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Synchronous Occurrence of Advanced Gastric Carcinoma with Retroperitoneal Liposarcoma: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 73-year-old
Final Diagnosis: Gastric cancer
Symptoms: Abdominal and/or epigastric pain
Medication: —
Clinical Procedure: —
Specialty: Pathology

Objective: Rare coexistence of disease or pathology

Background: Gastric carcinoma (GC) remains one of the most common and deadly neoplasms in the world. Liposarcoma (LPS) is the most common sarcoma of adults. However, synchronous or metachronous occurrence of GC with LPS seems to be very rare. Tumor staging and differential diagnosis with these cases are extremely difficult.

Case Report: The patient was a man in his 70s, who reported anorexia and weight loss of 4 kg over 2 months. Gastroscopy demonstrated a large tumor of Borrmann type 3, of which histology was moderately to poorly differentiated adenocarcinoma. The clinical stage was initially defined as IVb due to a 11×6 cm retroperitoneal (RP) tumor. Despite chemotherapy for GC, the RP tumor rapidly enlarged. Endoscopic ultrasound-guided fine-needle aspiration biopsy showed that it was an undifferentiated sarcoma. He died of hepatorenal failure secondary to severe jaundice. The autopsy revealed a synchronous occurrence of GC and RP sarcoma. GC had no areas admixed with sarcoma. Histology of RP sarcoma showed that it mainly consisted of undifferentiated sarcoma and focally of well-differentiated LPS characterized by well-differentiated adipocytes admixed with scattered atypical stromal cells. The tumor cells in both areas were positive for MDM2 and CDK4 by immunohistochemistry. The diagnosis of the RP sarcoma was revised to dedifferentiated LPS.

Conclusions: There were no previous case reports of synchronous occurrence of GC with LPS in the English and Japanese literature. GC and LPS pose challenging problems in their diagnoses, staging, and treatments when they occur synchronously or metachronously.

Keywords: Neoplasm Staging • Retroperitoneal Liposarcoma • Stomach Neoplasms

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Background

The incidence of sarcoma is very low worldwide [1-4]. Liposarcoma (LPS) is the most common sarcoma of adults, accounting for 15-25% of all sarcomas [2]. The upper leg was found to be the most common location and the retroperitoneum was the second [3]. However, gastric carcinoma (GC) remains one of the most common and deadly neoplasms in the world [5]. There seem to have been no case reports of metachronous or synchronous GC and LPS in the English literature. However, if such a case occurred, it would pose challenging problems in diagnoses, staging, and treatment.

The tumor-node-metastasis (TNM) classification by the Union for International Cancer Control is a global standard used to stage malignant tumors [6]. The standard treatments for GC are mainly based on the TNM staging system [7]. The algorithm is first divided into 2 groups according to absence or presence of distant metastasis. In addition to metastasis to distant organs, nodal metastasis beyond the regional lymph nodes is considered as distant metastasis. Patients with stage IV disease are usually treated by chemotherapy, radiotherapy, and palliative surgery.

The extra-regional sites of GC nodal deposits may be the retropancreatic, mesenteric, and retroperitoneal (RP) lymph nodes. These anatomic regions can harbor a variety of rare benign and malignant neoplasms that can be either primary or metastatic [8]. Most of the primary malignant neoplasms of the retroperitoneum are malignant lymphoma and carcinoma of the kidney, pancreas, and adrenal glands. Primary mesenchymal tumors of the retroperitoneum are far more likely to be malignant [9]. Around 10% of all sarcomas occur in the retroperitoneum [10]. The most common sarcomas are LPS and leiomyosarcoma. The retroperitoneum is the most common site of dedifferentiated LPS (DDLPS) [10,11].

Synchronous or metachronous occurrence of GC with RP sarcoma seems to be very rare. We report the first case with synchronous GC and RP DDLPS for which the tumor staging and differential diagnosis could not easily be determined. We review reports with synchronous or metachronous occurrence of GC with LPS of soft tissue. Additionally, we discuss challenging problems in proper diagnoses, staging, and management with these cases.

Case Report

The patient was a man in his 70s, who reported anorexia and weight loss of 4 kg over 2 months. Laboratory work-up revealed a hemoglobin of 7.5 g/dl, and CEA and CA19-9 were elevated to 16.3 ng/ml and 109.62 U/ml, respectively. Computed tomography (CT) showed marked mural thickening of gastric antrum and duodenal bulb with several up to 3.5-cm size enlarged regional lymph nodes. He also had a 11×6 cm RP mass (**Figure 1A, 1B**). Gastroscopy demonstrated a large tumor of Borrmann type 3, extending from the antrum to the duodenal bulb with an area of stenosis that was 9 cm in length (**Figure 2**). The histology showed moderately to poorly differentiated adenocarcinoma (**Figure 3**). The TNM classification comprised T2 and M1 [LYM] since the RP mass was thought to be a large RP lymph node metastasis. The clinical stage was defined as IVb. He was treated with 2 courses of combination chemotherapy with Cisplatin 70 mg and Tegafur/Gimeracil/Oteracil 100 mg for 30 days. Two weeks after finishing the treatment, the patient had progressive anemia and tarry stools. CT demonstrated rapid growth of the RP tumor with central necrosis, while the GC

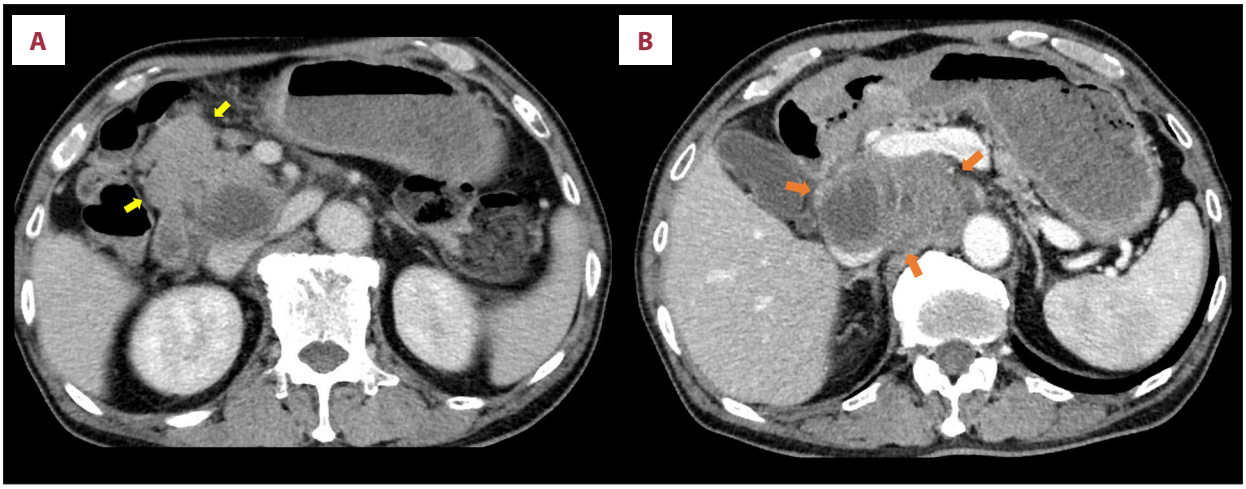

Figure 1. (**A**) Two up to 3.3-cm enlarged lymph nodes (yellow arrows) involving gastric regional lymph nodes. (**B**) A large, 11×6 cm, retroperitoneal tumor (orange arrows). The lesion was unusual in its large size and heterogeneous density compared with an ordinary GC nodal metastasis.

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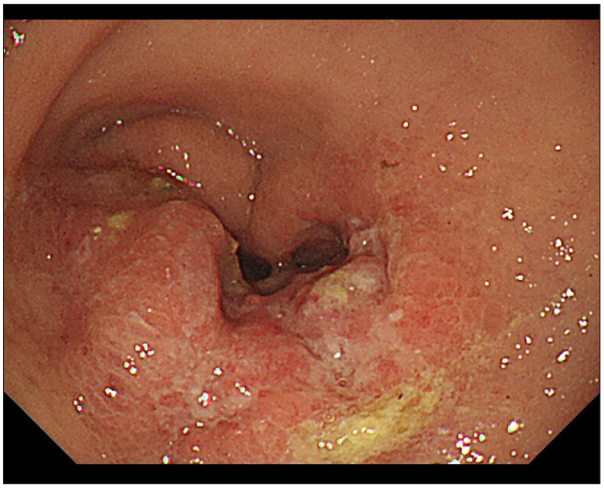

Figure 2. A Borrmann type 3 antral tumor with stenosis of the stomach on gastroscopy.

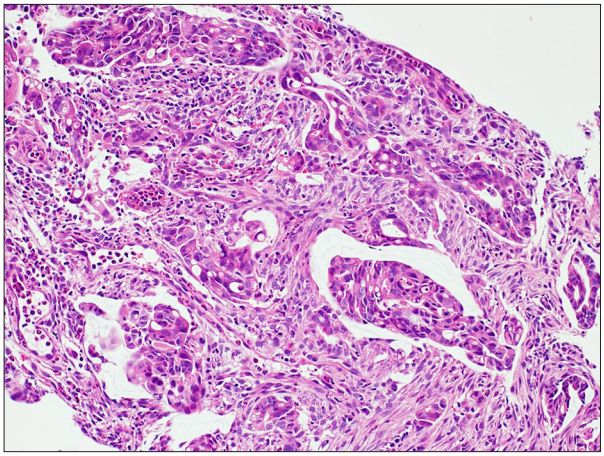

Figure 3. Gastric biopsy revealed a moderately to poorly differentiated invasive adenocarcinoma. H&E original magnification (OM) ×200.

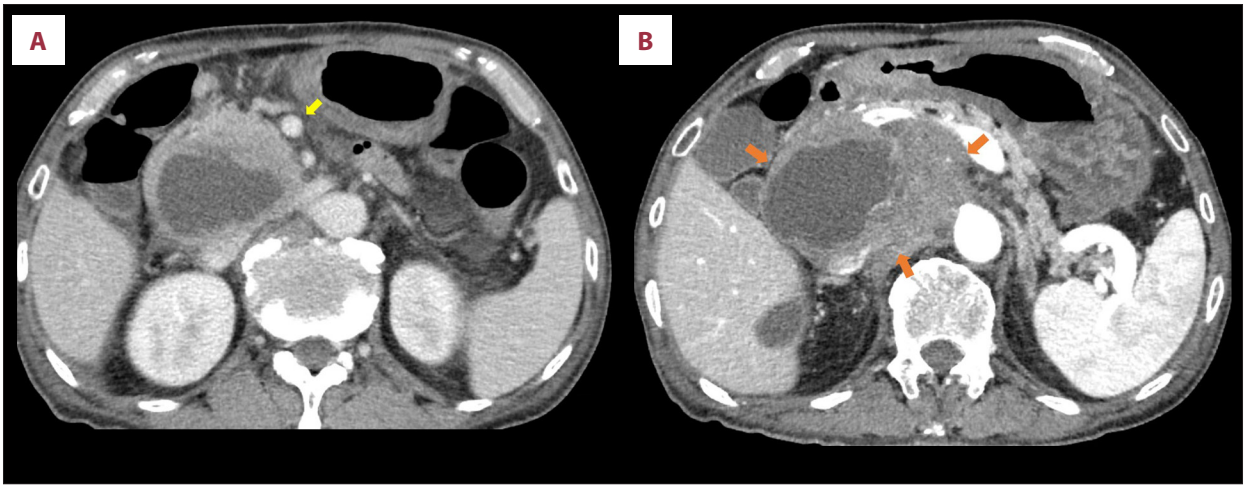

Figure 4. (**A**) After therapy, the regional lymph nodes decreased in size in comparison with Figure 1a (yellow arrow). (**B**) The RP tumor rapidly increased in size from 11 cm to 16 cm during therapy (orange arrows).

remained stable or slightly decreased in size (**Figure 4A, 4B**). The gastroscopy showed external compression of the upper part of the stomach, including the upper body and the esophagogastric junction.

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) was performed to classify the RP tumor. The biopsy showed a densely cellular proliferation of atypical spindle cells arranged in sheets (**Figure 5**). There were scattered necrotic and hemorrhagic foci. The tumor cells were immunohistochemically positive for vimentin and negative for AE1/AE3, CAM5.2, EMA, CD34, c-kit, DOG-1, CD3, CD20, CD68, and CD79a. Ki-67 index was more than 60%, which is high.

The tumor was classified as a high-grade malignant mesenchymal tumor, not otherwise specified. Three weeks after EUS-FNA, the RP tumor further enlarged and was associated with

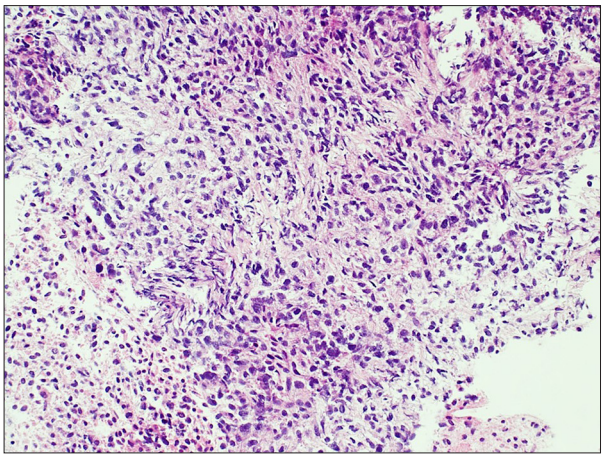

Figure 5. EUS-FNA of the RP tumor showed a proliferation of atypical spindle cells arranged in sheets. H&E OM ×200.

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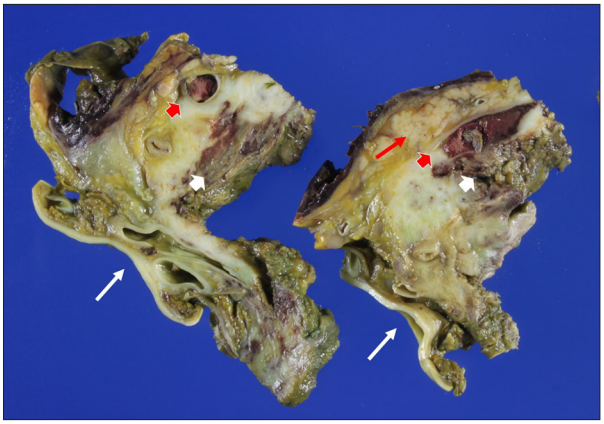

Figure 6. Gross examination at autopsy demonstrated the retroperitoneal tumor near the aorta (white arrows) and pancreas (red arrow) with massive central necrosis (white arrow heads) and invasion into the large vessels (red arrow heads).

pain, ascites, and inferior vena cava syndrome. The pain was controllable with hydromorphone hydrochloride (4 mg/day), while the ascites did not decrease with diuretic therapy. The patient died of hepatorenal failure secondary to severe jaundice 3.5 months after his first admission.

An autopsy was conducted with permission of the patient's family. A, 7×10 cm gastric tumor was observed, as well as less than a dozen regional lymph nodes up to 2×1.5 cm in size. The histology demonstrated moderate to poorly differentiated adenocarcinoma with focal treatment effect, replaced by fibrotic tissue. There were no foci of spindle cell sarcoma in the gastric tumor. A gross exam of the RP tumor reveled a firm, white-yellow tumor with extensive central necrosis. The latter RP tumor surrounded the abdominal aorta and inferior vena cava (IVC) with focal invasion of their walls and severe compression of IVC (**Figure 6**). The tumor also invaded the pancreas, soft tissue surrounding the extrahepatic bile ducts, and soft tissue adjacent to the stomach,

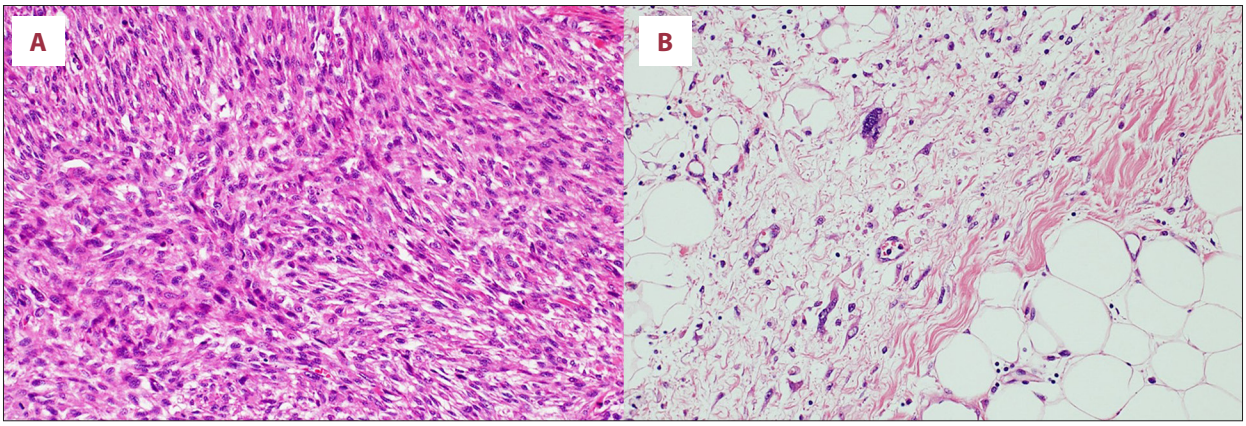

Figure 7. (**A**) Histology of the retroperitoneal tumor showed a monotonous proliferation of undifferentiated cells with a vaguely storiform pattern. H&E OM ×200. (**B**) Histology showed that focal areas of the RP tumor had well-differentiated LPS characterized by mature adipocytes and scattered atypical stromal cells. H&E OM ×200.

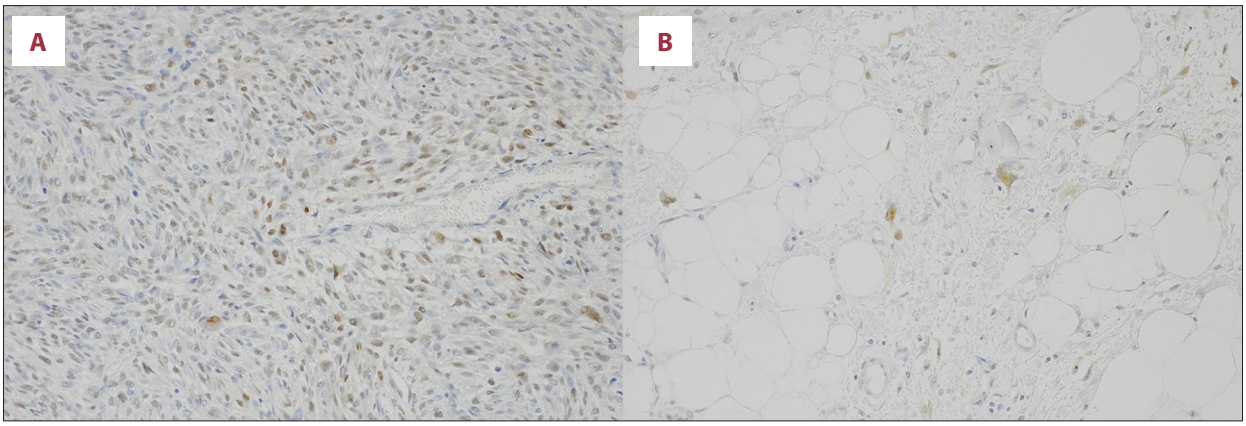

Figure 8. (**A**) Many tumor cells within the dedifferentiated areas are positive for MDM2. MDM2 OM ×200. (**B**) Scattered cells are positive for MDM2 in the well-differentiated LPS areas. MDM2 OM ×200.

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without any mingling with the GC. There was no organ metastasis from GC or RP tumors except for a tiny peritoneal deposit of the RP tumor within the rectovesical pouch. Four liters of hemorrhagic ascites and 600 ml and 1000 ml of pleural effusion were drained from the left and right pleural spaces, respectively.

Histology of the RP tumor showed that it mainly consisted of undifferentiated spindle cell sarcoma and focally of well-differentiated LPS characterized by well-differentiated adipocytes admixed with scattered atypical stromal cells (**Figure 7A, 7B**). The tumor cells in both areas were positive for MDM2 and CDK4 by immunohistochemistry. Based on these immunohistochemical findings, the diagnosis of the RP tumor was revised to DDLPS (**Figure 8A, 8B**).

Discussion

The incidence of sarcoma is less than 1%, 1.5%, and about 0.2%, in the world, USA, and Japan, respectively [1-4]. LPS is the most common sarcoma of adults, accounting for 15-25% of all sarcomas [2]. According to the Japanese Orthopaedic Association (JOA) clinical guidelines for management of soft tissue tumors, LPS was found to be the most common soft tissue sarcoma (4868/12 608 cases=38.6%) in Japan from 2006-2015 [3]. The upper leg was found to be the most common location (54%) and the retroperitoneum was the second most common anatomic site (8%), followed by the upper arm (6%), lower leg (6%), and buttocks (6%). Moreover, most DDLPS occur in the retroperitoneum and these account for the majority of pleomorphic sarcomas in the retroperitoneum [10,11]. Hence, DDLPS should always be considered as a potential candidate diagnosis in the differential diagnosis of undifferentiated malignant tumors of the retroperitoneum. Positive immunohistochemistry with MDM2 and/or CDK4 and/or demonstration of *MDM2* gene region amplification help to distinguish DDLS from other undifferentiated sarcomas [11].

There have been 6 reports including 11 cases of metachronous GC and LPS of the soft tissue in the Japanese literature [12-17]. The location of the sarcomas was the extremities (6 cases), retroperitoneum (3 cases), mesentery (1 case), and mediastinum (1 case). The diagnosis of GC preceded the diagnosis of LPS in 4 cases. To the best of our knowledge, there are no case reports of synchronous occurrence of GC with LPS in the English or Japanese literatures. In an English review, a total of 1845 cases of LPS had no concurrent or second primary cancer of the stomach [18]. A total of 269 patients developed a second cancer, of which the most common sites were the retroperitoneum, soft tissues, or kidney. A US population-based study demonstrated 10 secondary malignancies involving the soft tissue and the heart in 33 720 adult patients with GC [19]. There seems to be no increased risk of secondary sarcomas of the soft tissue in these patients while there was significant excess risk observed for additional gastrointestinal malignancies and thyroid and pancreatic cancer.

The TNM classification is a universal system for staging a wide variety of malignant tumors [6]. Treatments for patients with GC are mainly based on the TNM staging system. Since metastasis to RP lymph nodes is regarded as distant metastasis [7], the clinical stage of the case described in this report was initially defined as Stage IVb with TNM of T2 and M1 [LYM]. However, the RP tumor showed rapid growth when the primary gastric tumor and metastatic tumors of the regional lymph nodes were controlled by chemotherapy. EUS-FNA demonstrated that the RP tumor was an undifferentiated sarcoma, not otherwise specified, and we failed to make a diagnosis of DDLPS at initial assessment. Although synchronous occurrence of GC with RP LPS has not been reported, there are a few cases with synchronous well-differentiated/DDLPS and other tumors, including gastric gastrointestinal stromal tumor, colorectal, pancreatic, and renal carcinomas [18,20-23]. Moreover, there are rare cases of RP benign and malignant tumors that were clinically confused with RP GC lymph node metastasis [24,25].

Clinical management of RP LPS can be very challenging [26]. The mainstay of management for RP LPS is surgery [26,27]. However, complete resection of the tumor is frequently difficult because the tumor can be large at diagnosis and involves nearby vital organs and critical structures [10,27]. Chemotherapy and radiotherapy are still controversial in their effectiveness for treatment of RP LPS [28-31]. The main histological type of RP LPS is of well-differentiated-/dedifferentiated LPS [10]. The prognosis of the LPS differs based on classification and grading. DDLPS has a much lower overall survival rate than well-differentiated LPS [11]. High grade has a lower 5- and 8-year survival rate compared with intermediate grade in DDLPS [30]. In the case described in this report, it would have been very difficult to perform surgery for the GC and RP DDLPS even if the lesions had been classified properly at initial diagnosis. Nonetheless, careful staging of GC with an unusual tumor should be considered when faced with tumors in extra-regional sites.

Conclusions

We reported the first case with synchronous GC and RP DDLPS for which the tumor staging and differential diagnosis could not easily be determined. We reviewed reports with metachronous occurrence of GC with LPS of soft tissue in the Japanese literature. There were no previous case reports of synchronous occurrence of GC with LPS in the English and Japanese literature. Cases with synchronous or metachronous occurrence of GC and any type of sarcoma would pose challenging problems in their diagnoses, staging, and treatments, although they are very rare.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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