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Case Report

Early Gastric Cancer Associated With Gastric Sarcoidosis

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Sarcoidosis is a multisystemic disorder that is characterized by the formation of noncaseating granulomas. Although sarcoidosis can affect any organ, gastrointestinal tract involvement in sarcoidosis is very rare, and gastric cancer associated with gastric sarcoidosis has hardly been reported. A 64-year-old female with a 10-year history of the medical treatment of gastric sarcoidosis received a routine follow-up gastrointestinal endoscopy and an irregular-shaped, elevated lesion was detected in the gastric corpus. The gastric mucosal surface was nodular and ulcerated throughout the stomach. The gastric lumen was narrow, and the gastric wall was stiff and nondistensible, resembling linitis plastica. The biopsies of the elevated lesion in the gastric corpus revealed well-differentiated adenocarcinoma. An endoscopic ultrasonography was then performed, but it failed to assess precisely the depth of cancer invasion because of sarcoidosis-related gastritis and fibrosis of the gastric wall. The patient underwent a laparoscopic total gastrectomy under the diagnosis of gastric cancer associated with gastric sarcoidosis. Histologic examination of the surgical specimen demonstrated well-differentiated adenocarcinoma in the gastric corpus, and the histologic mapping of cancer cells revealed that the tumor spread within the mucosal layer of the stomach. No lymph node metastasis was found. The patient's postoperative course was uneventful. We experienced a rare case of early gastric cancer associated with gastric sarcoidosis, which identified the troublesome issue that the assessment of depth of cancer invasion is difficult, because patients with longstanding gastric sarcoidosis may involve various degrees of fibrosis of the gastric wall.

Key words: Laparoscopic gastrectomy – Gastric carcinoma – Gastric sarcoidosis

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Sarcoidosis is a systemic inflammatory disease of unknown etiology that is characterized by the formation of noncaseating granulomas, and it usually affects the lung and mediastinal or hilar lymph nodes. Virtually any organ system may be involved in sarcoidosis, involvement of the gastrointestinal tract is rare, and it occurs in only 0.1 to 0.9% of patients with sarcoidosis.[1] The stomach is the most common site of gastrointestinal tract involvement with sarcoidosis. Although malignancies at various sites of the gastrointestinal tract have been recognized in longstanding Crohn's disease that can present systemic granulomatous inflammation,[23] to the best of our knowledge, only 1 case of gastric cancer associated with gastric sarcoidosis has been reported.[4]

We herein present a rare case of early gastric cancer associated with gastric sarcoidosis.

Case Presentation

A 64-year-old female with a 10-year history of the medical treatment of gastric sarcoidosis was referred to our hospital in September 2012. In 2003, the patient complained of epigastralgia and appetite loss, and she was diagnosed as gastric sarcoidosis, because endoscopic findings included thickened mucosa, nodular mucosal irregularities, and multiple ulcers throughout the stomach (Fig. 1) and gastric biopsies demonstrated noncaseating epithelioid cell granulomas. A further examination of the distribution of sarcoidosis using chest X-ray, computed tomography (CT) scan, and colonoscopy was performed, but sarcoidosis-related systemic disease was not detected. Serum level of angiotensin converting enzyme was within the normal range. Since then, the patient had been treated with prednisolone and followed by gastrointestinal endoscopy examination once a year for the last 10 years. The gastric wall thickness gradually became aggravated and, recently, the patient often complained of early satiety. In 2012, a routine follow-up gastrointestinal endoscopy revealed an irregular-shaped, elevated lesion in the gastric corpus (Fig. 2), and biopsy examination demonstrated well-differentiate adenocarcinoma. The patient was then referred to our hospital. On physical examination, she was skinny, and her body mass index was less than the normal value. No lymphadenopathy was observed. The laboratory data revealed a slight elevation of serum CA19–9 value. Serum angiotensin converting enzyme level and other blood tests were within the normal range. In the upper gastrointestinal series, the gastric mucosal surface was nodular and ulcerated. The gastric lumen was narrow and the gastric wall was stiff and nondistensible, resembling linitis plastica (Fig. 3). An endoscopic ultrasonography judged the tumor to be an early gastric cancer confined to the mucosal layer,

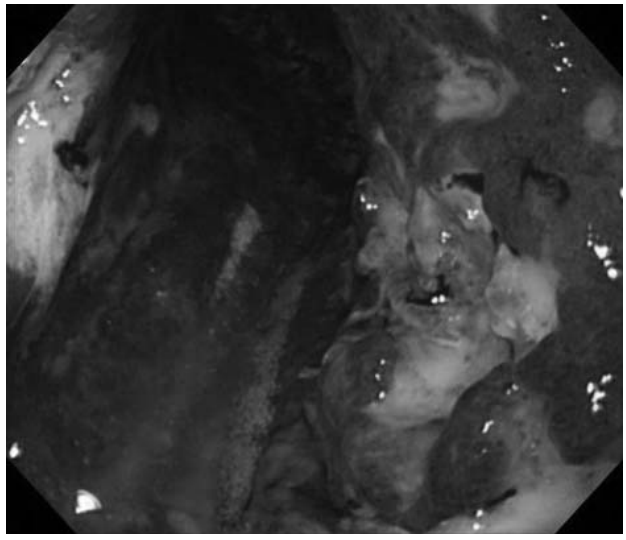

Fig. 1 Severe gastritis and multiple ulcers of active stage were recognized in the entire gastric mucosa in 2003. Gastric biopsies revealed noncaseating epithelioid cell granulomas.

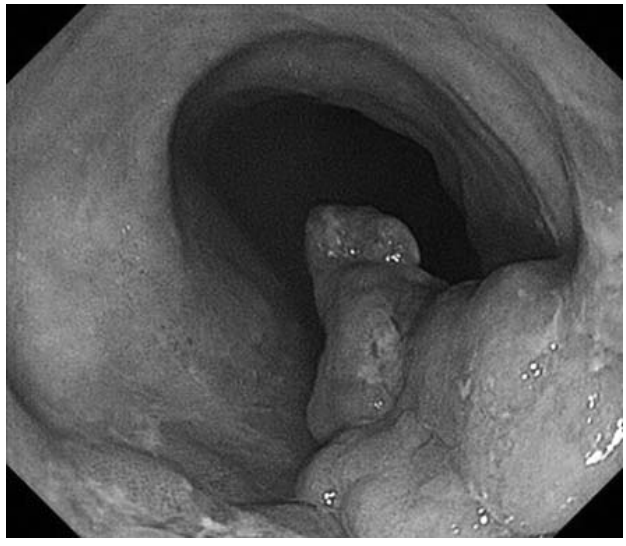

Fig. 2 An irregular-shaped, elevated lesion was noted in the gastric corpus, and microscopic examination of the biopsy specimen revealed well-differentiated adenocarcinoma. An endoscopic ultrasonography was then performed, but it failed to assess precisely the depth of the tumor, because of coincidental sarcoidosis-related gastritis and fibrosis of the gastric wall.

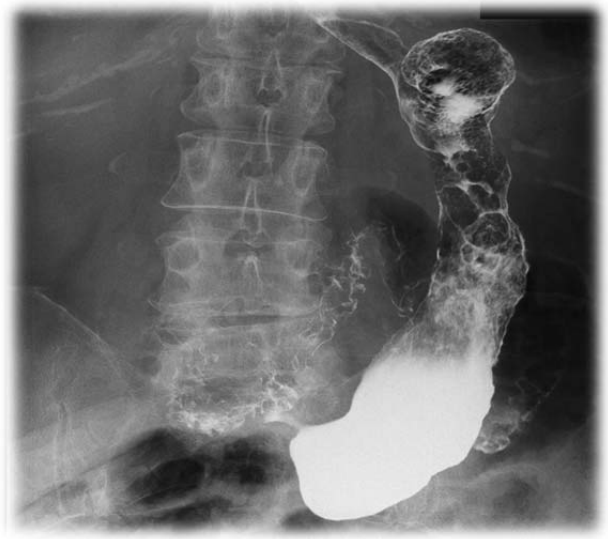

Fig. 3 In the upper gastrointestinal series, the gastric mucosal surface was nodular and ulcerated. The gastric lumen was narrow, and the gastric wall was stiff, resembling linitis plastica.

but it failed to assess precisely the depth of cancer invasion due to gastritis and fibrosis of the gastric wall associated with longstanding gastric sarcoidosis. A laparoscopic total gastrectomy was planned for the patient, because the gastric wall was stiff and nondistensible throughout the stomach and, moreover, the depth of cancer invasion was uncertain. Meanwhile, a whole body CT examination depicted a small nodule in the right upper lung and the lesion was diagnosed as primary lung cancer by transbronchial lung biopsy (TBLB). At first, video-assisted thoracic surgery (VATS) was carried out for the lung cancer and the tumor was confirmed to be pStageIA.[5] Six months later, the patient underwent a laparoscopic total gastrectomy. The operation went smoothly and as planned. Histologic examination of the surgical specimen demonstrated well-differentiated adenocarcinoma (tub1 > pap) in the gastric corpus. The histologic mapping of cancer cells revealed that the tumor spread within the mucosal layer of the stomach. No lymph node metastasis was found (pStageIA)[6]. Histologically, severe fibrosis was evident in the mucosa and submucosal layer of the entire stomach and noncaseating granuloma was identified nearby carcinoma (Figs. 4, 5). The patient's postoperative course was uneventful and she was discharged 14 days after surgery. At follow-up 24 months after gastrectomy, the patient remained well without any symptoms and recurrent gastric disease.

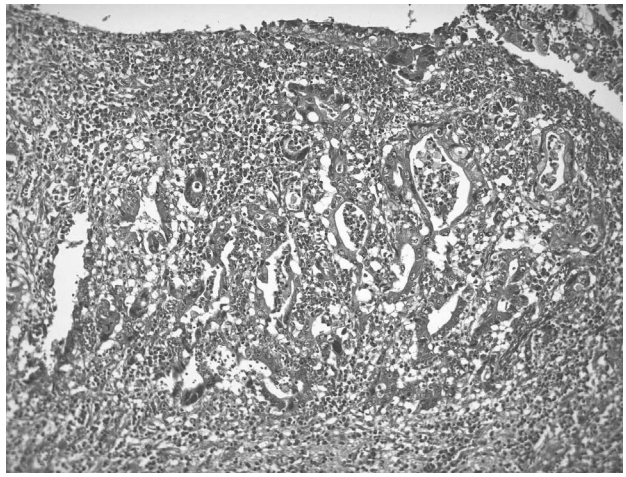

Fig. 4 Histologic examination of the surgical specimen demonstrated well-differentiated adenocarcinoma in the gastric corpus, and histologic mapping of cancer cells revealed that the tumor spread within the mucosal layer of the gastric wall (hematoxylin and eosin staining ×100).

Discussion

Gastrointestinal tract sarcoidosis, first described by Schaumann in 1936,[7] is rare and may present in the context of generalized disease or as an isolated finding.[8] Recent epidemiologic data indicated that the prevalence of gastrointestinal tract sarcoidosis was 1.6% among Japanese patients with sarcoidosis.[9] In our case, gastric sarcoidosis is an isolated type, because no other organs were found to be involved in sarcoidosis. In fact, pathologic exami-

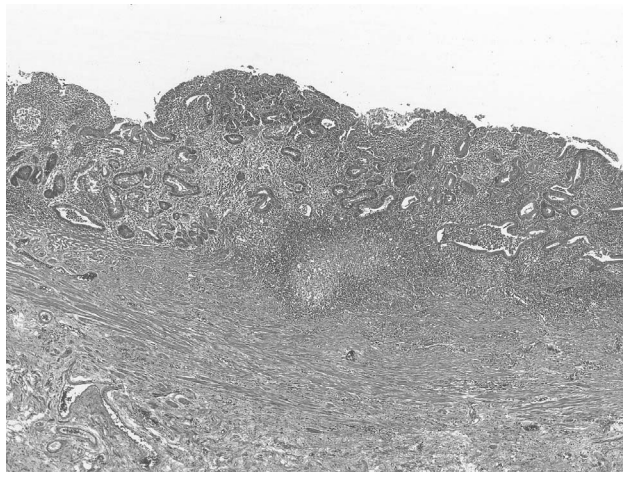

Fig. 5 Noncaseating granulomas with severe fibrosis were evident in the mucosa and submucosal layer of the stomach (hematoxylin and eosin staining ×200).

nation of the resected specimens for the lung cancer, including the hilar lymph nodes, did not show any noncaseating epithelioid cell granulomas.

Symptoms of gastric sarcoidosis include epigastralgia, nausea, vomiting, hematemesis, and melena, which are usually related either to peptic ulceration or narrowing of the gastric lumen. Based on previous reports, there are 2 main manifestations of gastric sarcoidosis; one is gastric ulcer formation, in which localized mucosa is infiltrated with sarcoid granulomas, and the other involves extreme, diffuse infiltration with sarcoid granulomas and fibrosis throughout the gastric wall.[1,10,11] Inflammation, edema, ulceration, and fibrosis may cause thickening of the mucosa and of all other layers of the stomach as well, resulting in enlargement of gastric folds and narrowing of the gastric lumen. Wall thickening or luminal narrowing of the stomach with gastric wall rigidity resembles the linitis plastic.[12]

While gastric involvement is the most common manifestation of sarcoidosis in the gastrointestinal tract, the definitive diagnosis of gastric sarcoidosis is difficult and is dependent on histologic evidence of noncaseating granulomas on mucosal biopsies. Proper interpretation of the biopsy specimens is crucial because tuberculosis, *Helicobacter pylori*, syphilis, Crohn's disease, foreign body reactions, and fungal infections can all present granulomatous disease.[13]

It is well known that sarcoidosis or sarcoid reaction can occur in association with malignancy.[14] Although malignancies at various sites of the gastrointestinal tract have been reported in longstanding Crohn's disease, an increasing risk of cancer among patients with sarcoidosis is also indicated by reports from Japan[9] and Sweden,[15] in which chronic inflammation is proposed to be a putative mediator of carcinogenesis in the lung, lymph tissue (non-Hodgkin's lymphoma), skin, and the liver. In general, chronic inflammation is associated with an increased risk of cancers in the affected tissues, and some hypotheses for the pathogenesis of gastric carcinoma propose that chronic inflammation, such as *H. pylori* infection, may result in gastric mucosal atrophy, intestinal metaplasia, dysplasia, and eventually gastric cancer.[2,3,15] On the basis of the above findings, gastric mucosal damage and regeneration caused by chronic inflammation may be considered to be an essential step in the carcinogenesis of sarcoid-associated gastric cancer. However, gastric cancer associated with gastric sarcoidosis is hardly experienced in clinical settings. Only 1 case of gastric cancer associated with gastric sarcoidosis, a 31-year-old male, has ever been reported, and that was in 1994.[4] The patient complained of abdominal pain, nausea, vomiting, and weight loss due to gastric sarcoidosis, and he had been treated with steroids for 19 years. The gastric sarcoidosis gradually became unresponsive to steroid therapy, and endoscopy revealed diffuse severe gastritis with ulceration. Gastric biopsy showed poorly differentiated adenocarcinoma involving the antrum, and CT scan showed liver metastases. Twelve weeks later, he died of gastric cancer. In this case, routine gastrointestinal endoscopic examinations were not employed.

Corticosteroid therapy shows a dramatic clinical improvement in about 66% of patients with systemic gastric sarcoidosis.[10] Prednisone with an initial dose of 20 to 40 mg can be started with gradual dose reduction. In patients with gastric sarcoidosis, however, surgical intervention may be necessary when gastric outlet obstruction, perforation, or massive hemorrhage is present after an intensive medical treatment. Although a laparoscopic total gastrectomy was indicated for our patient due to the presence of gastric cancer as well as narrowing of the gastric lumen, the primary staging of gastric cancer was difficult. In our case, an endoscopic ultrasonography failed in precise assessment of the depth of cancer invasion and an extensive fibrosis in the mucosa and submucosal layer of the stomach was evident histologically, which may contribute to difficulties in assessing the depth of cancer invasion and also making a strategic plan to manage gastric cancer in patients with longstanding gastric sarcoidosis. In addition, enlargement of lymph nodes with noncaseating granuloma can be recognized in any organs in patients with sarcoidosis, often creating difficulty in differentiating these lesions from metastases and leading to an inappropriate treatment of the patients coincided with malignancy.

In conclusion, we experienced a rare case of early gastric cancer associated with gastric sarcoidosis, which identified the troublesome issue that the assessment of depth of cancer invasion is difficult because patients with longstanding gastric sarcoidosis may involve various degree of fibrosis of the gastric wall.

Acknowledgments

Written informed consent was obtained from the patient for publication of this case report and any

accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. The authors declare that they have no competing interests. NH carried out the operation with TM and RH. NH, YF, SK, and TT have been involved in drafting the manuscript or revising it critically for important intellectual content. YT has given final approval of the version to be published. All authors read and approved the final manuscript.

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