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CASE REPORT

Uterine Manifestation of Sarcoidosis Diagnosed in the Setting of Fever of Unknown Origin

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Abstract: We report a rare case of uterine sarcoidosis. A 28-year-old woman presented with periodic fever over 38°C for the past 5 months. One year prior, splenomegaly was noted. The serum angiotensin-converting enzyme levels were elevated; however, the lungs, lymph nodes, eyes, and skin appeared normal. Fluorine-18-fluorodeoxyglucose positron emission tomography revealed accumulations in the uterine body and spleen. Magnetic resonance imaging showed multiple irregular uterine masses. Intraoperative frozen section assessment of the uterine masses suggested sarcoma; therefore, total hysterectomy was performed. However, formalin-fixed specimens of the resected organs revealed noncaseating epithelioid cell granulomas in the myometrium and fallopian tubes, indicating the final diagnosis of uterine sarcoidosis. Clinicians should recognize that sarcoidosis can affect the uterus.

Keywords: sarcoidosis, female genital tract, uterus, fever of unknown origin, fluorine-18-fluorodeoxyglucose-positron emission tomography

Introduction

Sarcoidosis is a multisystem inflammatory disease of uncertain etiology that is histologically characterized by non-caseating epithelioid cell granulomas. It typically involves the lungs and hilar and mediastinal lymph nodes, and has been reported in many body organ systems.[1] However, sarcoidosis involving the female reproductive organs is extremely rare, with only isolated case reports.[1–5] Among the female genital organs, uterine lesions are the most frequently reported, most of which are diagnosed using endometrial curettage, whereas other cases are diagnosed using hysterectomy, polypectomy, and examination of autopsy specimens.[6]

Sarcoidosis occasionally presents with fever, and when characteristic lesions are present in the lungs, lymph nodes, or skin, the diagnosis of sarcoidosis is not difficult; however, in its absence, it is often difficult to diagnose the condition. International reviews suggest that sarcoidosis should be listed as a cause of fever of unknown origin (FUO).[7,8] Herein, we report a case of uterine sarcoidosis diagnosed during examination for FUO. The consent for publication has been obtained from the patient.

Case Report

A 28-year-old woman visited our department for periodic fever for the past 5 months. One year prior, she developed abdominal pain and visited a nearby hospital when an ultrasound incidentally revealed a cystic lesion in the pancreas. Two months later, she was referred to our hospital (Department of Gastroenterology) because of an increased size of pancreatic cyst. Abdominal computed tomography (CT) scans performed at our hospital revealed a pancreatic cyst and mild splenomegaly (Figure 1A) without intrathoracic lymphadenopathy (Figure 1B). The patient was scheduled for follow-up observations.

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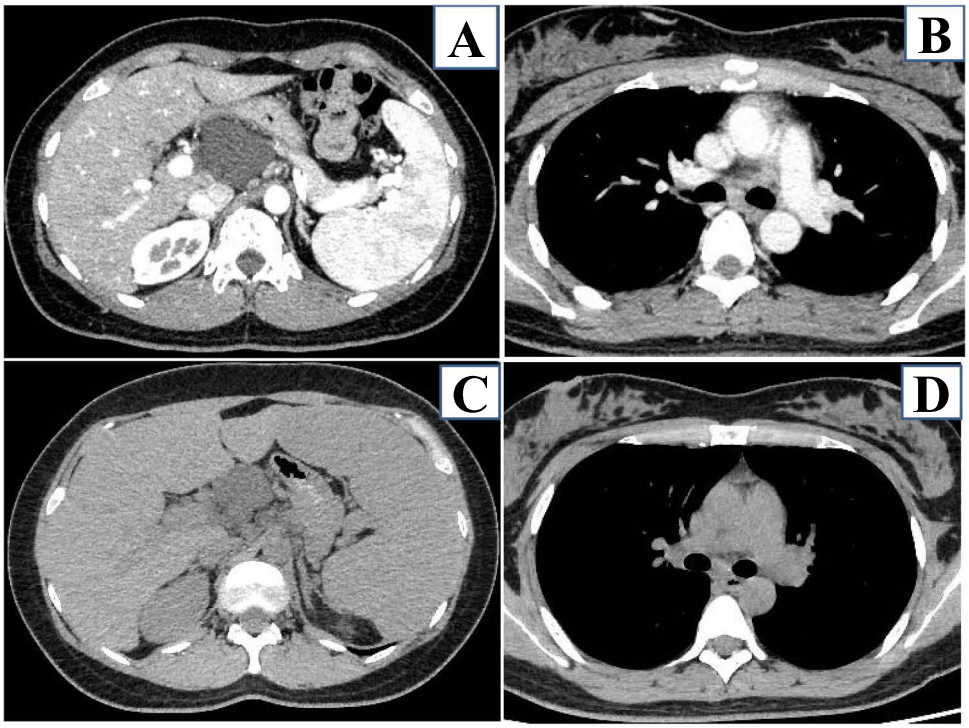

Figure 1 Computed tomography at the initial visit to our hospital shows a cystic mass in the pancreatic head and mild splenomegaly (**A**) without enlarged lymph nodes in the mediastinum or pulmonary hilum (**B**). Ten months later, an obvious increase in splenomegaly (**C**) but no significant lymph node enlargement in the thorax is seen (**D**).

Six months after, she visited to our hospital, the patient began to have occasional fever (body temperature in 37.5°C to 38.2°C). No abnormalities were noted after blood tests and chest radiography at a nearby hospital, and the fever resolved spontaneously within a few days. The recurrence of the fever and spontaneous resolution continued for nearly 5 months, and the attending surgeon at our hospital referred the patient to our department to examine the cause of the fever.

On her visit to our department, her vital signs were as follows: temperature, 38.1°C; regular pulse, 109 bpm; blood pressure, 130/79 mmHg; and oxygen saturation, 98%. Auscultation of heart sounds was normal, without a murmur. The lung sounds and abdominal examination results were normal. She did not exhibit a skin rash or eschar. The lymph nodes were not palpable. The patient's laboratory values were as follows: leukocyte count, 3500 /μL; erythrocyte count, 410×10^4/μL; platelet count, 11.6×10^4/μL; hemoglobin level, 11.7 g/dL; C-reactive protein, 4.35 mg/dL; total protein, 7.26 g/dL; albumin, 3.34 g/dL; aspartate aminotransferase, 38.2 IU/L; alanine aminotransferase, 63.3 IU/L; lactate dehydrogenase, 265 IU/L; alkaline phosphatase, 798 U/L; creatinine, 0.59 mg/dL; Na, 138 mEq/L; K, 3.97 mEq/L; and Cl, 103 mEq/L; and calcium, 8.39 mg/dL. The ALP isozymes were 18% ALP1, 73% ALP2, and 7% ALP3. The levels of angiotensin-converting enzyme, lysozyme, and soluble interleukin-2 receptor were elevated (25.7 U/L, 12.1 μg/L and 2665 U/L, respectively). Whole-body CT scans revealed that splenomegaly had increased since the previous visit, and the abdominal lymph nodes were enlarged (Figure 1C); however, there was no evidence of lung involvement or hilar and mediastinal lymphadenopathy (Figure 1D).

Splenomegaly, abdominal lymphadenopathy, and elevated angiotensin-converting enzyme levels suggested the possibility of sarcoidosis; however, no characteristic findings of sarcoidosis were observed in the skin, eyes, heart, or lungs. Other diseases that should be differentiated include malignancy, especially malignant lymphoma, and hematological diseases. Therefore, we performed fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)-CT to determine the appropriate biopsy site. The results showed FDG accumulation in the enlarged spleen and para-aortic regional lymph nodes as well as in the bone marrow of the vertebral body, pelvic bone, and femur (Figure 2A and B). Therefore, a bone marrow biopsy was performed, which showed no abnormality. Another striking feature was the intense mass-like FDG accumulation within the muscularis propria of the uterine fundus (Figure 2C and D). Magnetic resonance imaging (MRI)

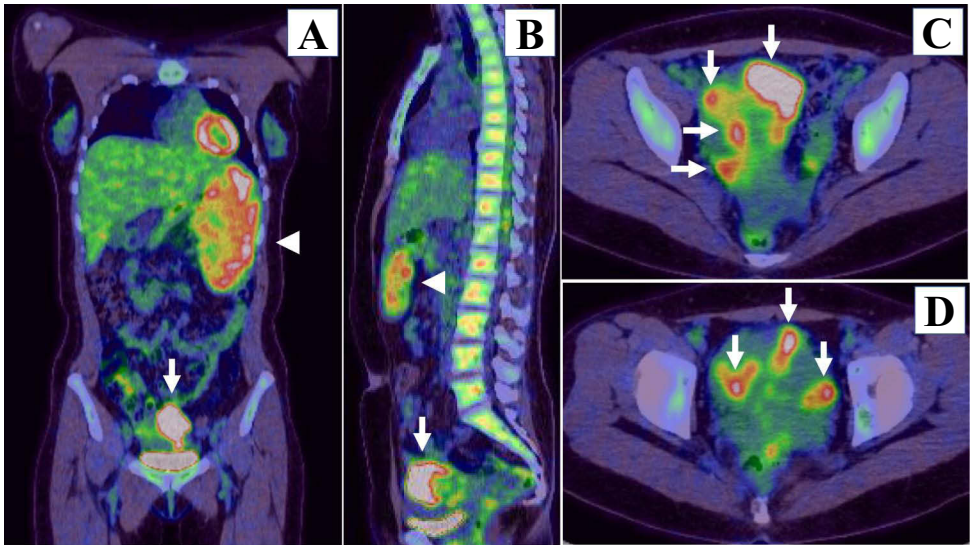

Figure 2 Maximum intensity projection images obtained using fluorodeoxyglucose (PDG) positron emission tomography reveal strong FDG uptake in the enlarged spleen (arrow head) and uterus (arrow) (**A**) as well as weak uptake in vertebral bodies (**B**). Mass-like FDG accumulation is seen in the uterine body (**C**). Nodular accumulations are also seen in the surrounding area (**C** and **D**).

showed a mass in the uterine body, with an intermediate signal on the T2-weighted image (Figure 3A) and a similar signal on the T1-weighted image (Figure 3B). Diffusion-weighted images revealed a mass of 40 mm in diameter (Figure 3C) with surrounding nodular lesions (Figure 3D).

Since the images of these uterine lesions suggested lymphoma, sarcoma, and hematologic disease, we requested a uterine biopsy by a gynecologist to confirm the diagnosis. Initially, endometrial aspiration cytology was performed with a negative result. The next step was to attempt a surgical uterine biopsy. In the preoperative informed consent, unless

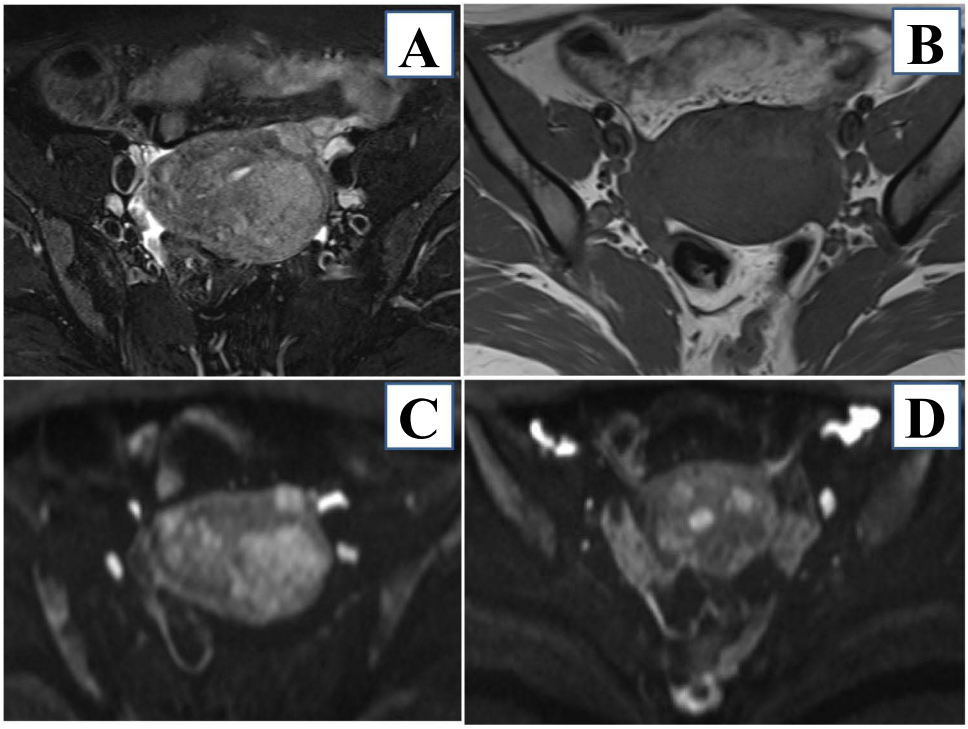

Figure 3 Magnetic resonance images show an ill-margined mass in the uterus, with an intermediate signal on the T2-weighted image (**A**) and a similar signal on the T1-weighted image (**B**). Diffusion-weighted image clearly shows a mass of 40 mm in diameter (**C**) and surrounding nodular lesions (**D**).

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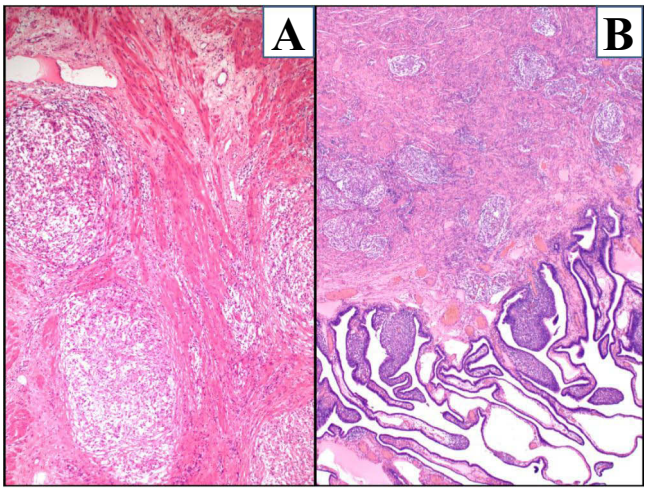

Figure 4 Histopathological findings reveal numerous noncaseating epithelioid cell granulomas in the myometrium (**A**) and fallopian tubes (**B**). (Hematoxylin and eosin staining; A, ×100 original magnification; B, ×40 original magnification.

intraoperative frozen specimen evaluation completely could rule out malignant diseases, the patient and her husband preferred a total hysterectomy rather than reoperation after the final pathology. Consequently, intraoperative frozen section assessment of the uterine mass was suspected sarcoma; therefore, the gynecologist again provided informed consent to the husband, and a total hysterectomy and bilateral adnexectomy were performed. Ultimately, however, the formalin sections of the extracted organs revealed numerous granulomatous lesions (Figure 4) in the myometrium, fallopian tube apparatus, and lymph nodes in the specimens. No necrosis was observed and the antimicrobial and fungal staining studies showed negative results. Based on these findings, a final diagnosis of uterine sarcoidosis was performed.

Regarding progressive splenomegaly, the patient had a persistent low-grade fever and slight thrombocytopenia after surgery; therefore, corticosteroid treatment was initiated with a diagnosis of splenic sarcoidosis (prednisolone, 0.5 mg/day/kg). The fever resolved quickly after the initiation of treatment; however, it took 3 months for the spleen to shrink and approximately 2 years for the platelet count to stabilize.

Discussion

Here, we report a rare case of uterine sarcoidosis. This case is also unique in that the diagnosis was prompted by a close examination of FUO. Evaluation of the uterine lesion was very difficult. Both imaging and frozen specimen pathology indicated malignant disease, resulting in a total hysterectomy. Ultimately, formalin-fixed specimens revealed numerous granulomas in uterus tissues; thus, comprehensively, the diagnosis of sarcoidosis was reached. Previous publications have cited foreign body reaction[9] and history of uterine instrumentation as etiologies of uterine granulomas,[10] but these were not applicable to this case.

Previous studies have shown that female genital involvement in sarcoidosis occurs in less than 1% of all cases, with the uterus being the most commonly affected organ.[2] Most patients with uterine sarcoidosis are of reproductive age (6), consistent with the present case. Clinical manifestations include amenorrhea, menorrhagia, dysmenorrhea, postmenopausal bleeding, and cervical erosions, and is often discovered when a patient known to have sarcoidosis in other organs presents with the above symptoms.[6] Most of uterine sarcoidosis is diagnosed by endometrial biopsy.;[5,6] however, as observed in this patient, granulomas are found in the myometrium as well as the endometrium. Granulomas were also found in the fallopian tube sheath and mucosa in this case. Once uterine sarcoidosis is diagnosed, the clinical outcome is favorable with corticosteroid therapy.

Uterine sarcoidosis is often discovered while investigating the cause of abnormal uterine bleeding in patients with a history of sarcoidosis in other organs.[4] In this case, sarcoidosis diagnosis was challenging because of the absence of sarcoidosis-specific symptoms and findings, such as bilateral hilar lymphadenopathy, pulmonary infiltrates, skin lesions, and uveitis. The patient also had no irregular menstruation, menstrual cramps, dysmenorrhea, or postmenopausal

bleeding and was diagnosed during hysterectomy. In our clinical reasoning, fever and splenomegaly made sarcoidosis a candidate diagnosis, but FDG PET and MRI showed extensive lesions in the uterus, which forced differentiation from malignancy and ultimately led to a total hysterectomy. Similarly, there is a case report of an asymptomatic patient who was diagnosed with hysterectomy.[9]

To the best of our knowledge, there have been no literature reports on MRI findings in patients with uterine sarcoidosis. On MRI, in this case, the uterine lesion appeared as a mass with an irregular outline and intermediate T2 signal intensity. This is similar to the MRI features of uterine sarcoma,[10] suggesting that it is difficult to differentiate between the two diseases on imaging. Conversely, nodular shadows around the larger mass may be characteristic of uterine sarcoidosis, reflecting histologically skipped granulomatous foci. In this case, treatment with corticosteroids would have avoided a total hysterectomy if the characteristic images had strengthened the suspicion of sarcoidosis rather than sarcoma. Accumulation of MRI images of uterine sarcoidosis is desirable.

The ACCESS study in the United States[11] and a European study[12] reported splenic involvement in 6.7% and 3.9% of patients with sarcoidosis, respectively. Because splenic sarcoidosis is often asymptomatic and not clinically problematic, most patients do not require treatment. Our patient had massive splenomegaly, mild hypersplenism, and persistent fever. In general, splenectomy is indicated for massive splenomegaly, severe splenic hyperplasia, suspected lymphoma, or other malignancies and as a precaution against splenic rupture.[13] In this case, we decided to administer corticosteroids because the patient had already undergone uterine surgery. To date, few studies have reported the efficacy of steroid therapy for massive splenomegaly. In the present case, it took a long time for the spleen to shrink and the platelet count to normalize despite the immediate resolution of the fever. We also noted that ALP was elevated in this patient. The isozyme pattern would reflect the presence of liver lesions in association with splenomegaly, rather than bone origin.

In the literature, sarcoidosis has been implicated as a cause of FUO.[7,8] FDG PET/CT is useful for the diagnostic workup of patients with FUO.[7,8] It allows imaging of large areas of the body and is an excellent method for identifying the most metabolically active lesions. A recent meta-analysis reported that FDG PET/CT successfully identified the source of fever in 58% of patients with classic FUO, for whom a series of fever workup studies failed.[14] In this case, the FDG PET results confirmed that extrapulmonary lesions of sarcoidosis in the spleen and uterus were the causes of FUO.

Conclusion

This was an unusual case presenting with several rare conditions, including recurrent fever, massive splenomegaly, and uterine masses. Clinicians should be aware that sarcoidosis can affect the uterus.

The approval of the organization (Oita University Hospital) was not required to publish the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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