Discovery of Splenic Sarcoidosis Concurrent with the Diagnosis of Ovarian Cancer: A Case Report

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Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized by noncaseating epithelioid granuloma formation. Although the relationship between sarcoidosis and malignancy has been noted in recent decades, there are few case reports describing the concurrent diagnosis of sarcoidosis and malignancy. Herein, we describe a case of biopsy-proven splenic sarcoidosis mimicking metastasis at the time of ovarian adenocarcinoma. Imaging studies including positron-emission tomography-computed tomography were not useful for differentiating sarcoidosis from malignancy. Thus, our case highlights the importance of histopathological examination to rule out nonmalignant conditions before the diagnosis of metastatic disease is made. (J Rheum Dis 2016;23:130-135)

Key Words. Sarcoidosis, Ovarian neoplasms, Granuloma, Positron-emission tomography

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized by the development and accumulation of noncaseating epithelioid granuloma in any organ system. In most cases, the lungs are affected, but the lymph nodes, parotid gland, liver and spleen can also be involved. Diagnosis of sarcoidosis is based on compatible clinical features and histological tissue examination. However, owing to the uncertainty of its cause and the variability in the clinical manifestations of sarcoidosis, diagnosis of this disease is often difficult. Over the past decades, the relationship between sarcoidosis and malignancy has been noted [1,2]; however, the conclusions are conflicting [3]. In previous studies, sarcoidosis has more often been observed in association with hematologic malignancy than with solid tumors [4]. It has been reported that malignancy developed after the diagnosis of sarcoidosis and that sarcoidosis occurred in patients with malignant tumor [4,5]. Otherwise, case reports of the concurrent discovery of sarcoidosis and malignancy are lacking. In the present paper, we describe a case of the splenic sarcoidosis mimicking metastasis at the time of diagnosis of ovarian adenocarcinoma.

CASE REPORT

A 66-year-old South Korean woman, gravida 4 para 1, visited to Pusan National University Hospital complaining of low abdominal discomfort and weight loss. She denied any cutaneous or ocular symptoms. The patient was a housewife with no history of smoking or occupational exposure to chemical agents. She had a history of hypertension and her brother died from colon cancer. Computed tomography (CT) of the abdomen showed a 100x47 mm sized multiseptated cystic mass in the right ovary; multiple extensive lymphadenopathy including multiple 2 to 6 cm sized lymph nodes in the splenic hi-
Sarcoidosis in Ovarian Cancer

Abdominal computed tomography (CT; A, B) and magnetic resonance imaging (MRI; C, D) showed 100×47 mm sized multiseptated cystic mass (arrowheads in A and C) and multiple extensive lymphadenopathy including multiple 2 to 6 cm sized lymph nodes. In the spleen, a low density lesion measuring approximately 12×27 mm on CT (arrow in B) and a 62 mm sized mass lesion on MRI (arrow in D) were observed.

Histopathologic findings revealed noncaseating granulomatous inflammation without tumor cells. A polymerase chain reaction-based assay was negative for mycobacterium tuberculosis, leaving sarcoidosis as the probable diagnosis (Figure 3). Slit lamp examination did not reveal any evidence of uveitis. Laboratory findings were as follows; white blood cell 6,050 cells/mm³, neutrophils 4,640 cells/mm³, lymphocytes 847 cells/mm³, hemoglobin 11.2 g/dL, platelet 250,000 cells/mm³, erythrocyte sedimentation rate 39 mm/h, C-reactive protein 0.35 mg/dL, calcium 11.1 mg/dL (reference, 8.5 to 10.3 mg/dL), ionized calcium 1.36 mg/dL (references, 1 to 1.2 mg/dL), phosphorus 2.9 mg/dL (reference, 2 to 4.6 mg/dL), total protein 8.1 g/dL, albumin 4.1 g/dL, blood urea nitrogen 19.3 mg/dL, creatinine 1.96 mg/dL, 25-OH vitamin D3 28.3 ng/mL (reference, 30 to 150 ng/mL), 1,25-OH vitamin D3 56.74 pg/mL (reference, 19.6 to 54.3 pg/mL), intact parathyroid hormone 16.61 pg/mL (reference, 10 to 57 pg/mL), angiotensin converting enzyme (ACE) 98.8 U/L (reference, 9 to 47 U/L), CA-125 32.55 U/mL (reference, 0 to 35 U/mL) and CA19-9 15.51 U/mL (reference, 0 to 39 U/mL). Lymphopenia, hypercalcemia with an increased 1,25-OH vitamin D3 and an elevated ACE level were recognized to be consistent with sarcoidosis. Based on the imaging, histologic and laboratory results, two types of diagnoses were considered, 1) coexisting ovarian cancer and splenic sarcoidosis or 2) sarcoidosis with extensive organ involvement including ovary, lymph node and spleen without malignancy. However, the patient denied the possibility of malignancy and refused further diagnostic work-up including surgical biopsy of an ovary or
lymph node. Thus, we empirically initiated 40 mg of prednisolone for presumed sarcoidosis.

After 1 month of glucocorticoids therapy, a follow-up PET-CT scan revealed the $^{18}$F-FDG uptake was dramatically decreased in the spleen but increased in extent and intensity in the right ovary and multiple lymph nodes in the abdominal cavity. Serum creatinine level was decreased to 1.32 mg/dL and the calcium concentration had normalized. At that time, a diagnostic laparotomy was performed and biopsy of the omentum revealed metastatic adenocarcinoma with positive estrogen receptor staining that was morphologically and immunohistochemically consistent with ovarian serous carcinoma (Figure 4). The prednisolone was tapered off and the patient received chemotherapy with paclitaxel and carboplatin.

**DISCUSSION**

Since Brincker and Wilbek [1] reported a significantly increased risk of malignant tumor, such as lung cancer and lymphoma in patients with sarcoidosis in 1974, the clinical and epidemiological association between sarcoidosis and malignancy has been increasingly recognized based on numerous case reports and registry data [2,4,5], even though other studies argued that this association is more likely to be due to selection bias and misclassification [3,6]. There are 3 types of clinical settings in which sarcoidosis and malignancy are found together. First, a hematologic malignancy or solid tumor can develop after the diagnosis of sarcoidosis. Several studies have shown that sarcoidosis is associated with an increased risk of malignant tumor [1,2,5]. Secondly, a sarcoid reaction, typically limited to the regional lymph nodes or the organ of tumor origin, or systemic sarcoidosis can occur following the diagnosis of malignancy [7,8]. Lastly, although very rare, sarcoidosis can present concurrently with the diagnosis of a malignant tumor including, breast [9], colorectal [10], gastric [11] and ovarian cancer [12], as in the present case. To our knowledge, this is the first case report of splenic sarcoidosis diagnosed concurrently with ovarian adenocarcinoma in a Korean patient.
Sarcoidosis in Ovarian Cancer

Figure 3. Microscopic findings in the spleen (hematoxylin and eosin staining). Noncaseating granulomas with aggregations of inflammatory cells (arrow in A), multinucleated giant cells (arrow in B), asteroid body (arrow in C), and eosinophils (arrow in D) were observed. (A, B) ×200, (C, E) ×400.

Because sarcoidosis of the lymph nodes or spleen in an oncology patient is often assumed to be metastatic spread from the primary tumor, making the correct diagnosis in this situation can be challenging. Imaging studies including CT, MRI and even ¹⁸F-FDG labeled PET-CT are not usually helpful for differentiating malignant tumor from sarcoidosis. In addition, a majority of patients with sarcoidosis are asymptomatic, which can lead to misdiagnosis or delayed diagnosis. In our case, because the magnitude of ¹⁸F-FDG uptake in the splenic mass on PET-CT scan was similar to that of a primary tumor and metastatic lymph node, we initially concluded it was metastatic ovarian cancer. Although our patient was found to have characteristic laboratory findings such as increased ACE and 1,25-OH vitamin D3 levels after histopathologic confirmation of sarcoidosis, these markers are not routinely obtained as part of the assessment in patients with ovarian cancer. Moreover, our patient did not have any symptoms of sarcoidosis. Only after histological examination, we were able to make the diagnosis of splenic sarcoidosis. Similar to our case, Mapelli et al. [12] reported 4 cases of histologically confirmed sarcoidosis of the lymph nodes mimicking metastases in gynecological malignancies including ovarian, cervical and endometrial cancer and ¹⁸F-FDG labeled PET-CT imaging was not useful for differentiating sarcoidosis from malignant lymph nodes. Taken together, this highlights the need for clinicians to pay special attention to the potential linkage between sarcoidosis and malignancy to avoid an erroneous diagnosis of cancer progression and inappropriate treatment.

For the treatment of sarcoidosis, the organ involvement and severity of symptoms should be considered. While patients with no or mild symptoms may not require treatment, symptomatic patients with multiple organ involve-
ment require systemic glucocorticoids. In addition, glucocorticoids therapy may be considered for patients with an abnormal calcium level or neurologic, cardiac or ocular involvements. Glucocorticoids remain the initial drugs of choice for sarcoidosis, but hydroxychloroquine, methotrexate, azathioprine and anti-tumor necrosis factor agents may also be used. In our case, we introduced 40 mg of prednisolone due to hypercalcemia and the possibility of sarcoidosis with extensive organ involvement. With prednisolone therapy, our patient’s hypercalcemia corrected and the size of the splenic sarcoidosis lesions dramatically decreased. Not all cases of sarcoidosis of the lymph nodes or spleen diagnosed concurrently with a malignancy required treatment in previous reports [9-12]. Thus, an appropriate therapeutic approach based on the extent of disease involvement and clinical symptoms should be considered in cases of sarcoidosis associated with cancer.

The clinical course and prognosis of sarcoidosis associated with malignancy are not well established. There have been several reports of sarcoidosis developing or flaring after a patient received anti-neoplastic agents or biologic modifiers such as interleukin-2 [4,7,8]. The presence of a sarcoid reaction in patients with Hodgkin lymphoma and gastric carcinoma was reported to be associated with positive prognostic significance [4]. However, due to the rarity of this condition, the effect of sarcoidosis on the prognosis of malignant tumor and vice versa remains elusive.

Although a relationship between sarcoidosis and malignant tumors has been proposed over the past decades, the exact mechanisms by which sarcoidosis promotes oncogenesis is not well understood. Considering that chronic inflammation has been presumed to be the putative me-

Figure 4. Microscopic findings of the omentum. (A) Hematoxylin and eosin staining showed metastatic adenocarcinoma on desmoplastic changed omentum (×200). (B) Calretinin staining was negative (×100). (C) The tumor was estrogen receptor positive, suggesting an ovarian origin (×100). (D) The tumor protein p53 was positive (×100).
mediator for the increased cancer risk, this would theoretically also apply to sarcoidosis [5]. In addition, although sarcoidosis has been known to be a T helper-1 cell mediated immune response, recent studies have shown that the expression and function of regulatory T cells are diminished in patients with sarcoidosis [13,14]. In ovarian cancer, study reported that decreased expression of regulatory T cells within the tumor microenvironment is associated with cancer progression [15]. Thus, impairment of regulatory T cell function may be a common mechanism in the development of both sarcoidosis and ovarian cancer. However, further studies are needed to elucidate the molecular and immunological mechanism of linking sarcoidosis and malignancy.

**SUMMARY**

We describe a case of the splenic sarcoidosis discovered concurrently with the diagnosis of ovarian adenocarcinoma. The present case highlights the importance of histopathological examination in patients with suspected splenic metastases of malignant disease including ovarian cancer because imaging studies including PET-CT were not useful for differentiating sarcoidosis from malignancy. Added awareness of the potential association between sarcoidosis and malignant tumor is needed.

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**CONFLICT OF INTEREST**

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

**REFERENCES**