Long-Term Control for a Retroperitoneal Metastasis of Malignant Gastrointestinal Stromal Tumor after Chemoradiotherapy and Immunotherapy

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Traditionally, primary mesenchymal spindle-cell tumors of the gastrointestinal tract were almost uniformly classified as smooth muscle tumors (leiomyomas, leiomyosarcomas or leiomyoblastomas). However, recent immunohistochemical studies have shown that these tumors are divided into tumors composed of cells displaying smooth muscle or nerve sheath characteristics and tumors with cells of an unclear lineage (1–3). The term gastrointestinal stromal tumor (GIST) was introduced by Mazur et al. in 1983 as a histogenetically neutral term referring to gastrointestinal mesenchymal tumors with rudimentary if any differentiation (1). GIST has also been used as an umbrella term to cover all mesenchymal tumors, whether they are leiomyomas, shwannomas or neither.

In the treatment for malignant mesenchymal tumors, total surgical excision of the tumor is considered to offer the only hope for cure; the roles radiotherapy and/or chemotherapy have not yet been established. Here we report on a case of retroperitoneal metastasis of a GIST successfully treated by chemoradiotherapy and immunotherapy.

Case report. A 75-year-old woman had a history of total gastrectomy, distal pancreatectomy and splenectomy for sarcoma of the stomach in November 1990. In February 1993, she got discomfort in the right lower abdomen. Computed tomography (CT) revealed a huge retroperitoneal tumor 11 cm in diameter (Fig. 1a). The pathological examination of the specimen obtained by percutaneous needle biopsy revealed a solid nest of spindle-shaped atypical cells proliferating in interacting pattern in the fibrous tissue. The retroperitoneal tumor was diagnosed as a metastasis from the gastric sarcoma. Immunohistologically, tumor cells were negative for EMA, desmin or muscle-specific actin (HHF-35). The case surgeon in the hospital judged that this tumor was unresectable because of the invasion to adjacent organs. Therefore, the woman was presented to the Department of Radiology at Kyushu University Hospital for treatment.

The only abnormal laboratory data on admission was an elevated serum lactate dehydrogenase (LDH) level of 2142 IU/L (normal range: 261–483). Positron emission tomography using ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG PET) showed a high uptake of FDG in the tumor [standardized unit volume (SUV): 2.77] (Fig. 1b). Angiographical study revealed that the tumor was hypervascular and mainly fed by the right adrenal artery, which was a branch of the right infraphrenic artery, and the third lumbar artery.

A retrospective histological study of the primary gastric lesion revealed fascicular and interlacing proliferation of spindle-shaped tumor cells with large, hyperchromatic and cigar-shaped nuclei with mitotic figures (Fig. 2). The mitotic rate of this tumor was 55/50 high power fields (HPF). The tumor cells were positive for c-kit and CD34 but negative for myogenic markers (α-smooth muscle actin, HHF-35, desmin) and neurogenic marker (S-100 protein).

Radiotherapy was the primary mode of treatment. Six-megavolt linear accelerator (linac) x-rays were used with anterior-posterior ports with a conventional fractionation schedule of 1.5 gray (Gy) per day, 5 times per week.

At a total dose of 18 Gy, arterial chemotherapy with carboplatin and epirubicin was performed concurrently. Four hundred milligrams of carboplatin and 40 mg of epirubicin were infused from the right infraphrenic artery and the first, second, and third lumbar arteries, equally divided. The radiotherapy was performed without rest by arterial chemotherapy. The total radiation dose was 51 Gy.

The serum LDH level decreased gradually beginning at the start of radiotherapy, and it had reached a normal range (402 IU/L) by the completion of radiotherapy. Follow-up CT at that time revealed no significant change in tumor size, but there was a decrease in tumor density (Fig. 3a). In addition, ^{18}F-FDG PET showed a decrease of FDG uptake (SUV = 1.66) in comparison to

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the level before treatment (Fig. 3b). The patient was discharged in good condition 2 weeks after the treatment. The immediate follow-up treatment consisted of four intratumoral injections of a biological response modifier, OK432 (5 KE), given percutaneously at 1-week intervals as an outpatient at the hospital.

The patient has been followed as an outpatient without any other anti-cancer therapy. Follow-up CT carried out 6 years after the treatment revealed that the tumor markedly decreased in size to a small low-density structure 20 mm in diameter (Fig. 4).

Discussion. GIST is the designation for the major subset of mesenchymal tumors of the gastrointestinal tract that differ from typical leiomyomas, leiomyosarcomas and schwannomas. They occur predominantly in persons over 40 years of age with an equal sex incidence (4–6). GISTs are most common in the stomach and small intestine and occur, though rarely, in the esophagus, colon and rectum (4). GISTs are histologically similar to the other mesenchymal tumors of the gastrointestinal tract in hematoxylin-eosin (HE) stain, but they show specific immunohistochemical features in that most of them are positive for CD34 and c-kit (CD117) (2, 7). Although the cell of origin is not fully understood, recent immunohistochemical studies have suggested that this tumor originates from Cajal cells (7) or from multipotential cells that can differentiate into Cajal and smooth muscle cells (3). The primary gastric tumor, in our case, was initially diagnosed as a leiomyosarcoma and resected surgically. However, our retrospective immunohistochemical study revealed that this tumor is included in the category of GIST.

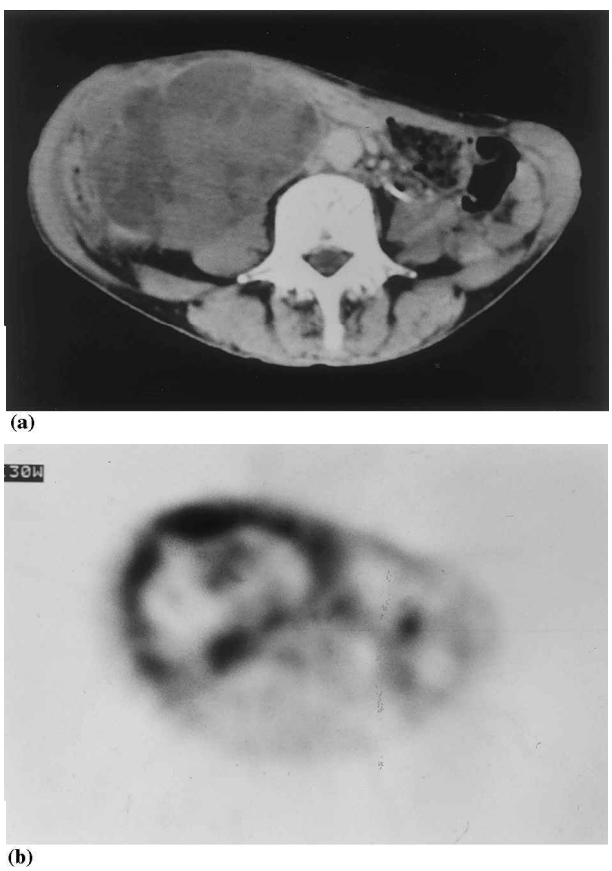


Fig. 1. (a) Abdominal CT scan demonstrates a large retroperitoneal tumor 11 cm in diameter. (b) Positron emission tomography using ^{18}F-FDG PET shows a high uptake of FDG in the tumor, especially in the marginal region (SUV = 2.77).

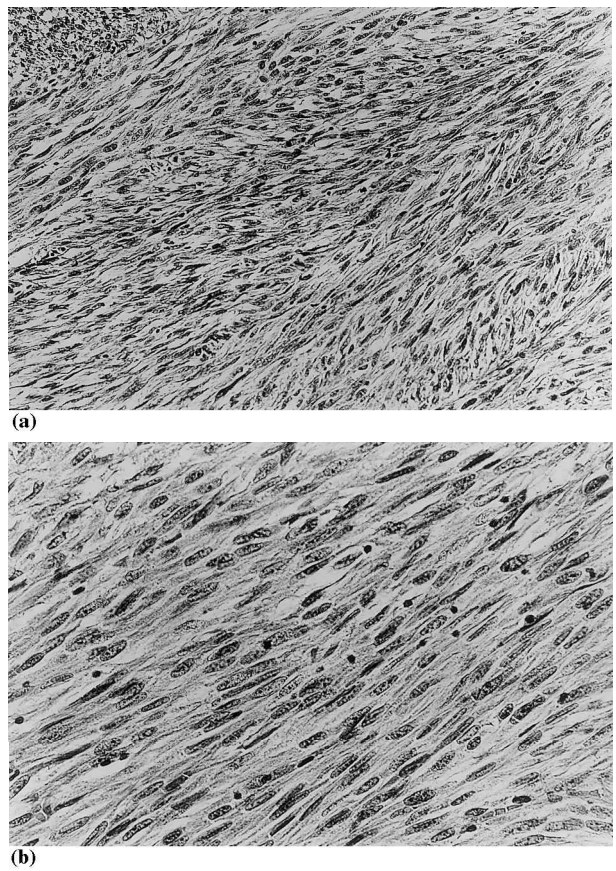
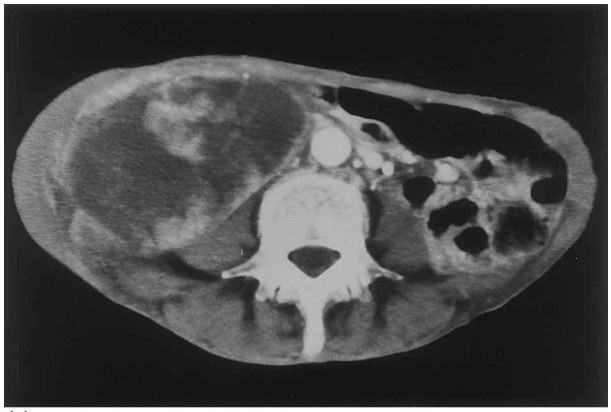


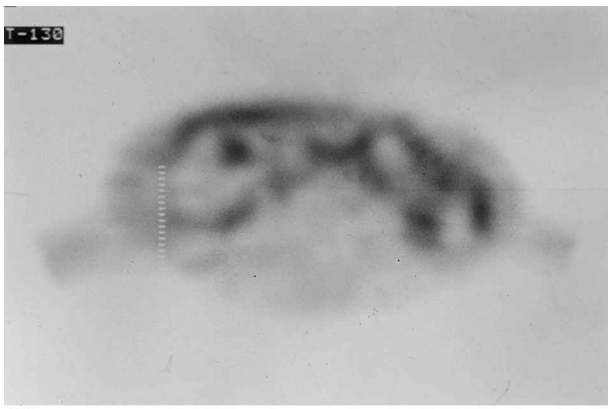
Fig. 2. Pathological findings of primary gastric lesion. (a) Fascicular and interlacing proliferation of spindle-shaped tumor cells (HE stains, original magnification × 33). (b) Tumor cells showing rather large, hyperchromatic and cigar-shaped nuclei with mitotic figures (HE stain, × 100).

Ten to 30% of GISTs are considered to have malignant potential (3, 4). Clinical and pathological criteria to differentiate benign from malignant GISTs are not well established. However, large tumor size (> 5 cm in diameter), the presence of necrosis, high mitotic counts (> 5 mitoses/10 HPF) and extra-gastrointestinal spread are commonly considered as important features, predicting biological behavior and outcome (3, 4, 6). Prognosis of the patients with malignant GIST is generally not favorable because of uncontrolled metastatic disease (8). The most common metastatic sites are peritoneal surfaces, especially serosa covering the mesentery, omentum and abdominal viscera, and also metastases to the liver or lung often develop (4). In particular, large tumor size and high-grade tumor have been reported to perdict poor clinical outcome (9). The primary gastric tumor of our case showed not only high mitotic rate (55/50 HPF) but also other pathological features suggesting its malignant potential, such as extramural spread of the tumor cells, massive hemorrhage and necrosis.

The standard treatment for a malignant GIST is thought to be radical surgical resection much like the treatment for other sarcomas, whereas the roles of radiotherapy and chemotherapy have not been well established. Even in adjuvant setting, the efficacy of radiotherapy and chemotherapy for sarcomas of gastrointestinal tract has not been well determined (10, 11). The decrease in serum LDH levels immediately after the start of radiotherapy suggests that radiotherapy had a major effect in this recurrent tumor in



(a)



(b)

Fig. 3. (a) Follow-up CT scan immediately after the completion of radiotherapy. There is no significant change in tumor size, but there is a decrease of density inside. (b) ^{18}F-FDG PET at the same time as (a) showed a decrease in FDG uptake (SUV = 1.66) in comparison to that before treatment.

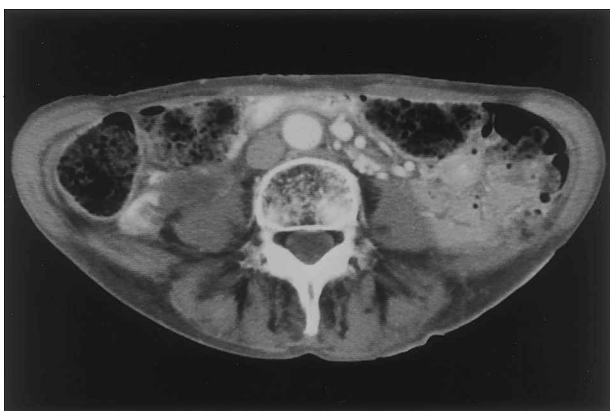


Fig. 4. Follow-up CT scan at 6 years after the treatment. The tumor, markedly decreased, is a small low-density structure 20 mm in diameter.

our case. This speculation was supported by the results of CT and ^{18}F-FDG PET. The arterial chemotherapy might have had an additive or enhancing effect on the treatment, but the contribution is unclear.

OK432 is a pharmaceutical preparation of Streptcoccus pyogenes that has been used in the treatment of malignant diseases (12), and that can activate neutrophils, natural killer cells and macrophages (13, 14). There have been no reports of immunotherapy for GISTs or other sarcomas. Therefore, the contribution of immunotherapy to the outcome cannot be assessed.

In conclusion, we have presented a case of unresectable retroperitoneal metastasis, which was durably controlled by radiotherapy combined with arterial chemotherapy and immunotherapy.

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