Pyogenic Spondylitis in Multidisciplinary Therapies of Gynecologic Malignancies: Three Cases Reports

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(Received February 22, 2021; Accepted April 9, 2021)

Both during and after cancer treatment, pyogenic spondylitis is an uncommon but serious complication. Because pyogenic spondylitis is often recognized as a complication of a distant process causing bacteremia, it initially may be misdiagnosed the primary infection such as urinary tract infection. Consequently, a considerable delay in diagnosis frequently occurs. In addition, estrogen deprivation caused by cancer treatments including RT/CCRT, CT and surgical therapy promotes changes of the immune system.

We report two cases of pyogenic spondylitis in a patient with vaginal cancer that occurred delay of the diagnosis, and in a patient with endometrial cancer that had chronic steroid use, and one case of suppurative osteomyelitis in a patient with vulvar cancer that had diabetes mellitus with obesity.

Gynecologic oncologists must consider the diagnosis of pyogenic spondylitis based on clinical symptoms such as localized lumbago and medical history. Estrogen deprivation, repeated cancer treatment, diabetes mellitus with obesity, immunosuppression by chronic steroid use are risk factors of pyogenic spondylitis. To prevent delay in diagnosis of pyogenic spondylitis, it is necessary that we must have careful management and follow-up considering all of information such as clinical features and medical history on patients during and after treating for gynecologic malignancies.

Key words: gynecologic malignancy, cancer treatment, estrogen deprivation, complication, pyogenic spondylitis

INTRODUCTION

In Japan approximately 42,000 women were diagnosed with gynecologic malignancies in 2017 [1]. The multidisciplinary approach including radiation therapy (RT), concurrent chemoradiotherapy (CCRT), chemotherapy (CT), and surgical therapy is frequently used and effective to treat gynecologic malignant tumors, such as cervical cancer [2], endometrial carcinoma [3], vulvar cancer [4], and vaginal cancer [5]. However, acute and late complications are always a concern [6]. Although pyogenic spondylitis caused by many microorganisms as a complication of multidisciplinary therapy is extremely rare, it is a severe adverse event that precludes cancer treatments and decreases quality of life [7].

We report two cases of pyogenic spondylitis in patients with vaginal cancer and endometrial cancer, and one case of suppurative osteomyelitis in a patient with vulvar cancer.

Case 1

A 66-year-old woman with stage I vaginal cancer was admitted for lumbago and low-grade fever during CT for the second recurrence with para-aortic and left supraclavicular nodes. She underwent RT (39.6 Gy for the whole pelvis, 25 Gy for RALS, total 64.6 Gy) for primary treatment at age 61years. The field of irradiation covered the whole pelvis (Fig. 1). Again, she underwent RT (60 Gy for inguinal) for the first recurrence with left inguinal nodes at age 62 years. Her medical history included a modified radical hysterectomy, bilateral adnexectomy and pelvic lymph node dissection for stage IB1 cervical cancer at age 52 years.

Laboratory results showed a white blood cell (WBC) level of $11.2 \times 10^3 / \mu$ L, a C-reactive protein (CRP) level of 20.31 mg/dL, an erythrocyte sedimentation rate (ESR) level of 105 mm/h, and *Streptococcus agalactiae* in the blood culture and *Staphylococcus hamolyticus* in the urine culture. The patient had no obvious symptoms except for lumbago, and slight redness and swelling of right leg, therefore we suspected urinary tract infection or cellulitis and administered antibacterial drug.

However, because her lumbago gradually worsened, magnetic resonance imaging (MRI) was performed on 22nd day after the patient developed this symptom. Lumbar MRI revealed the hypo-intensity of the vertebral bodies L3 and L4 on T1-weighted images (Fig. 2A), and the L3 and L4 intervertebral discs showed the high-intensity areas on T2-weighted images (Fig. 2B) and short T1 inversion recovery (STIR) (Fig. 2C). She was diagnosed with pyogenic spondylitis, and thus, the antibacterial drug, ampicillin sodium, was continued for 6 weeks, and CT was discontinued. Echocardiography did not reveal a vegetation or peri-

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Fig. 1 The field of irradiation covered the whole pelvis.



Fig. 2 Magnetic resonance imaging (MRI) findings of pyogenic spondylitis in 66-year-old woman. (A) The T1 weighted sagittal image shows the hypointense signal in the L3-L4 vertebral bodies and disc space (arrow). (B) The T2 weighted sagittal image shows the hyperintense signal in the L3-L4 disc space (arrow). (C) The short T1 inversion recovery (STIR) sagittal image shows the hyperintense signal in L3-L4 vertebral bodies and disc space (arrow).

valvular abscess suggestive of infective endocarditis. The diagnosis of pyogenic spondylitis and infective endocarditis was not established simultaneously in this case. Afterward, the lumbago improved, and the patient was discharged wearing a corset. To date, she has not experienced any recurrence.

Case 2

A 70-year-old woman with stage IB endometrial cancer was admitted for lumbago and fever. She underwent RT (40 Gy for the whole pelvis, 24 Gy for RALS, total 64 Gy) for primary treatment at age 65 years. For recurrence, she underwent CT at age 66 years, surgical therapy (simple hysterectomy and bilateral adnexectomy) at age 69 years, and RT (30 Gy for vagina) at age 70 years. Her medical history included rheumatoid arthritis (RA) and Sjogren's syndrome, and she was administered prednisolone (5–7 mg) for a long.

Laboratory results showed a WBC level of $1.9 \times 10^3 / \mu$ L, a CRP level of 7.95 mg/dL, *Escherichia coli*,

Enterococcus faecium, and *Corynebacterium sp.* in the urine culture and no bacterium in the blood culture. Although causative microorganisms were not isolated in blood culture in this case, bone biopsy was not performed because of her obsolete vertebral compression fractures (Th12-L1) and lumbar spondylosis (L3-L5).

The patient complained of localized lumbago with limited range of motion. MRI was performed, and she was diagnosed with pyogenic spondylitis of the vertebral bodies L4 and L5. Antibacterial drugs were administered (tazobactam/piperacillin hydrate for 2 weeks and vancomycin for 6 weeks), with improvement of symptoms. The patient was discharged wearing a corset. One year later, she experienced local recurrence, dissemination, and died of the primary disease without undergoing cancer treatment.

Case 3

A 59-year-old woman with stage II vulvar cancer was admitted to a local hospital for right leg pain with limited range of motion, localized tenderness near



Fig. 3 Magnetic resonance imaging (MRI) findings of pyogenic spondylitis in a 59-year-old woman. (A) The short T1 inversion recovery (STIR) sagittal image shows the hyperintense signal in the sacrum and ilium.

the affected area and fever. She was diagnosed with suppurative osteomyelitis of the sacroiliac joint and abscess of piriformis. The abscess caused by *methicillin-resistant Staphylococcus aureus (MRSA)* was drained, and antibacterial drugs were administered for 2 months. However, the patient was transferred to our hospital because her symptoms did not improve sufficiently. She underwent a radical local excision and bilateral inguinal lymphadenectomy for primary treatment at age 52 years, and RT (54 Gy for the whole pelvis) for recurrence of left inguinal node at age 53 years in our hospital. Her medical history included type 2 diabetes mellitus. She was also obese with a height of 159 cm and a weight of 105 kg (BMI 42).

Laboratory results obtained at our hospital showed a WBC level of $5.1 \times 10^3 / \mu L$, a CRP level of 0.91 mg/ dL, an ESR level of 58 mm/h, and no bacterium in the blood or urine culture. Infective endocarditis was not suggested by echocardiography. There was no relationship between suppurative osteomyelitis and infective endocarditis in this case. Pelvic MRI revealed the high-intensity of the sacrum and ilium on STIR (Fig. 3). Imaging showed osteomyelitis, but no abscess formation, pain, fever, and inflammation were resolved. The patient was discharged 1 week later.

Two months later, the patient was admitted for recurrence of suppurative osteomyelitis of the sacroiliac joint and abscess of piriformis. The abscess caused by MRSA was drained again, and the antibacterial drug, daptomycin, was administered for 4 weeks. Six months later, she was admitted again for recurrence of suppurative osteomyelitis of the sacroiliac joint, and the antibacterial drug, daptomycin, was administered for 8 weeks. Repeated recurrences of osteomyelitis in this patient were well reflected by the ESR. The ESR level was high on a long-term basis, consequently, she had to take oral antimicrobials for long term suppression of bacterial growth to avoid recurrence. The patient has not experienced recurrence of the primary disease or suppurative osteomyelitis, but she has been currently suspected of endometrial cancer and an operation has been planned. Recurrence of suppurative osteomyelitis is concerned after the operation.

DISCUSSION

We found out two important clinical features from these case reports. First, pyogenic spondylitis with lowor high-grade fever can be present as a new onset of localized prolonged lumbago that has not improved with non-steroidal anti-inflammatory drugs. This symptom is often misdiagnosed and leads to diagnostic delay because it is similar to the urinary tract infection that we frequently see as complications of multidisciplinary cancer treatments. Especially, bladder dysfunction is a common complication following radical hysterectomy, caused by the damage to pelvic autonomic nerves that innervate the muscles of the bladder, urethral sphincter, and pelvic floor fasciae, and increases the rates of urinary tract infection.

Second, in addition to long-term steroid therapy or diabetes mellitus with obesity, it is suggested that estrogen deprivation caused by cancer treatments including RT/CCRT, CT and surgical therapy promotes changes of the immune system. This is a characteristic of gynecologic malignancies in which ovarian function is completely and drastically eliminated by cancer treatments.

In this stage of estrogen deprivation, there is an increase in pro-inflammatory serum markers (IL1, IL6, TNF-alpha), an increasing response of the body's cells to these cytokines, a decrease in CD4 T and B lymphocytes and in the cytotoxic activity of NK cells [8, 9]. Low levels of estrogen and DHEA sulfate result in decreased number of cells secreting ITF-G contributing to the decline of immunologic reactivity. Several studies have also shown an increase in circulating levels of IL-6 and TNF-alfa after surgical menopause [10, 11]. Following total abdominal hysterectomy and bilateral salpingo-oopherectomy, the percentage of CD8 + cells was increased while the percentage of CD19 + cells, serum IL-4, and IFN- γ concentration and the ratio of CD4 + to CD8 + cells were decreased [12]. Consequently, attenuated immune response and higher susceptibility to microbial invasion and infection are more common. Gender and its specific hormones affect changes associated with the function of the immune system and this seems to be associated with an onset of pyogenic spondylitis and osteomyelitis.

The onset of symptoms of pyogenic spondylitis is usually insidious and its symptom is nonspecific [13]. Hopkinson *et al.* reported that patients presented with spinal pain (96%), fever (70%) and raised inflammatory markers [14]. The most common sites of infection are the lumbar spine (45%–50%), the thoracic region (35%), the cervical region (3%–20%), and the sacral region [15]. Fever is typically not present and occurs in less than 20% of patients.

The patient in case 1 experienced prolonged lumbago, but we did not suspect pyogenic spondylitis because of the presence of Staphylococcus hamolyticus in the urine culture, and swelling and redness in the unilateral lower extremity. Instead, we suspected urinary tract infection or cellulitis caused by a weakened immune system due to CT. However, the patient in case 1 had undergone a modified radical hysterectomy, which might have predisposed her to urinary tract infection after surgery, and RT (124.6 Gy) for vaginal cancer after pelvic lymph node dissection. These conditions could precipitate the development of the primary infection of pyogenic spondylitis. It was suggested that urinary tract infection was the primary infection, giving rise to bacteremia, and that the infection spread through the arterial or venous route and developed into pyogenic spondylitis.

Pyogenic spondylitis commonly arises from the hematogenous spread of bacteria, and the common pyogenic organisms that cause this disease are Staphylococcus aureus and Streptococcus species, which account for more than 50% of cases [16, 17]. In addition, Escherichia coli and Proteus may be present in urinary tract infection as occurred in case 2. A delay in diagnosis is common and can range from 2 to 12 weeks, and, on occasion, after 3 months [18]. Pyogenic spondylitis initially may be misdiagnosed the primary infection such as urinary tract infection because it is often recognized as a complication of a distant process causing bacteremia. Therefore, we must consider the diagnosis of pyogenic spondylitis based on clinical symptoms and signs such as localized pain and fever. A new onset of localized prolonged lumbago with little improvement in patients undergoing repeated cancer treatments is an important finding that suggests pyogenic spondylitis.

Furthermore, risk factors for the development of pyogenic spondylitis and suppurative osteomyelitis are diabetes mellitus; infections including urinary tract and other infections; disorders of different organ systems or body regions including malignancy, chronic renal insufficiency, systemic lupus erythematosus, and other systemic disorders; long-term steroid use; trauma; and invasive procedures [19]. Most patients reportedly have more than one underlying medical illness, such as diabetes mellitus (24%); immunosuppression (7%); malignancy (6%); rheumatic disease (5%); liver cirrhosis (4%); renal failure (4%); and previous deficit of the vertebrae from radiation or osteopenic fracture (3%) [20].

In case 2, the patient was a long-term steroid user with RA and Sjogren's syndrome, and had repeated cancer treatments for recurrence. In case 3, the patient had diabetes mellitus with obesity and RT for recurrence. In case 1, the patient underwent repeated cancer treatments for recurrence. They had more than one underlying medical illness and were high risk group for pyogenic spondylitis and suppurative osteomyelitis. Steroid mediated immunosuppression disarms both the humoral and cellular responses to infectious agents. The association of pyogenic spondylitis/osteomyelitis and diabetes mellitus may be explained by the reduced immunocompetence of patients with diabetics. Inadequately treated blood glucose concentrations are associated with reduced cellular immunity as occurs with reduced chemotaxis, phagocytosis, and bactericidal activity of neutrophilic granulocytes [21]. Obesity, especially when combined with diabetes mellitus, is associated with a higher proportion of Staphylococcus aureus infections and is a risk factor for a severe course of spondylitis [22]. Patients with cancer may also experience reduced immunocompetence. In addition, higher doses of radiation and repeated CT may lead to chronic myelosuppressive effects by damaging the bone marrow microenvironment [22]. A decrease in the number of hematopoietic stem cells and progenitorsa, and reduction in self-renewal capacity of stem cells are caused by cytotoxic agents and radiation. Protection against these chronic effects of RT/CCRT and CT is difficult.

In conclusion, for early diagnosis of pyogenic spondylitis and osteomyelitis, gynecologic oncologists must consider all the patients' factors such as estrogen deprivation caused by cancer treatments, clinical symptoms, repeated cancer treatments for recurrence, chronic steroid use, diabetes mellitus, obesity, and presence of underlying bone weakness, in the management and long-term follow-up of gynecologic malignancies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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