

Primary gastrointestinal stromal tumor of the liver in an anorectal melanoma survivor: A case report

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Abstract. The majority of gastrointestinal stromal tumors (GISTs) arise in the stomach and small intestine; primary GIST of the liver is extremely rare. GISTs share specific immunohistological features with melanoma, therefore, determining a definitive diagnosis can be difficult. However, electron microscopy can be used to aid the differential diagnosis of GIST. The present study reports the first case of a *KIT*/platelet-derived growth factor receptor α (*PDGFRA*) wild-type, primary GIST arising from the liver in a long-term survivor of anorectal melanoma. The patient underwent APR for treatment of malignant melanoma of the anorectum in 2001 with no adjuvant therapy and remained disease-free until 2009. In 2009, the patient presented with a solitary, rapidly growing hypervascular liver tumor, which was subsequently diagnosed as a primary GIST of the liver. Imatinib treatment (400 mg/day) was initially administered for two months, however, disease progression occurred. Therefore, the patient underwent chemotherapy with doxorubicin (50 mg/m²) and cisplatin (50 mg/m²) every three weeks. Although this temporarily resulted in stable disease, progression occurred five months later. Finally, oral sunitinib (37.5 mg/day) was administered; however, the patient succumbed to the disease one month later. Despite the current GIST patient exhibiting a poor response to imatinib, the present study highlights the importance of considering a second primary malignancy and performing immunohistochemical analysis upon the occurrence of a newly developed lesions in long-term remission cancer survivors.

Introduction

Anorectal melanoma, the third most common site of mucosal melanoma, is a rare tumor with an incidence rate of 1.7 cases per million in the global population (1). Surgery, including abdominoperineal resection (APR) or wide local excision (WLE), is the primary treatment strategy for localized disease; however, these two surgical approaches result in similarly poor clinical outcomes, with five-year recurrence rates of 79 and 81% following APR and WLE, respectively (2). Furthermore, the five-year overall survival rate following curative resection ranges from 15 to 22%, with the majority of patients succumbing to recurrent disease. Recurrence predominantly occurs in the liver, followed by the lung and brain (3,4).

Gastrointestinal stromal tumors (GISTs), characterized by the expression of cluster of differentiation (CD) 117 and a high incidence of *KIT* or platelet-derived growth factor receptor α (*PDGFRA*) mutations, are uncommon tumors with an incidence range of 6-15 cases per million individuals (5). The majority of GISTs arise in the stomach and small intestine, and GISTs originating from the esophagus, colon and extra-gastrointestinal organs, such as the retroperitoneum and liver, are rare (6). To the best of our knowledge, only five cases of primary hepatic GIST have previously been reported in the English literature (7-11). The most common *KIT* mutation sites involve exon 11 (66.1%) followed by exon 9 (13%); however, 12% of cases exhibit no detectable *KIT* mutation and are therefore categorized as *KIT* wild-type GISTs (12).

The present study reports the case of a long-term survivor of anorectal melanoma who, seven years after APR surgery, developed a solitary rapidly growing tumor in the liver.

Case report

A 58-year-old Taiwanese male was diagnosed with malignant melanoma of the anorectum and underwent APR at Kaohsiung Medical University Hospital (Kaosiung, Taiwan) in 2001. Microscopically, the anorectal tumor was composed of spindle-shaped neoplastic cells beneath the squamous epithelium with brownish pigments and adjacent junctional activity. Furthermore, the tumor was immunohistochemically positive for human melanoma black (HMB-45) and S-100 (Fig. 2A-D).

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No surgical margin or lymph node involvement was apparent, therefore, stage I anorectal melanoma was diagnosed. The patient did not receive any adjuvant therapy and was regularly followed up by physical examination every two weeks at Kaohsiung Medical University Hospital for five years after surgery.

In 2009, after a further two years and at the age of 65 years, the patient presented to the Department of General Surgery at Kaohsiung Medical University Hospital with a two-month history of general malaise, loss of appetite and progressively worsening dull pain over the epigastrium. An appropriate physical examination revealed no abnormalities, with the exception of the APR surgical scar on the abdominal wall. However, a follow-up contrast-enhanced computed tomography (CT) scan revealed a 12x11-cm solitary tumor within the left lobe of the liver (Fig. 1A). Serum α -fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9 levels were all within normal limits. Subsequently, a percutaneous CT-guided biopsy of the liver tumor was performed. Microscopically, the liver tumor was composed of spindle cells arranged in interlacing fascicles with hyperchromatic, round or oval to spindle pleomorphic nuclei. Immunohistochemical (IHC) staining revealed that the neoplastic cells were diffusely and strongly positive for CD117, but negative for HMB-45, S-100 melan-A and CD34. Furthermore, the mitotic activity of the tumor cells was five mitoses per 10 high-power fields. Retrospectively, positive CD117 staining was also observed in the anorectal melanoma and the basal layer squamous epithelium. The results of the histological and IHC staining of the anorectal melanoma are shown in Fig. 2A-D, and the liver tumor in Fig. 2F-I. In addition, polymerase chain reaction followed by direct sequencing was performed using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissue, revealing that the anorectal melanoma and hepatic tumor were negative for *BRAF*^{V600E} (data not shown).

To confirm the diagnosis, transmission electron microscopy (TEM) of the FFPE-derived tumors was performed to determine the ultrastructure of the two tumors. Analysis of the anorectal tumor showed a number of electron-dense granules around the nucleus, which were considered to be atypical melanosomes, and inconspicuous microtubules within the cisternal space of the cytoplasm (Fig. 2E). These features were considered to correspond with the diagnosis of melanoma. Due to damage of the fine structures of the small paraffin-embedded tissue during formalin fixation and subsequent xylene treatment, artifacts were present in the sample and a collapsed cytoplasmic structure was observed. Thus, the quality of the liver TEM image was poor. Therefore, no villous cytoplasmic processes or dispersed intermediate filaments, which are considered to be characteristic ultrastructure features of GISTs, could be identified (13). However, hyperchromatic nuclei and a vesicular cytoplasm without melanosomes were present (Fig. 2J), indicating that the liver tumor may have a different histology from the prior melanoma.

Despite testing negative for *KIT* and *PDGFRA* mutations, the liver tumor was diagnosed as primary GIST of the liver based on its IHC profiling (diffusely strongly CD117-positive, and negative for HMB-45 and S-100), and TEM features when compared with anorectal melanoma, as well as the lack of other intra-abdominal tumors identified on abdominal CT imaging. Due to the presence of left portal vein invasion, the

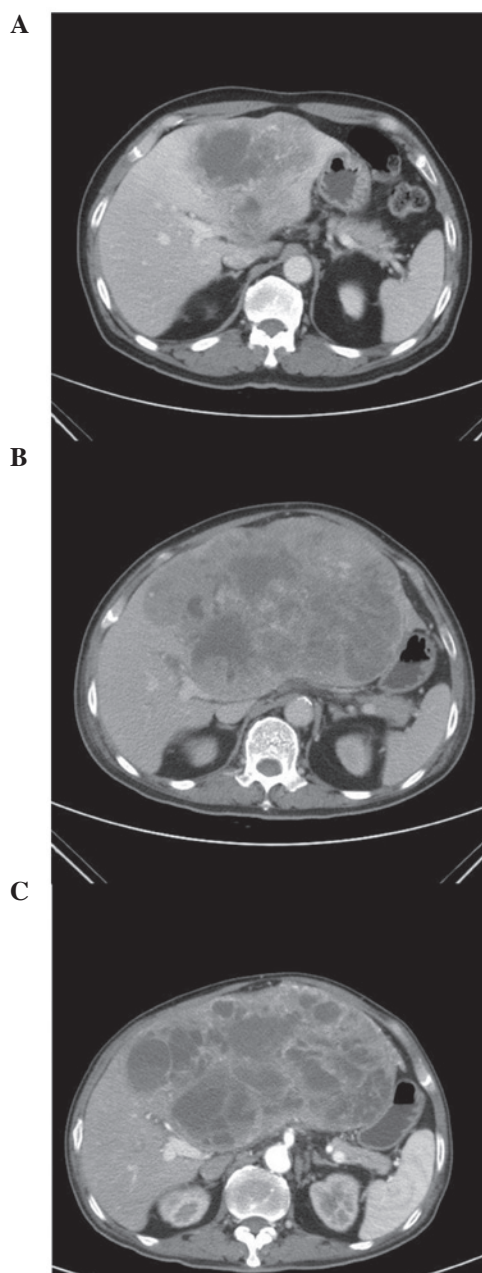


Figure 1. (A) Initial CT scan indicating a heterogeneous contrast-enhanced mass in the left hepatic lobe with left portal vein invasion at diagnosis. (B) CT scans three months after imatinib treatment (dose, 400 mg/day), and (C) two months after chemotherapy with doxorubicin (dose, 50 mg/m²) and cisplatin (dose, 50 mg/m²). CT, computed tomography.

hepatic GIST was considered as unresectable, therefore, oral imatinib was administered at a dose of 400 mg/day for two months. However, a follow-up CT scan after two months of imatinib therapy demonstrated that the tumor had progressed to 22x13 cm in size (Fig. 1B). While awaiting the approval of sunitinib from regulatory authorities, systemic chemotherapy consisting of 50 mg/m² doxorubicin and 50 mg/m² cisplatin was administered every three weeks for five months. This regimen resulted in symptomatic improvement manifesting as a decrease in dull epigastric pain and tumor size by palpation after the first cycle of treatment. Thus, this chemotherapeutic treatment strategy was continued. A follow-up CT scan, conducted two months later, demonstrated that the tumor had stabilized

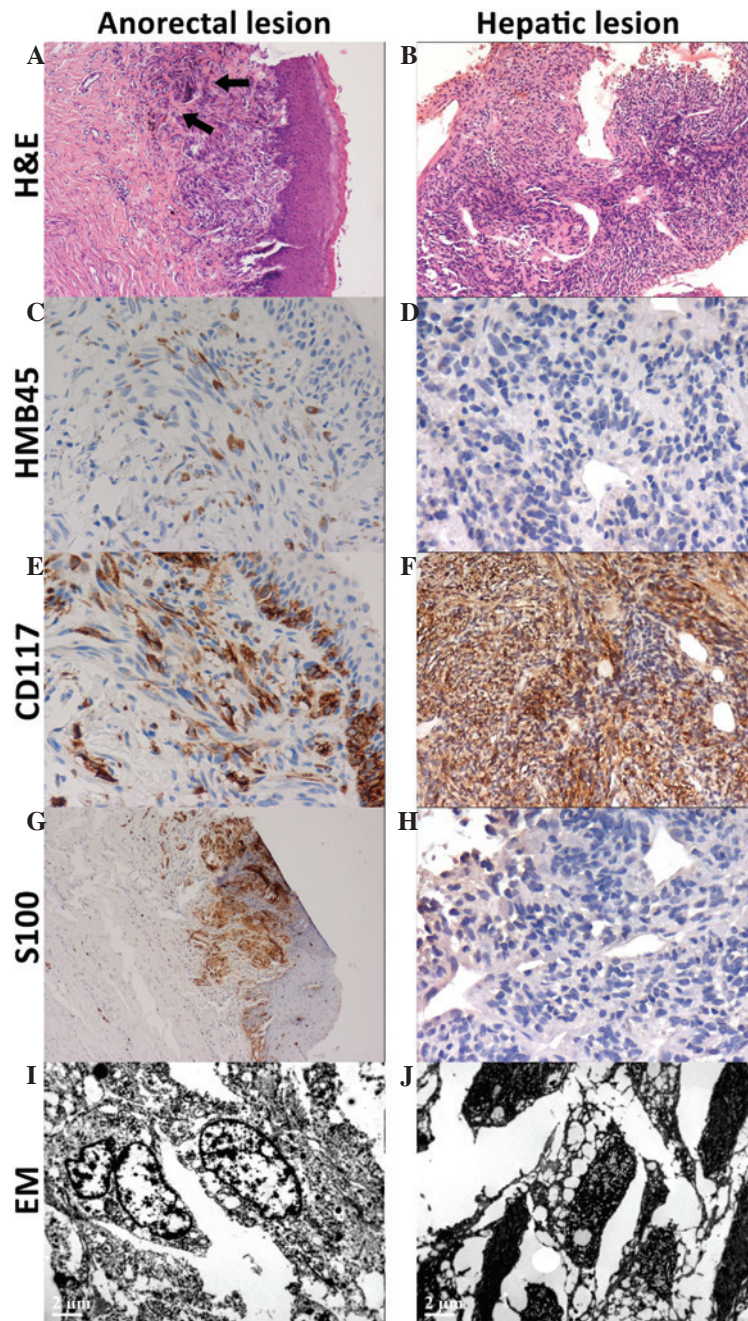


Figure 2. Histology: (A-H) IHC analysis and (I and J) EM of the primary anorectal melanoma and second primary hepatic gastrointestinal stromal tumors. For the anorectal lesion, (A) H&E staining revealed subepithelial spindle neoplastic cells with brownish pigments (arrows), which were positive for (C) HMB45, (E) CD117 and (G) S-100 in IHC analysis, and (I) positive for atypical melanosome in EM examination. For the hepatic lesion, (B) H&E staining revealed spindle neoplastic cells arranged in whorls or intervening fascicles, which were (D) negative for HMB45, (F) strongly positive for CD117 and (H) negative for S-100 in IHC staining. (J) EM showed hyperchromatic nuclei and vesicular cytoplasm. IHC, immunohistochemical; H&E, hematoxylin and eosin; HMB-45, human melanoma black-45; CD117, cluster of differentiation 117; EM, electronic microscopy.

with minimal regression to a size of 19x11 cm (Fig. 1C). The chemotherapy was continued for an additional three months, substituting with 37.5 mg/day sunitinib after disease progression. However, the patient did not respond to sunitinib and succumbed to the disease one month later.

Discussion

The current study describes the case of a unique patient who was found to have a solitary hypervascular liver tumor that

was subsequently diagnosed as a second primary GIST of the liver by IHC. The patient had undergone APR for a stage I anorectal melanoma seven years prior. Clinically, it is not possible to distinguish between a metastatic melanoma and a metastatic or primary GIST in the liver, as the two types of tumor can be hypervascular in the early arterial phase of a CT scan, and grow rapidly. Considering the history of anorectal melanoma and the absence of a *KIT/PDGFR*A mutation during genotyping, the diagnosis of GIST in the present patient may be disputable. However, if the patient did not have

Table I. Five cases of primary gastrointestinal stromal tumors of the liver.

Author (Reference)	Cell type	Age, years	Gender	Tumor size, cm	Immunohistochemical staining					Mitotic index	KIT/PDGFR status
					CD117	CD34	Vimentin	S100			
Hu <i>et al</i> (7)	Spindle	79	Female	15	+	+	+	-	-	4/10	Not performed
De Chiara <i>et al</i> (8)	Spindle	37	Male	18	+	-	+	-	-	20/50	Not performed
Ochiai <i>et al</i> (9)	Mixed	30	Male	Large ^a	+	+	+	-	-	75/50	No KIT exon 11 mutation ^b
Luo <i>et al</i> (10)	Spindle	17	Male	5.1	+	+	+	-	-	Not performed	Not performed
Yamamoto <i>et al</i> (11)	Epithelioid	70	Male	20	-	+	+	-	-	1/50	PDGFR, exon 12
Current case	Spindle	65	Male	12	+	-	+	-	-	5/10	Wild-type KIT/PDGFR

^aDescribed as a large tumor, no exact dimensions provided. ^bOnly KIT exon 11 was analyzed. CD, cluster of differentiation; PDGFR, platelet-derived growth factor receptor α .

a history of mucosal melanoma, the tumor could be easily diagnosed as GIST based on the results of the CD117 staining, irrespective of its *KIT/PDGFR* genotyping. Therefore, a final diagnosis of hepatic GIST was determined, based on the diffusely strong CD117 staining, negativity for HMB-45 and S100 (two positive markers noted in his anorectal melanoma) and the difference in ultrastructure between the two tumors, as noted by performing TEM.

Initially, the diagnosis of GIST was considered to be more favorable for the current patient compared with those exhibiting metastatic melanoma, with disease-specific median survival periods of 19.0 and 13.3 months, respectively (14). However, following the approval of imatinib in 2002, results indicated that metastatic or unresectable GIST was more treatable compared with metastatic melanoma, with a notable increase in survival to 38.4-60 months (according to the kinase genotype) (15). Imatinib markedly improved the survival of GIST patients, regardless of the *KIT/PDGFR* mutation status. Despite imatinib typically producing a poorer response in wild-type GIST compared with exon 11-mutated GIST, imatinib does provide a benefit to patients with wild-type GIST, exhibiting a disease control rate of >60% (15). Furthermore, in patients with wild-type GIST, Asian populations appear more likely to benefit from imatinib treatment compared with Western populations. In the CALGB 150105 study, clinical benefit rates were 78-95% in the Asian population and 64% in the Western population (15). Additionally, five-year survival rates of 60-70% and 40-45% were noted for Asian and Western populations, respectively (15-17). Although the differences may have been caused by the small-size bias of Asian studies, the possibility of higher pharmacokinetic parameters in Asian populations following fixed-dose imatinib treatment should also be considered. Despite the increased benefit in Asian populations, the current patient did not receive any benefit from imatinib treatment and the tumor progressed rapidly within two months, which indicates that the nature of primary hepatic GIST may be different from those arising in the alimentary tract.

To the best of our knowledge, to date, only five cases of primary hepatic GIST have been previously reported (Table I) (7-11). Among these five cases, two cases received imatinib therapy (8,9). One of the imatinib-treated cases lacked mutation analysis data, however, the patient exhibited a good response to imatinib, resulting in a disease-free status for three years (8). The other imatinib-treated case had no mutation of *KIT* exon 11 (only *KIT* exon 11 was analyzed) and responded well to imatinib, with a long-term survival period of nine years (9). As only a small number of cases of primary hepatic GIST have been reported thus far, the correlation between the *KIT* genotype and response to imatinib, a tyrosine kinase inhibitor, remains inconclusive; thus, additional studies are required to address the issue.

In conclusion, despite the poor response to imatinib of the primary hepatic *KIT/PDGFR* wild-type GIST in the current patient, the present study highlights the importance of considering a second primary malignancy and performing immunohistochemical analysis upon the occurrence of a newly developed lesions in long-term remission cancer survivors. With the emergence of modern molecular technologies, such as next-generation sequencing, it may be possible to precisely determine genetic alterations that exist between the two tumors. This may aid in determining the nature of the second

tumor (delayed recurrence versus second primary), as well as providing useful information to guide therapeutic treatment of the disease.

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