Malignant Gastrointestinal Stromal Tumor Originating in the Lesser Omentum, Complicated by Rapidly Progressive Glomerulonephritis and Gastric Carcinoma

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Abstract

A 69-year-old man was admitted with a large elastic mass in the upper abdomen. Computed tomography revealed a massive tumor in contact with the liver and gastrointestinal endoscopy revealed a gastric adenocarcinoma. He developed acute renal failure with massive proteinuria and died with a marked enlargement of the tumor. Autopsy revealed a tumor located in the lesser omentum. The tumor was considered to be a Gastrointestinal Stromal Tumor (GIST) because it was positive for c-kit. In addition, crescent formations and immune complexes in glomeruli were observed. We report the first case of GIST complicated by rapidly progressive glomerulonephritis and gastric carcinoma.
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Key words: double cancer, acute renal failure, and C-Kit

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract. GISTs typically express CD117 (c-kit), often express CD34, and sometimes express α-smooth muscle actin (SMA) or S-100. GISTs are thought to arise from interstitial cells of Cajal (ICCs), which express c-kit and CD34, in the gastrointestinal (GI) tract. The c-kit proto-oncogene encodes a type III receptor tyrosine kinase (KIT), the ligand of which is stem cell factor (SCF). The SCF-kit interaction is essential for the development of melanocytes, erythrocytes, germ cells, mast cells and ICCs. Products of mutant c-kit induce malignant transformation (1). Some papers have reported that most cases of this tumor have this mutation (2, 3). Thirty to forty percent of the tumor is found in the stomach, 20 percent in the small intestine, 30 percent in the colon or rectum, and less than 10 percent elsewhere, such as omentum or mesentery (4). GIST arising from the lesser omentum is rare, and omental GIST has been reported to have a lower tumor-related mortality rate than other GISTs (5, 6).

Malignant tumors are occasionally complicated by glomerulonephritis, such as membranous nephritis or crescentic glomerulonephritis (CrGN), clinically in less than 1 percent of cases (7).

Patients with cancer sometimes have multiple malignancies, at a reported rate about 7.5 percent in Japanese autopsy series. High occurrences of a second cancer are seen with cancer of the oropharynx, intestine, larynx, and bladder in males (8). In this case study, we report, to our best knowledge, the first case of GIST complicated by rapidly progressive glomerulonephritis (RPGN) and gastric carcinoma.

Case Report

A 69-year-old man was admitted to the Kanazawa Municipal Hospital for treatment of generalized edema and fatigue. These symptoms had been present for four months before his admission. He had been treated for diabetes mellitus without retinopathy and hypertension since the age of 59 by his general practitioner. Physical examination at the time of admission revealed a large elastic immobile mass in the upper abdomen, anemic conjunctivae, and pitting edema of

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the lower limbs. His blood pressure was 200/86 mmHg, and fasting glucose level was 130 mg/dl. Laboratory investigations revealed a lowered hemoglobin of 7.5 g/dl (normal levels 13.5–15.0), and elevated levels of serum LDH 7,445 IU/ml (250–452), CEA 4.6 ng/ml (<3.5), and soluble IL2-receptor 1,001 U/ml (190–650). PIVKA-II and AFP were negative. Urinalysis showed massive proteinuria (3.5 g/day) with microscopic hematuria, hyaline casts and oval fat bodies. Serum total protein was 4.9 g/dl and albumin, 2.5 g/dl. Serum levels of C3 and C4 were also lowered at 36.5 mg/dl (84–151) and 5.5 mg/dl (17–40).

Computed tomography revealed a massive tumor (14×9×6 cm) in contact with the left lateral segment of the liver and displacing the anterior wall of the stomach posterioinferiorly (Fig. 1). Ultrasonography showed a sharp demarcation between the tumor and the liver edge. The tumor had components with both solid and cystic density. [67] Gallium scintigraphy also delineated the tumor, with accumulation in the outer area. Gastrointestinal endoscopy revealed a Borrmann III lesion on the gastric angle of the antrum, and biopsy showed a poorly differentiated adenocarcinoma (Fig. 2). Cytology of ascites fluid was negative for tumor cells. To differentiate between extramural advance of the gastric carcinoma and another tumor, such as malignant lymphoma, leiomyosarcoma or neuroma, we performed an open biopsy of the tumor. Histological examination of the tumor showed large epitheloid cells, with large vesicular nuclei and poorly stained minimal cytoplasm, with a proliferating medulla and necrosis in some areas. More than 50 mitoses were observed per 10 HPF (high power field). On immunohistochemical examination, tumor cells were positive for HHF35 (actin) and negative for c-kit, CEA, AFP, NSE, and s-100. We accordingly made the diagnosis of a poorly differentiated leiomyosarcoma.

The patient then developed oliguric acute renal failure (ARF) with a serum creatinine level of 3.3 mg/dl, postoperatively, and underwent daily hemodialysis, but failed to recover from ARF. No chemotherapy or radical surgery could be undertaken because of the ARF, and he died on the 68th day of admission from cardiac arrest, the tumor having become markedly enlarged by that time.

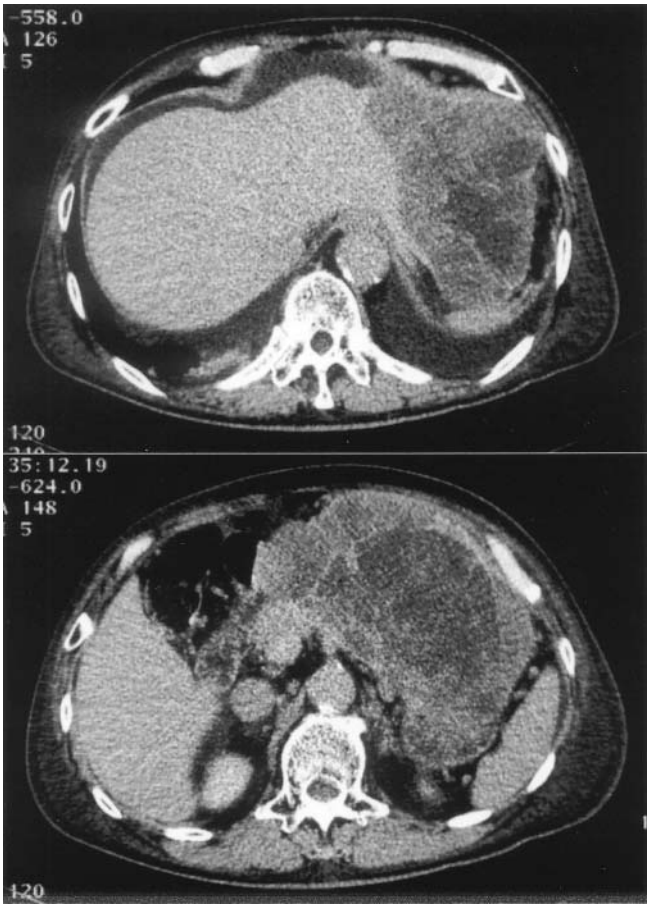


Figure 1. Enhanced computed tomography, delayed phase: The tumor with dimensions of (14×9×6 cm) is in contact with the left lateral segment of the liver, and displaces the stomach posteroinferiorly. Some ascites is seen on surface of the liver. The tumor has components with both solid and cystic density. The outer solid area of the tumor was enhanced, whereas the inner area remained unchanged.

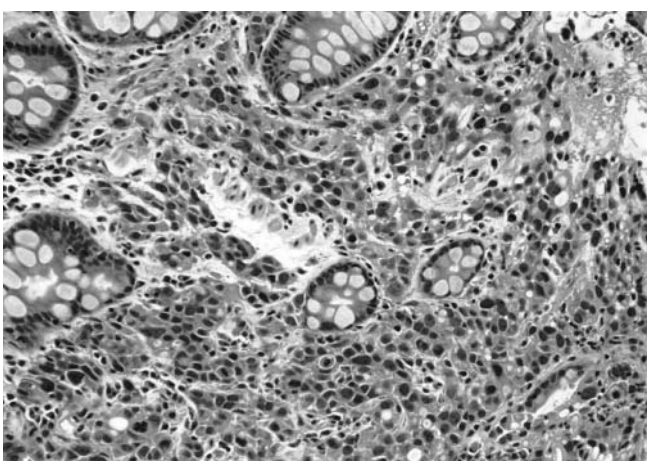
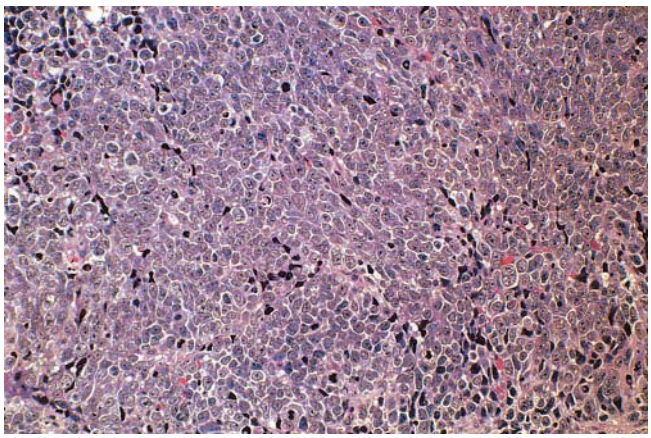


Figure 2. Gastric biopsy of a Borrmann III lesion on the gastric angle of the antrum showed a poorly differentiated adenocarcinoma (HE stain, ×200).

Autopsy Findings

An autopsy was conducted immediately after his death. Massive bloody pleural effusions and ascites were seen. A massive solid tumor (21×15×9 cm) was located in the lesser omentum, directly invading the left lateral segment of the liver and macroscopically metastasizing to the diaphragm. No involvement of the GI tract could be detected. Microscopically, the tumor was medullary and predominantly composed of round or oval cells with large vesicular nuclei (Fig. 3A). Some tumor cells were spindle-shaped. They were compactly arranged to show an epitheloid pattern. Mitoses were frequently observed (more than 50/10×HPF). Immunohistochemically, tumor cells were positive for c-kit



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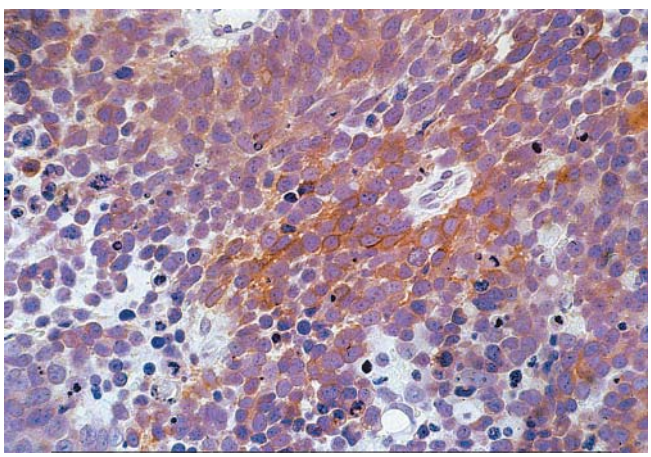

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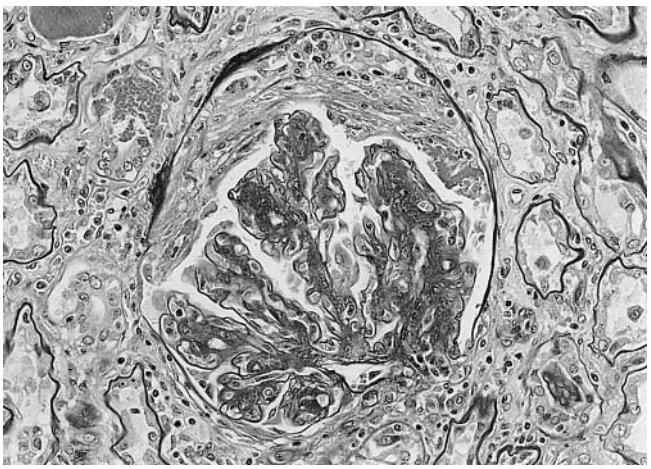
Figure 3. A: Autopsy (GIST): large epitheloid cells with large vesicular nuclei and minimal cytoplasm with a proliferating medulla and some necrotic tumor cells. Mitoses are frequent (more than 50/10 HPF) (HE stain, ×200). B: Immunohistochemical studies were strongly positive for c-kit (×400).



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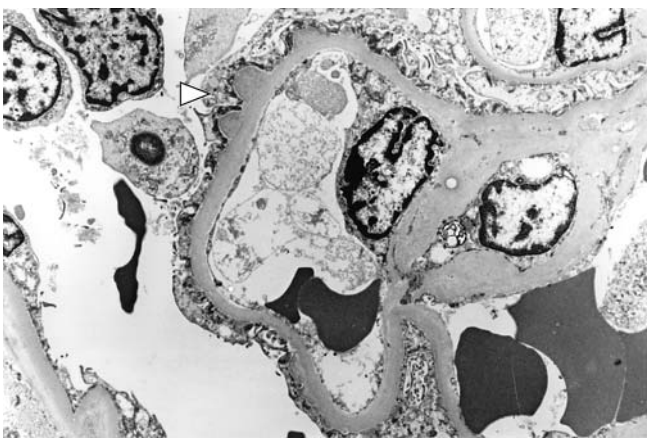

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Figure 4. A: Autopsy (kidney); Cellular crescent formations, lobulation and double contour of capillary walls were seen. Mild diffuse changes of diabetic nephropathy are also present (PAS ×400). B: Electron microscopy (kidney); Hump-like electron dense deposits (arrowhead) were seen in subepithelial lesions, but not in the mesangial or subendothelial regions (×4,000).

(Fig. 3B), and some were positive for HHF35, NSE, and synaptophysin. These findings indicated a GIST (epitheloid) originating in the lesser omentum.

A Borrmann's type III tumor (3.5×2.5 cm in size) found in the gastric antrum was a moderately to poorly differentiated adenocarcinoma infiltrating the muscle layer of the gastric wall. No distant metastases of the gastric carcinoma were detected.

Cellular crescent formations and lobulation could be observed in more than half of glomeruli. A double contour of the glomerular capillary wall was seen in some glomeruli, and mild diffuse changes of diabetic nephropathy were also seen in some glomeruli (Fig. 4A). Electron microscopy revealed huge immune complexes (ICs) on subepithelial lesions (Fig. 4B), however, findings were similar to the hump lesions seen in post-streptococcal acute glomerulonephritis, but not in mesangial or subendothelial areas. No evidence of vasculitis was present. The final pathological diagnosis was IC type CrGN.

Discussion

It has been reported that clinically about 20 percent of GISTs turn malignant. Predicting the malignancy of GISTs is very difficult, however. The most reliable criteria for the distinction of malignant GISTs are a tumor of greater than or equal to 5 cm in size with a mitotic rate of 5/50 HPF (high-power field) or more. Most reported GISTs with malignant character give rise to distant metastases. Since the present case fulfilled all of these criteria of malignancy, it was

thought to have significantly high grading for malignant characteristics.

After complete resection of GISTs, the 5-year survival rate is reported to be 42–54%, compared to 9% after incomplete resection. Survival is predicted by tumor size, the presence of distant metastases, and the number of mitoses (9, 10). GISTs are not responsive to cancer chemotherapy and radiation. Joensuu et al reported that STI571, an inhibitor of the tyrosine kinase activity of c-kit, is very effective for metastatic GIST (11) and Demetri et al reported more than one-half of advanced GIST patients who received STI571 had a partial response and only several percent of these patients progressed (12). Preclinical experiments showed rapid inhibition of ligand-independent KIT phosphorylation, decreased cellular proliferation, and induction of apoptosis of GIST cells after exposure to STI571 (13). STI571 is also known block the kinase activity of the oncogenic Bcr-Abl chimeric fusion protein of chronic myelocytic leukemia. It has been to become a standard therapy for malignant GISTs. We could not consider using STI571 for this patient, because GIST was only diagnosed by autopsy.

ARF in patients with malignancy is generally due to either prerenal azotemia induced by dehydration, or intrinsic renal azotemia triggered by chemotherapeutic drugs or products of tumor lysis. Tumor-associated glomerulonephritis is a very rare cause of ARF. The present case is therefore a particularly rare case of ARF due to IC type CrGN associated with the progression of malignant GIST. Immune complex deposition in the glomeruli of cancer patients is well known, although clinically most cases do not show signs of overt renal disease. Nephrotic syndrome in cancer patient most frequently takes the form of membranous glomerulonephritis. Occasionally specific tumor antigens, example for CEA, have been implicated in cases of clinical nephrotic syndrome (14). Petzel et al reported two cases of CrGN associated with malignant lymphoma. EM study revealed small deposits in subendothelial intramembranous, mesangial and subepithelial lesions of affected glomeruli (15). LDH levels in this case were significantly elevated and at autopsy most tumor cells were necrotic. This suggests a large load of soluble tumor antigens in the systemic circulation. We conjectured that soluble tumor antigens may induce an acute immunological response resulting in IC formation. Hump-like subepithelial IC lesions may then develop, causing CrGN and clinical RPGN. Immunohistochemical examination for c-kit failed, however, to confirm the presence of IC antigens in the glomeruli.

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