JHC; Visualization: JHC; Writing-original draft: MKK; Writing-review & editing: JGP.

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Effective strategy in the treatment of aortobronchial fistula with recurrent hemoptysis

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Aortobronchial fistula (ABF) involves the formation of an abnormal connection between the thoracic aorta and the central airways or the pulmonary parenchyma and is associated with an increased risk of mortality. An ABF typically manifests clinically with symptoms of hemoptysis, and currently, there is a lack of defined guidelines for its treatment. Here, we report the cases of two patients who suffered from recurrent hemoptysis due to ABF with pseudoaneurysm. We propose that removal of the aorta with concomitant lung resection and coverage of the aorta using the pericardial membrane is a definite treatment to lower recurrence of ABF and persistent infection.

Keywords: Aorta; Endovascular procedure; Hemoptysis; Surgery

Introduction

Aortobronchial fistula (ABF) is a rare and devastating complication if left untreated. It involves the formation of an abnormal connection between the thoracic aorta and the central airways or the pulmonary parenchyma and results in fatal complications [1]. With the increasing use of thoracic endovascular repair (TEVAR), the number of patients treated for ABF has increased [2,3]. Most ABFs occur in ill patients; therefore, there is no determined treatment. Conservative non-surgical therapy can result invariably in a fatal outcome from massive hemoptysis or chronic mediastinitis [4], and stent-graft insertion is safe and less invasive. However, there are limitations, and generally there is a higher risk of graft infection with repeated ABFs [4,5]. Here, we present patients with ABFs that have been successfully treated by removal of the aorta, concomitant resection of the lung, and coverage of the aorta using the pericardial membrane to prevent further erosive damage.

Cases

1. Patient consent

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

2. Case 1

A 65-year-old man visited an outpatient clinic with a complaint of recurrent hemoptysis. The patient was diagnosed with ABF with pseudoaneurysm 4 years previously (Fig. 1A) and underwent TEVAR (42×38×150 mm, 40×40×130 mm; S&G Biotech, Seongnam, Korea). Two years post-TEVAR, the patient presented with recurrent episodes of hemoptysis and chills during a routine follow-up visit.

Chest computed tomography (CT) imaging revealed a newly formed type 1a endoleak and an even larger pseudoaneurysm at

the previous stent insertion site (Fig. 1B). To rectify these problems, a hybrid debranching TEVAR was performed on the innominate artery and left common carotid artery (40×40×200 mm; S&G Biotech) via a medial sternotomy. After the second TEVAR, several episodes of sudden hemoptysis occurred that were initially negligible, but the symptoms gradually became severe. The patient was hemodynamically stable; however, mild signs of a systemic inflammatory response were noted. In the emergency department, chest CT revealed a type 1b endoleak from the previous stent-graft with progression of the pseudoaneurysm and lung consolidation with atelectasis (Fig. 1C, 1D).

The patient underwent surgery using extracorporeal circulation via femorofemoral cardiopulmonary bypass (CPB). An approach was made through the 4th and 7th intercostal spaces for proximal and distal graft anastomosis site manipulation, respectively. After removal of the lung adhesion, an opening was made in the pseudoaneurysm. The cut revealed a dark hematoma and inflammatory tissue within the vessel. Dissection between the visceral pleura and the aorta seemed unfeasible due to the large degree of adhesion. The presence of extensive lung hemorrhage and necrotic change led to the decision to entirely remove the affected lesion. Stent-graft removal, 30-mm Hemashield graft replacement, and

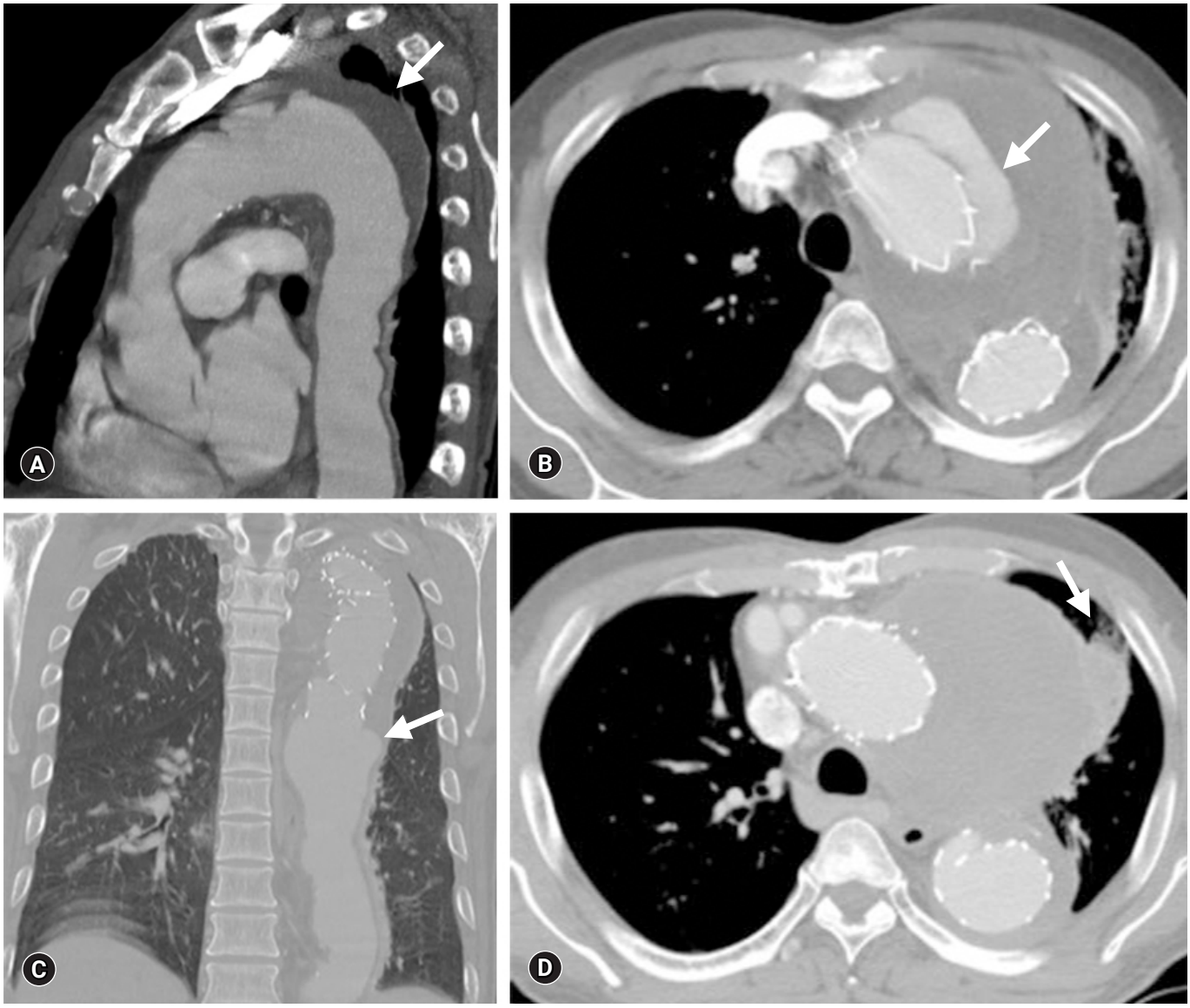

Fig. 1. Chest computed tomography (CT) findings. (A) Initial chest CT shows descending aortic pseudoaneurysm (arrow). (B) Two years later, chest CT reveals a newly formed type 1a endoleak (arrow) and an even larger pseudoaneurysm. (C) Chest CT on admission reveals type 1b endoleak (arrow) from the previous stent with progression of the pseudoaneury sm. (D) Lung consolidation with atelectasis (arrow).

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left apicoposterior-anterior segmentectomy were performed simultaneously. As a preventive measure, space between the stent-graft and pulmonary tissue was packed with the pericardial membrane. The patient's condition gradually improved, and he was discharged on postoperative day (POD) 22 (Fig. 2).

3. Case 2

A 66-year-old man was admitted to our medical center with massive and recurrent hemoptysis over a 4-year period. The patient was initially diagnosed with ABF with pseudoaneurysm and had undergone TEVAR (38×38×150 mm; Valiant Thoracic Stent Graft, Medtronic CardioVascular, Santa Rosa, CA, USA) (Fig. 3A). Two years post-TEVAR, the patient visited our medical center's emergency room with another episode of hemoptysis. A kinking stenosis of the aortic isthmus stent-graft was discovered via chest CT, and a new stent-graft (40×40×80 mm, Valiant Thoracic Stent Graft) was inserted (Fig. 3B).

Furthermore, the patient had displayed malaise, chills, and recurrent hemoptysis at admission; however, there were no clinical or biological signs of infectious disease, and vital signs were stable. There was no evidence of endoleaks via chest CT, but air entrapment within the thrombosed aneurysm and lung consolidation were found (Fig. 3C). Bronchoscopy revealed oozing at the left upper lobe orifice (Fig. 3D).

Due to the possibility of infection, we decided to perform open surgery to remove the ABF causing the hemoptysis. An initial incision was made in the 3rd or 4th intercostal space with the assistance of CPB. There was a severe adhesion between the previously inserted stent-graft and the left upper lobe. Upon exposing the pseudoaneurysm, the affected stent-graft was removed, and a 30-mm Hemashield graft was inserted as a replacement. The left lower lung was relatively well-preserved; however, an apicoposterior segment of the left upper lung was suspected of fistula formation. A left upper lobectomy was performed with coverage of the aorta using the pericardial membrane. After administration of adequate antibiotic therapy for 8 weeks, the patient was discharged after POD 30 with oral antibiotics (Fig. 4).

Discussion

ABF is a rare diagnosis and has a relatively low incidence, ranging from 0.56% to 1.7% [1,2,6]. There are several causes of ABF with persistent or newly developed endoleaks playing a crucial role after TEVAR [1]. The postulated cause of ABF post-TEVAR includes stent-graft coverage of the bronchial arteries leading to ischemic necrosis of the bronchial wall due to stent coverage of the feeding arteries, chronic endoleaks leading to erosion into the adjacent lung, and penetration of the stent-graft through the aortic wall into the lung [7]. In recent years, there has been an increase in the number of patients diagnosed and treated for ABF post-TEVAR [1,7,8]. Pseudoaneurysm as an indication for TEVAR represents a significant risk factor for ABF. Compression of the airways by the pseudoaneurysm may result in a local inflammatory response and the formation of stable adhesions and tissue necrosis, leading to erosion and finally fistulization [2]. In addition, longstanding atelectasis may indicate adherence to the aneurysmal aortic wall that is already lacking elasticity, and external compression of the bronchial tree might also occur [8].

Clinical presentation of ABF can be a display of hemoptysis at any degree [5,9,10]. A diagnosis is primarily determined by CT,

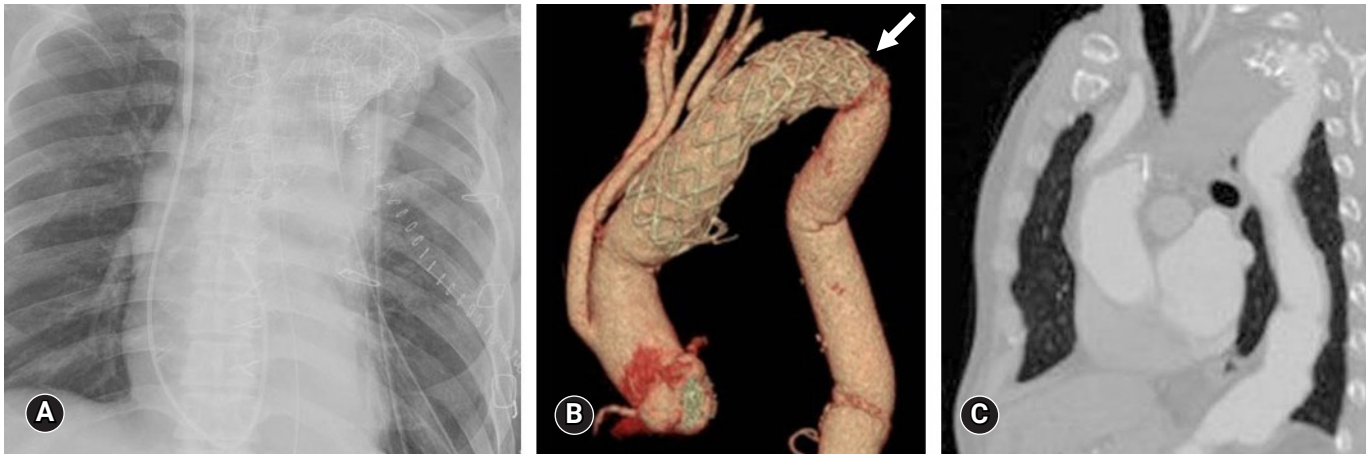

Fig. 2. Postoperative chest radiograph and computed tomography (CT) findings of case 1. (A) Postoperative chest radiograph indicates a well-functioning Hemashield graft. (B) Postoperative chest CT indicates the absence of endoleaks (arrow). (C) Postoperative chest CT confirms the absence of a lung lesion.

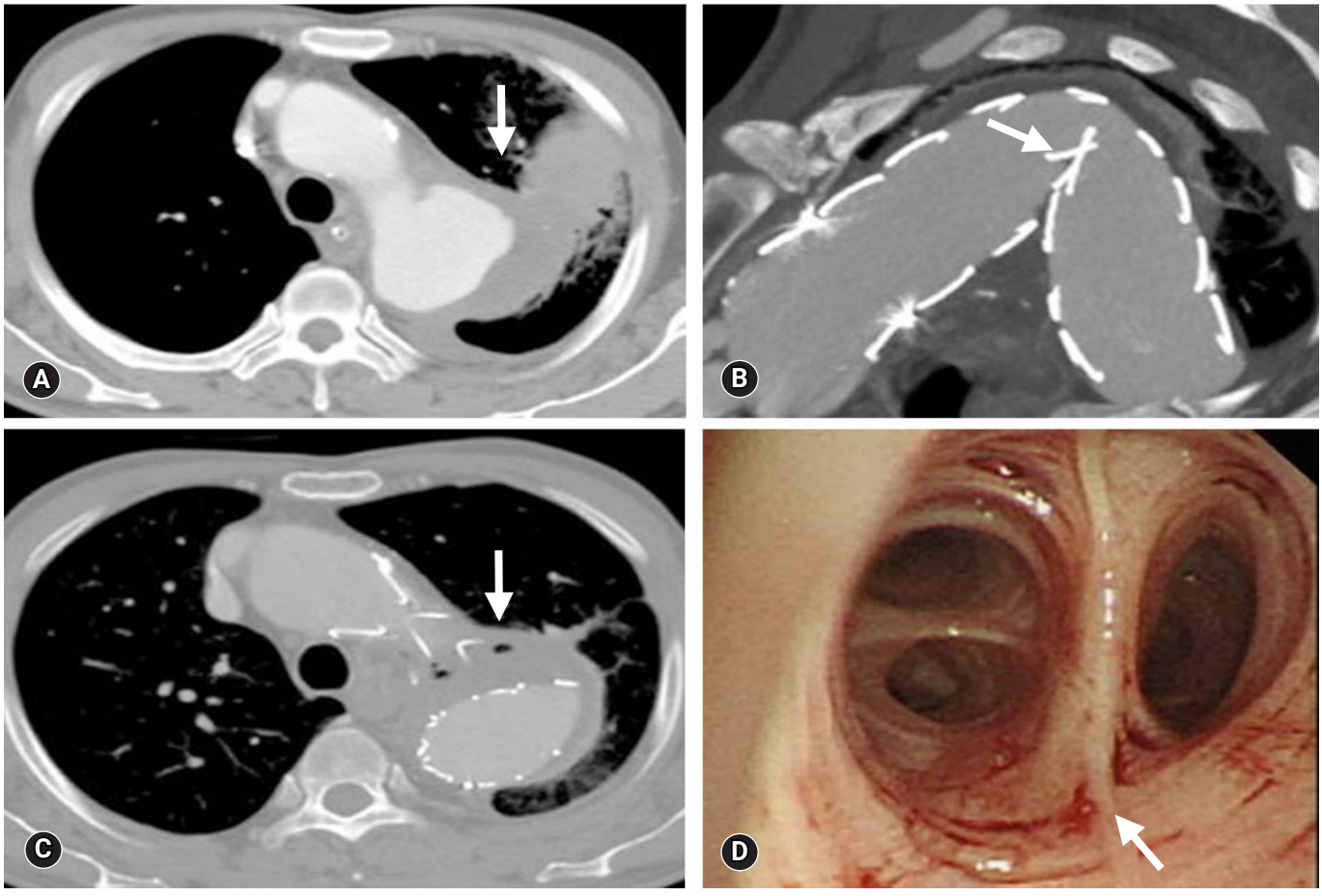

Fig. 3. Chest computed tomography (CT) findings of case 2. (A) Initial chest CT indicates a pseudoaneurysm with a suspicious aortobronchial fistula lesion (arrow). (B) A follow-up chest CT reveals kinking stenosis of the aortic isthmus stent-graft (arrow). (C) Chest CT on admission reveals air entrapment within the thrombosed aneurysm (arrow). (D) Brochoscopy shows oozing at left upper lobe orifice (arrow).

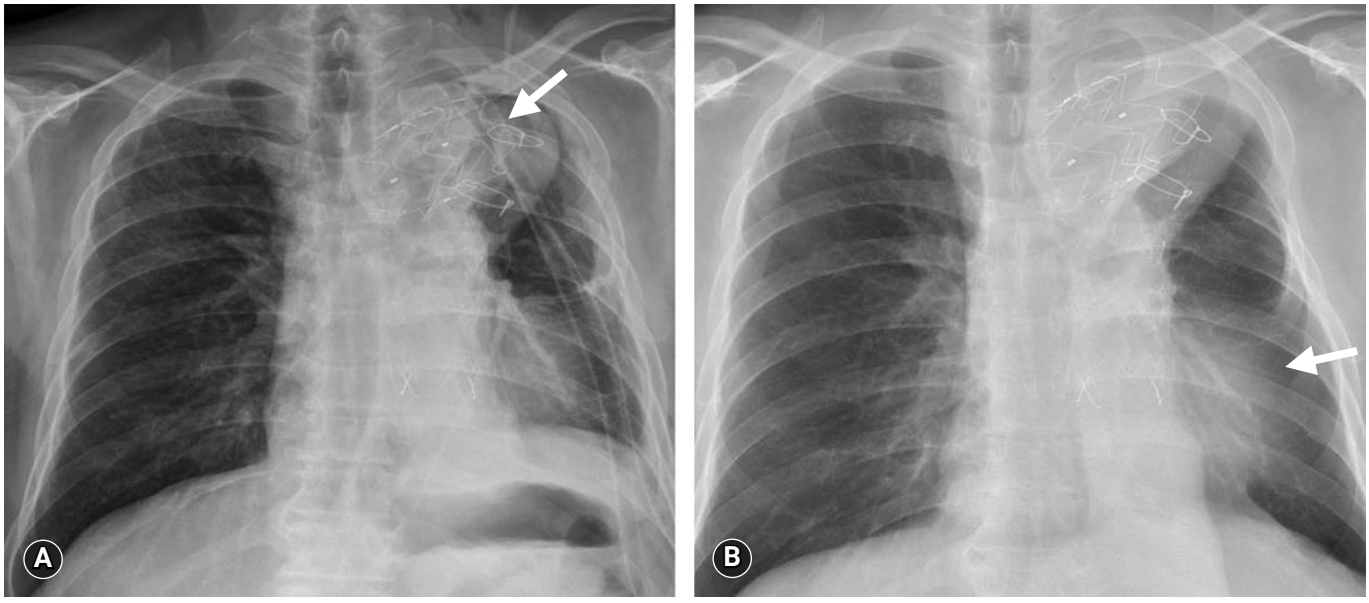

Fig. 4. Postoperative chest radiograph findings of case 2. (A) Postoperative chest radiograph shows remnant stent-graft (arrow). (B) Postoperative chest radiograph (followed-up after 4 years) shows the abscence of lung lesion (arrow).

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with CT angiography being considered the first diagnostic imaging study performed in the majority of cases due to its ease of use in emergency situations. Although CT rarely detects fistulous tracts, suggestive signs of ABF are present in most patients, which include air entrapment within the thrombosed aneurysm, periaortic fluid collection, bronchial wall thickening, and lung consolidation [11,12].

The most important factor in the prognosis of ABF patients is the presence of infection. Once infection has occurred within the vessel, it readily extends to the bronchial wall and lung parenchyma, which can ultimately lead to sepsis. When infection of the stent-graft or pseudoaneurysm is suspected, the majority of cases will require repair via open surgery [13]. Although surgical principles dictate control of infection, removal of all infected tissues and reconstruction in a clean field is not always achievable, as it places a huge demand on an already sick patient [13]. Moreover, operative mortality was approximately 50% in patients with infection [6,14].

The principles of treatment of ABFs are based on the condition of the patient. Conservative non-surgical therapy with antibiotic treatment is used in patients that do not consent to invasive treatment due to low levels of hemoptysis and/or multiple comorbidities. However, conservative non-surgical therapy results invariably in a fatal outcome as a result of massive hemoptysis or chronic mediastinitis [4]. Endovascular repair followed by antibiotic therapy is described in the treatment of ABF, particularly in cases unfit for open surgical treatment [15]. Within the last decade, several case reports have described initial success with treatment of ABF using stent-graft insertion, suggesting more widespread use of this approach. The perioperative outcomes of endovascular repair have been favorable with a low 30-day mortality rate (6.4%) [5]. It is uncertain whether endovascular repair alone provides a complete and reliable cure for an ABF as endovascular repair can result in risk of recurrence or stent-graft infection [4]. From these findings, direct contact between the involved aorta and the pulmonary tissue should be avoided to prevent further erosive damage and subsequent infection. Open ABF repair is associated with a high mortality rate, reported at 15% to 41%, related to the need for thoracotomy, thoracic aortic cross-clamping, and the surgical replacement or repair of the thoracic aorta with concomitant resection of the pulmonary segments [2,4,9,14].

In our cases, the most important factor for determining the cause of the ABF was the formation of a large pseudoaneurysm. If we considered more invasive surgical intervention initially or followed stricter indications for TEVAR, we could have avoided multiple procedures. From the operative findings, severe necrosis and inflammation of the lung and periaortic tissue were present in contrast to the mild symptoms of the patient. The presence of necrotic tissue increased the risk of infection, and we thought the presence of infection was critical to prognosis. To reduce the incidence of long-term persistent infection, we performed concomitant stent-graft removal and necrotic lung resection.

In the case of recurrent hemoptysis, ABFs should be managed unconditionally to prevent devastating complications, and either elective or emergent open repair should be determined according to the patient's symptoms and hemodynamics. The risk of infection and recurrent ABF is high if the bronchial lesion is left untreated; therefore, a TEVAR-only approach is not advisable [5]. To reduce the incidence of long-term persistent infection and recurrent ABFs, removal of the aorta and necrotic lung tissue must be performed simultaneously.

This report highlights the utility and benefits of a surgical approach to resolve ABFs and potentially eliminate infected lesions. On the basis of our experience with these cases, we would like to emphasize the importance of ABF management in pseudoaneurysm patients and recommend a surgical approach that involves total resection of the affected area as a guideline treatment for ABF with pseudoaneurysm.

Acknowledgments

Conflicts of interest

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

Author contribution

Conceptualization: SAS; Methodology: DHL, GJK; Resources: SAS; Writing-original draft, SAS; Writing-review & editing: DHL, GJK.

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Erratum to "Assessment of solid components of borderline ovarian tumor and stage I carcinoma: added value of combined diffusion- and perfusion-weighted magnetic resonance imaging"

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In the article entitled "Assessment of solid components of borderline ovarian tumor and stage I carcinoma: added value of combined diffusion- and perfusion-weighted magnetic resonance imaging" [1], the affiliation for the corresponding author was incorrectly listed as Kyungpook National University. It has been changed to "Kyungpook National University, Kyungpook National University Hospital".

Before correction

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After correction

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1. Kim SH. Assessment of solid components of borderline ovarian tumor and stage I carcinoma: added value of combined diffusion- and perfusion-weighted magnetic resonance imaging. Yeungnam Univ J Med 2019;36:231–40.

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Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after fem-

oral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

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