

[ CASE REPORT ]

## Gastric Cancer with Multiple Lymph Node Enlargement at the Time of the Sarcoidosis Diagnosis

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### Abstract:

An 80-year-old woman was found to have a 40-mm depressed-type gastric cancer. Computed tomography showed multiple lymph node enlargement, including paraaortic lymph nodes. The extent of lymph node enlargement was significant compared with the depth of the primary lesion. We conducted distal gastrectomy, D2 lymph node dissection, and a paraaortic lymph node biopsy. Microscopically, the tumor was diagnosed as mucosal cancer. In the dissected lymph nodes, noncaseating granuloma was found without metastasis of adenocarcinoma. Immunohistochemical staining using *Propionibacterium acnes*-specific antibodies showed a large number of *P. acnes*-positive cells in the granulomas. Finally, the tumor was diagnosed as early-stage gastric cancer and sarcoidosis.

**Key words:** gastric cancer, sarcoidosis, sarcoid reaction, *Propionibacterium acnes*, PAB antibody

(Intern Med 60: 3225-3229, 2021)

(DOI: 10.2169/internalmedicine.7218-21)

### Introduction

Sarcoidosis is a multisystemic granulomatous disorder characterized by the presence of noncaseating granulomas in the involved organs. This disorder commonly affects young and middle-aged adults who present with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions (1, 2). Furthermore, the liver, spleen, lymph nodes, heart, salivary glands, nervous system, muscles, and other organs may be involved (2).

The diagnosis of sarcoidosis is not standardized but is based on the pathological evidence of noncaseating granuloma and exclusion of alternative causes of granulomatous disease, including Crohn's disease, vasculitis syndrome, sarcoid reaction to malignancy, as well as infectious diseases, such as tuberculosis and syphilis (3, 4).

Several cases of concomitant sarcoidosis and malignancy have been reported (5-9). It is often challenging to differentiate lymph node metastasis from other conditions associated with lymph node enlargement, including sarcoidosis (5). Furthermore, sarcoidosis with malignancy is difficult to distinguish from sarcoid reaction with respect to granulomatous

diseases, as they are histologically similar (9).

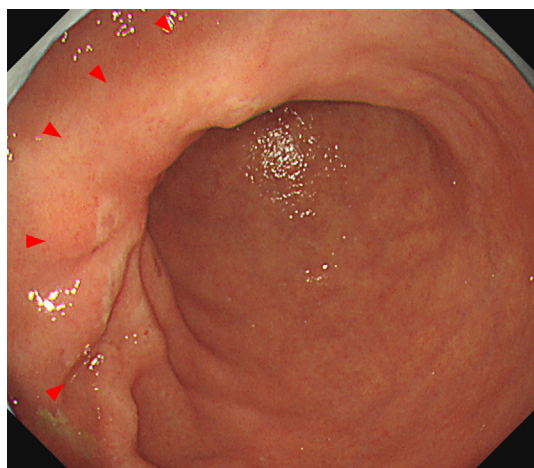
*Propionibacterium acnes* is an etiologic agent of sarcoidosis (10, 11). Immunostaining with *P. acnes*-specific monoclonal antibodies that react with cell membrane-bound lipoteichoic acid (PAB antibody) has been useful in differentiating sarcoidosis and sarcoid reaction (12).

We herein report a case of early-stage gastric cancer with multiple lymph node enlargement at the time of the sarcoidosis diagnosis that was difficult to stage due to the presence of multiple enlarged lymph nodes mimicking cancer metastasis.

### Case Report

An 80-year-old woman was referred to our hospital for the treatment of gastric cancer. Physical and laboratory examinations, which included an assessment of the tumor marker levels, revealed no abnormalities. Esophagogastroduodenoscopy (EGD) showed a 40-mm depressed-type lesion with an ulcer scar located at the anterior wall of the lower gastric body (Fig. 1). A biopsy of a specimen collected from the depressed area revealed poorly differentiated adenocarcinoma. The patient tested positive for anti-

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Received: February 1, 2021; Accepted: March 18, 2021; Advance Publication by J-STAGE: May 7, 2021  
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**Figure 1.** Esophagogastroduodenoscopy showed a 40-mm depressed-type lesion with an ulcer scar located at the anterior wall of the lower gastric body (red arrowheads).

*Helicobacter pylori* immunoglobulin G antibody.

Computed tomography (CT) showed enlargement of the bilateral supraclavicular, mediastinal, hilar, retroperitoneal, and paraaortic lymph nodes (Fig. 2a, b). In addition, positron emission tomography (PET) was performed to confirm the staging diagnosis. PET revealed a high fluorodeoxyglucose uptake in multiple lymph nodes, consistent with the lymph node enlargement confirmed on CT (Fig. 2c, d). The extent of lymph node enlargement was significant compared with the depth of the primary lesion. The primary lesion was diagnosed as early gastric cancer on EGD, and there was no regional lymph node enlargement. This result suggested the presence of a concomitant condition other than lymph node metastasis. Accordingly, we strongly suspected that the lymph node enlargement had been caused by systemic diseases, including sarcoidosis, sarcoid reaction to malignancy, infectious diseases, or malignant lymphoma.

Additional blood tests and infectious examinations were performed, and the patient's serum calcium (8.7 mg/dL, normal range: 8.2-10.0 mg/dL), lysozyme (6.9 µg/mL, normal range: 5.0-10.2 µg/mL), angiotensin-converting enzyme (16.4 U/L, normal range: 7.0-25.0 U/L), and soluble interleukin 2 receptor (482 U/mL, normal range: 122-496 U/mL) levels were within the normal limits. All infectious examinations showed negative results. Chest radiography, electrocardiogram, and ophthalmoscopy showed no abnormalities. Based on these examinations and PET-CT findings, systemic diseases, including sarcoidosis or sarcoid reaction to malignancy, were suspected. However, distant and regional lymph node metastasis could not be ruled out. A final diagnosis was still not obtained preoperatively.

We conducted distal gastrectomy with B1 reconstruction, D2 lymph node dissection, and a paraaortic lymph node biopsy for the histological diagnosis of multiple lymph node enlargement. A gross examination of the surgically resected specimen showed a 40-mm depressed lesion with an ulcer scar located at the anterior wall of the lower gastric body

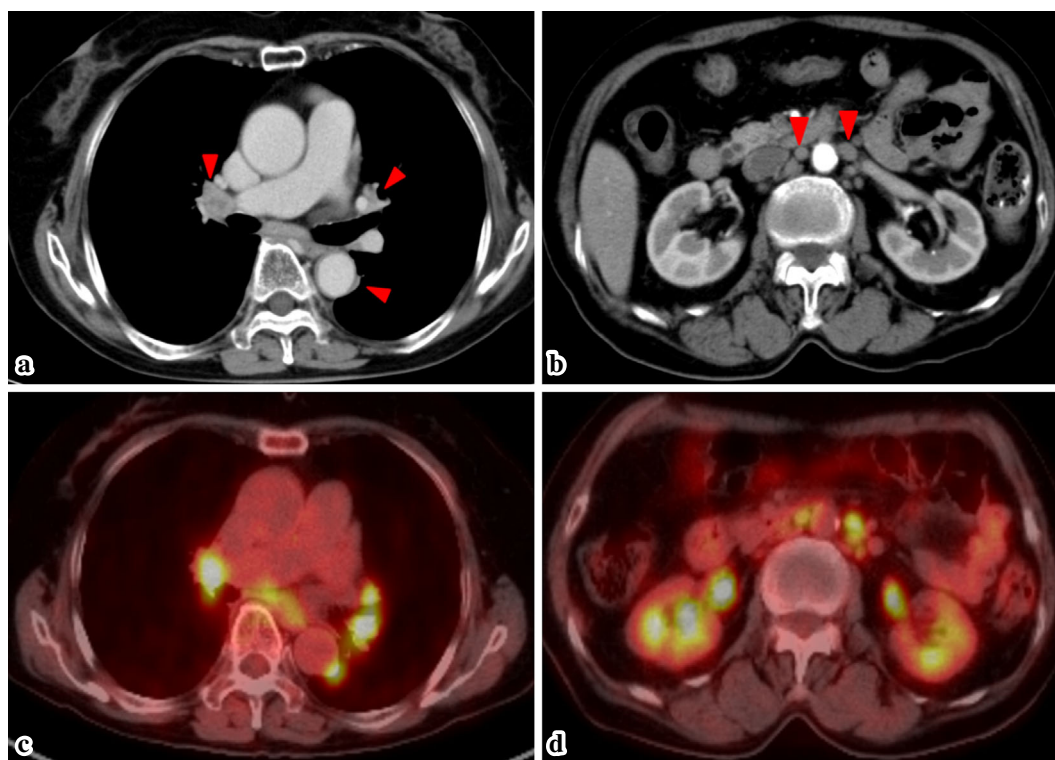
(Fig. 3). Microscopically, the tumor was diagnosed as poorly differentiated adenocarcinoma and signet ring cell carcinoma in the mucosal layer. In addition, severe fibrosis was evident in the mucosa and submucosal layer (Fig. 4a, b). In the dissected regional and paraaortic lymph nodes, noncaseating granuloma was found without metastasis of adenocarcinoma (Fig. 4c, d). The granuloma was not positive on Ziehl-Neelsen or Grocott staining. Immunohistochemical staining using PAB antibody, which is useful for the diagnosis of sarcoidosis, showed a large number of *P. acnes*-positive cells in the granulomas (Fig. 4e, f). Finally, the tumor was diagnosed as Type 0-IIc, 40×35 mm, por>sig, pT1a (M), Ly0, V0, pPM0, pDM0, pN0 (0/29), pStage IA gastric cancer (13) and sarcoidosis. One year after surgery, the patient experienced progression without recurrence. In addition, the extent of lymph node enlargement due to sarcoidosis had remained largely unchanged for one year. Currently, the patient has no clinical symptoms of sarcoidosis and is being followed.

## Discussion

We herein report a rare case of sarcoidosis identified during a gastric cancer diagnosis, highlighting the complexity of the diagnostic process. In this case, histological findings, including sampling of the distant lymph node, led to the diagnosis of concomitant gastric cancer and granulomatous disease. Furthermore, it was difficult to differentiate sarcoidosis from sarcoid reaction on imaging and histological examinations. However, the final diagnosis of sarcoidosis was made via PAB antibody staining, which was useful for differentiating the two diseases. In gastric cancer, the use of PAB antibody staining for differentiating sarcoid reaction from sarcoidosis has not previously been reported. Therefore, this case is extremely valuable.

Sarcoidosis is a systemic granulomatous disease of unknown cause that is pathologically characterized by non-caseating granulomas. Furthermore, it is diagnosed by ruling out other systemic granulomatous diseases (3, 4). In the present case, it was important to differentiate sarcoidosis from sarcoid reaction.

At present, *P. acnes* is the only microorganism isolated from sarcoid lesions (14, 15). Using quantitative polymerase chain reaction, Ishige et al. discovered that *P. acnes* resided or proliferated specifically in sarcoid lesions (10, 11). To elucidate the pathogenic role of *P. acnes*, Negi et al. used immunohistochemical methods with novel *P. acnes*-specific monoclonal antibodies that react with cell membrane-bound lipoteichoic acid (PAB antibody) or ribosome-bound trigger factor protein (TIG antibody) (12). Immunostaining with PAB antibody can detect *P. acnes* in granulomas in 74-100% of sarcoidosis cases, regardless of the affected organ (14), suggesting an etiological link between sarcoidosis and *P. acnes*. In addition, the treatment for sarcoidosis is not standardized, but antibiotics for *P. acnes* can be used. In fact, minocycline and doxycycline have been reported to be effective for sarcoidosis (16, 17), suggesting an etiological



**Figure 2.** Computed tomography (CT) and positron emission tomography (PET) images. (a, b) CT showed enlargement of the bilateral supraclavicular, mediastinal, hilar, retroperitoneal, and para-aortic lymph nodes (red arrowheads). (c, d) PET revealed a high fluorodeoxyglucose uptake in multiple lymph nodes, consistent with the lymph node enlargement confirmed on CT.



**Figure 3.** The macroscopic findings of the resected specimen. The gross appearance showed a 40-mm depressed lesion with an ulcer scar.

link between sarcoidosis and *P. acnes*.

Furthermore, Negi et al. showed that the granuloma was negative for PAB in patients with sarcoid reaction (12). Although a histopathological examination using PAB is not yet widely available, positivity for PAB in this case strongly supported the presence of sarcoidosis rather than sarcoid reaction.

The association between sarcoidosis and malignancy has been reported in several studies. However, the correlation remains controversial (5-9). In gastric cancer cases, cases of

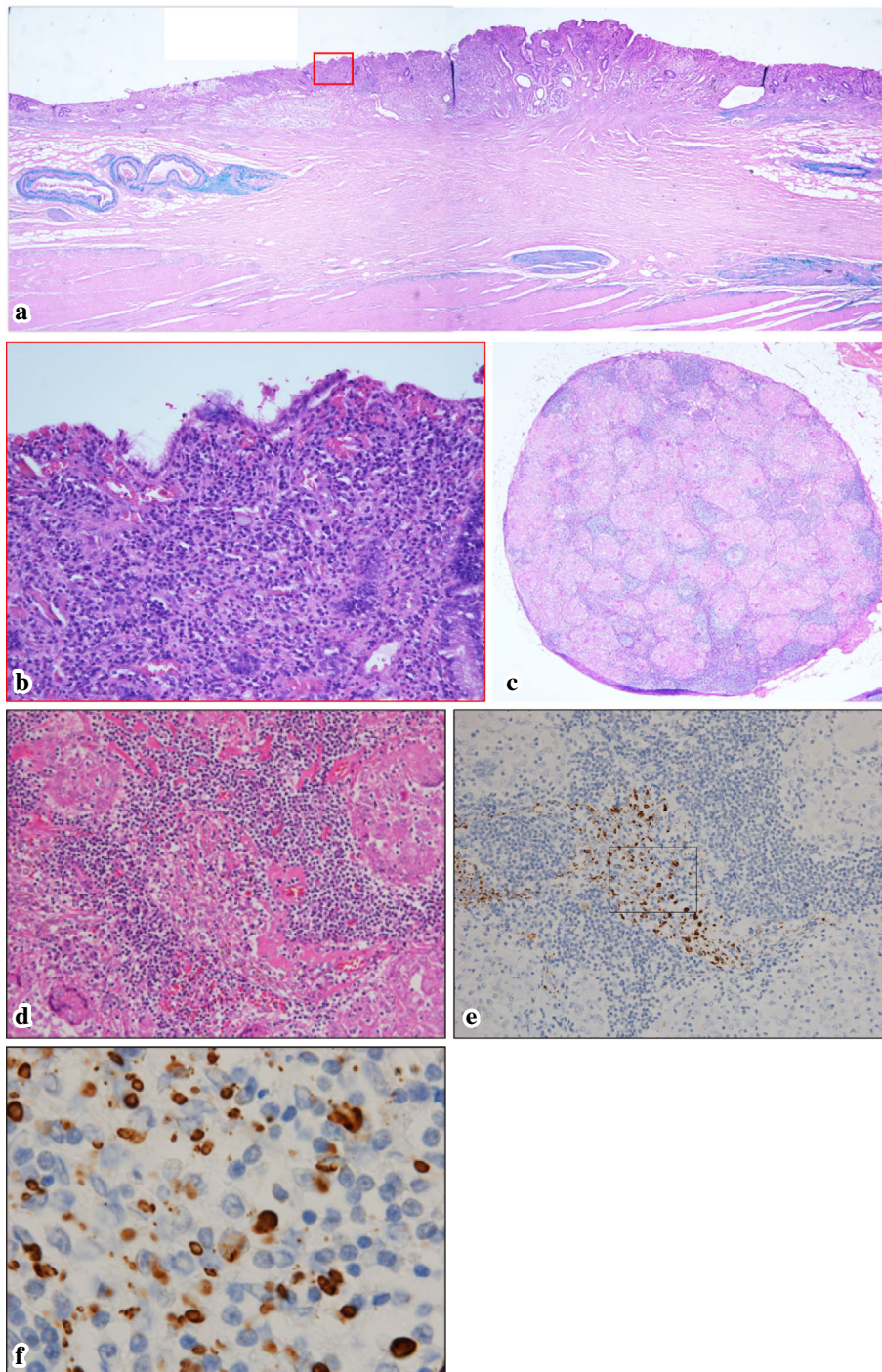
sarcoidosis mimicking metastatic cancer have been rarely reported (5, 6). In gastrointestinal cancers, it is important to differentiate sarcoid nodules from metastatic lesions preoperatively. However, in patients with sarcoidosis, sarcoid nodules can be found in any organs and lymph nodes, often hampering the differentiation of lesions correlated with metastases and leading to inappropriate treatment of concomitant malignancy (5). In the present case, a preoperative examination revealed multiple lymph node enlargement, which was not in accordance with the primary lesion progression. Therefore, concomitant gastric cancer and systemic disease with multiple lymph node enlargement were instead suspected.

We encountered a rare case of sarcoidosis with multiple lymph node enlargement identified at the time of the early-stage gastric cancer diagnosis. Immunohistochemical staining with PAB might be useful for detecting concomitant sarcoidosis and early-stage gastric cancer. If nonspecific multiple lymph node enlargement is found during the preoperative diagnosis of malignant diseases, it is important to determine the preoperative diagnosis and treatment plan while considering the possibility of concomitant sarcoidosis.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

We thank Dr. Yoshinobu Eishi (Department of Human Pathol-



**Figure 4.** Histological findings of the resected specimen. (a, b) The tumor was diagnosed as poorly differentiated adenocarcinoma and signet ring cell carcinoma in the mucosal layer. In addition, ulcer scar was observed in the mucosal and submucosal layer. (c, d) In the dissected lymph nodes, noncaseating granuloma was found without metastasis of adenocarcinoma. (e, f) Immunohistochemical staining using *Propionibacterium acnes*-specific antibodies showed a large number of *Propionibacterium acnes*-positive cells in the granulomas.

ogy, Tokyo Medical and Dental University Graduate School) for performing the pathological examination associated with this report.

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