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Case Report

Malignant glomus tumor of the ileum mimicking GIST with distant metastasis without BRAF V600E mutation

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Abstract: Glomus tumors arising in the gastrointestinal tract are rare and generally benign mesenchymal neoplasms that account for approximately 1% of all gastrointestinal soft tissue tumors. We report a unique case of malignant glomus tumor arising in the ileum of an elderly Chinese woman with widespread metastasis. The patient underwent local tumor resection for a presumed gastrointestinal stromal tumor (GIST). However, brain metastasis developed 2 years later, followed by a lesion in colon 6 months later and a subcutaneous mass of abdominal wall 12 months later. Then, local resections of all metastatic tumors were performed. Histopathology and immunohistochemical findings supported the diagnosis of malignant glomus tumor. Microscopic examination revealed that the primary and metastatic tumor cells shared common features: oval to spindle-shaped, with sharply defined cell membranes, round uniform nuclei, atypical mitotic figures, and variable necrosis. Immunohistochemical staining revealed positive expression of vimentin, SMA, caldesmon, MLH1, MSH2, MSH6, PMS2, SDHB and P53. Even with distant metastasis, the patient has been followed up for 28 months after the third operation without any radiotherapy and chemotherapy. To the best of our knowledge, this is the first report of a malignant glomus tumor arising from the ileum that metastasizes to the brain and abdominal wall with relatively favorable prognosis.

Keywords: Malignant glomus tumor, ileum, metastasis, brain, recurrence

Introduction

Glomus tumors are rare mesenchymal neoplastic lesions that commonly develop in the distal extremities, such as the subungual zones of the fingers and toes. These tumors are hypothesized originate from a glomus body, which plays an important role in skin thermoregulation. The distribution and amount of glomus bodies vary in different parts of the body. Glomus tumors occur usually in the subcutis and superficial soft tissues, but less frequently in visceral locations, such as tympanum, mediastinum, trachea, kidney, lungs, stomach, pancreas, liver, gastrointestinal tract, and genitourinary tract [1-8]. The overwhelming majority of reported glomus tumors in visceral organs are benign, while malignant glomus tumors are extremely rare. Abu-Zaid *et al*. reported the first malignant glomus tumor in the ileum [3]. However, no evidence of recurrence or metastasis was detected. Here, we reported a case of malignant glomus tumor arising from the ileum with metastasis to the brain, which had originally been diagnosed as GIST. The diagnosis was confirmed by PCR. We also reviewed the literature regarding the clinicopathological features of this rare neoplasm.

Materials and methods

Patient information and selection

A 75-year-old female woman, who had a history of digestive tract bleeding and anemia for 3 months, presented to the Capital Medical University Affiliated Beijing Shijitan Hospital (Beijing, China) in May 2015. Histopathologic diagnosis was malignant glomus tumor in GI tract with distant metastasis. The protocol of this study was approved by ethics committee of the Capital Medical University Affiliated Beijing Shijitan Hospital (Beijing, China). The patient has provided written informed consent for inclusion. The diagnosis was confirmed by three senior pathologists at 3 professional hospitals.

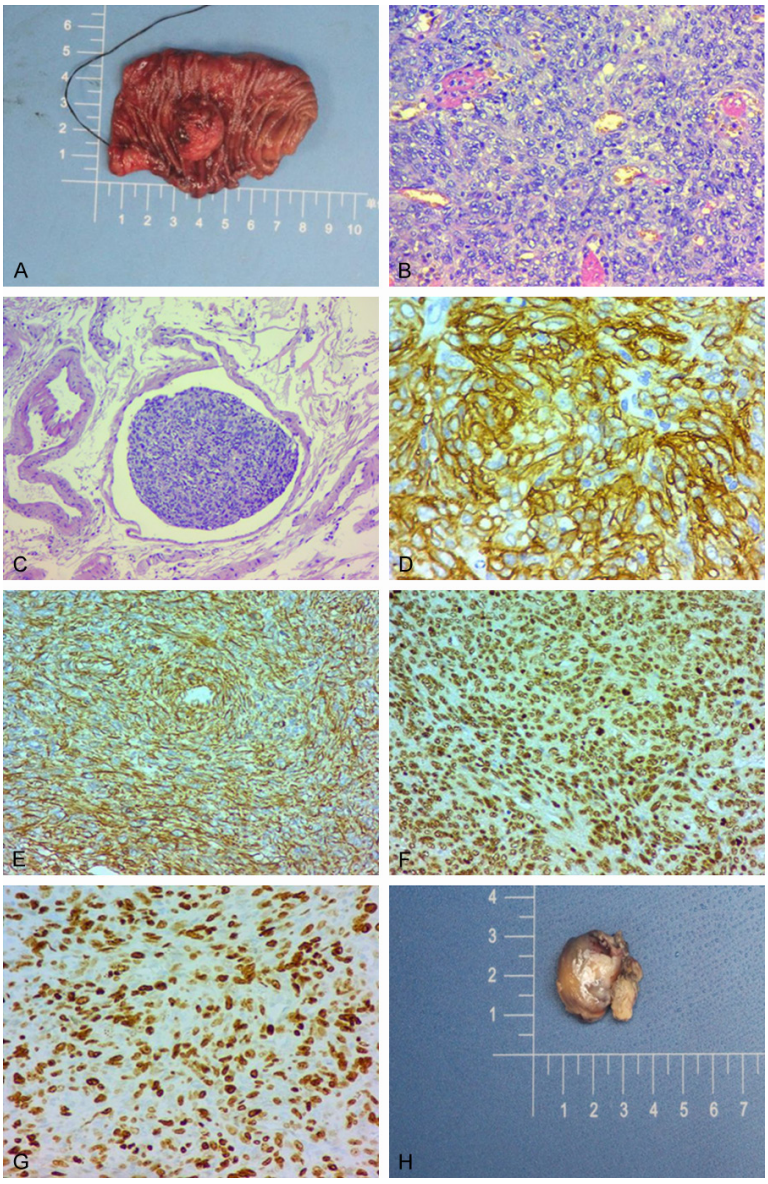

Figure 1. Histopathologic characteristics of malignant glomus tumor. A. Gross appearance. The lesion had invaded through the muscular layer of the ileum. B. Histologic features. The tumor cells were oval-to spindle-shaped, with sharply defined cell membranes, round uniform nuclei, delicate chromatin, and inconspicuous nucleoli (hematoxylin and eosin, ×20). C. Intravascular tumor embolus (hematoxylin and eosin, ×20). D. Positive expression of SMA (IHC, ×40). E. Positive expression of caldesmon (IHC, ×20). F. Positive expression of P53 (IHC, ×20). G. Ki-67 index of 80% (IHC, ×20). H. Tuberous mass surrounded by grey brain tissue.

ARMS-PCR

Genomic DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor sections using AmoyDx®FFPE DNA and RNA Extraction kits (Amoy Diagnostics Co., Ltd., Xiamen, China), according to the manufacturer's instructions. Specific DNA fragments of *KIT* gene exons 8, 9, 11, 13, 14, 15, and 17 as well as *PDGFRA* gene exons 12, 14, and 18 were amplified by polymerase chain reaction (PCR) with specific primers and sequenced as previously described [1]. Fluorescence signals were collected at 60°C. The mutations were identified with a specific probe labeled with Hydroxy fluorescein. Amplicons were detected using ABI7500 Fast Real-Time PCR System (ThermoFisher Scientific, MA, US).

Case report

A 75-year-old Chinese woman presented to Beijing Shijitan Hospital on May 5, 2015. She had a history of digestive tract bleeding and anemia for 3 months, without any associated symptoms, such as nausea, vomiting, and abdominal pain. A physical examination revealed no remarkable findings except anemia. Laboratory investigations demonstrated a plasma hemoglobin level of 90 g/L (normal: 110-160 g/L). The patient had undergone modified radical surgery for breast cancer in March 2010. The pathologic diagnosis for breast cancer was a malignant mesenchymal tumor without lymphoid metastasis (0/13), and no chemotherapy or endocrine therapy had been performed. Gastrointestinal capsule endoscopy detected a mass with a maximum diameter of 3 cm in the submucosa of the ileum. The patient subsequently underwent open resection of the tumor in the ileum, and the resected specimen was analyzed histopathologically.

Gross appearance of the resected ileum presented as a length of 12 cm and a maximum circumference of 6 cm, with a poorly circumscribed bulging soft mass (maximum diameter:

Table 1. Immunohistochemical characteristics of the tumor cells

Antigen	Source	Clone	Dilution	Staining
SMA	Dako	IA4	1:100	+
Caldesmon	Origene Technologies, Inc, Beijing, China	EP19	Ready to use	+
Vimentin	Amersham	V9	1:100	+
P53	GeneTeckCo, Ltd, Shanghai, China	GM700101	Ready to use	+
MLH1	OrigeneTechnologies, Inc	ES05	Ready to use	+
MSH2	OrigeneTechnologies, Inc	25D12	Ready to use	+
MSH6	OrigeneTechnologies, Inc	EP49	Ready to use	+
PMS2	OrigeneTechnologies, Inc	EP51	Ready to use	+
SDHB	OrigeneTechnologies, Inc	WK173613-27	Ready to use	+
CK	OrigeneTechnologies, Inc	ZM-0069	1:80	-
EMA	Gene Teck Co, Ltd	GM061329	1:200	-
Calretinin	OrigeneTechnologies, Inc	TA356330	1:60	-
HMB-45	OrigeneTechnologies, Inc	ZM-0187	Ready to use	-
WT-1	Gene Teck Co, Ltd	GM356102	Ready to use	-
CD117	Dako	Poly	1:50	-
Dog-1	OrigeneTechnologies, Inc	ZM-0371	Ready to use	-
CD34	Dako	Qbend/10	1:20	-
S-100	Dako	4C4.9	1:100	-
Desmin	Dako	D33	1:100	-
BCL-2	OrigeneTechnologies, Inc	EP36	Ready to use	-
Ki-67	OrigeneTechnologies, Inc	UM870033	1:100	index >80%

2.8 cm) in the middle of the ileum. The tumor's surface was rough, while the cut surface was homogeneous gray-pink, solid, delicate, and soft. No evident swollen lymph nodes were identified in the mesenteric adipose tissue.

Under microscopy, the ulcerated tumor had involved the mucosa and submucosa, and invaded the deepest muscular layer of the intestinal wall (**Figure 1A**). With low magnification, the tumor was composed of multiple cellular nodules that were separated by fibrous bands. The tumor nodules exhibited a typical solid pattern with pericytoma-like gaping capillary vessels. The tumor cells were oval to spindle-shaped, with sharply defined cell membranes, round uniform nuclei, delicate chromatin, and inconspicuous nucleoli (**Figure 1B**). The spindle tumor cells were densely arranged with obviously atypical mitotic activity (with a maximum of 10-20 mitoses per high-powered field). Areas of coagulative necrosis as well as an intravascular tumor embolus were observed (**Figure 1C**).

Immunohistochemical staining demonstrated positive expression of vimentin, smooth muscle actin (SMA; **Figure 1D**), caldesmon (**Figure 1E**), and P53 (**Figure 1F**). In addition, the tumor cells exhibited widespread immunoreactivity for MLH1, MSH2, MSH6, PMS2, and SDHB. The tumor cells were negative for CK, EMA, calretinin, HMB-45, WT-1, CD117, Dog-1, CD34, S-100, desmin, and BCL-2. Immunostaining for Ki-67 revealed a proliferative index of >80% (**Figure 1G**). The immunohistochemistry results are summarized in **Table 1**. The findings argued against GIST, although up to 5% of GISTs may lack immunostaining for CD117.

Direct sequencing of DNA extracted from the ileum tumor presented wild type sequences of *KIT* gene exons 9, 11, 13 and 17 (**Figures 2**, **3**), as well as *PDGFRA* gene exons 12, 14 and 18 (**Figure 4**). These features collectively supported diagnosis of a malignant mesenchymal tumor, most likely a malignant glomus tumor.

The patient received immunological therapy and traditional Chinese medicine (herbs) at another hospital; however, we were unable to obtain accurate information regarding those treatments.

On February 6, 2016, the patient returned to our hospital with dizziness and left leg weak-

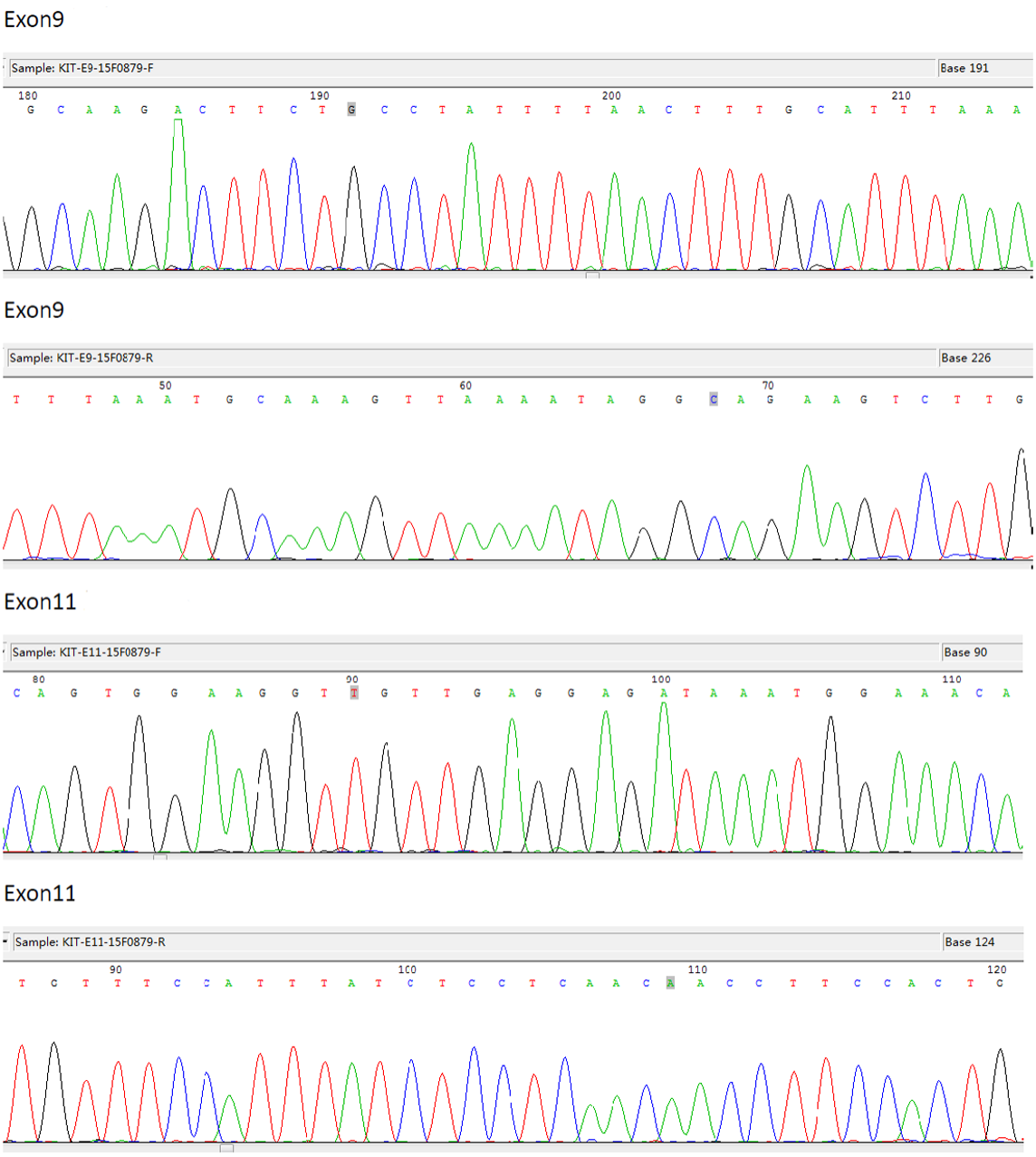

Figure 2. The forward and reverse sequences of Exon9 and Exon11.

ness. Magnetic resonance imaging revealed an intracranial lesion located in the right frontal lobe, which was identified as a metastatic tumor. The patient experienced good recovery after complete tumor resection, and the pathological evaluation confirmed diagnosis of malignant glomus tumor with metastasis to the brain. Gross appearance of the mass presented with a maximum diameter of 2.5 cm, surrounded by grey brain tissue (**Figure 1H**). Unver microscopy, the metastatic tumor cells exhibited similar morphology to the primary lesion. Immunohistochemical staining also indicated the diagnosis of a malignant glomus tumor.

On August 10, 2016, the patient was readmitted because of a 1-day history of abdominal pain. The fecal occult blood test was positive, and electron colonoscopy identified several polyps in the transverse colon adjacent to the liver and sigmoid colon. These polyps were resected and the postoperative pathologic examination confirmed malignant glomus tumor. The patient has experienced good recov-

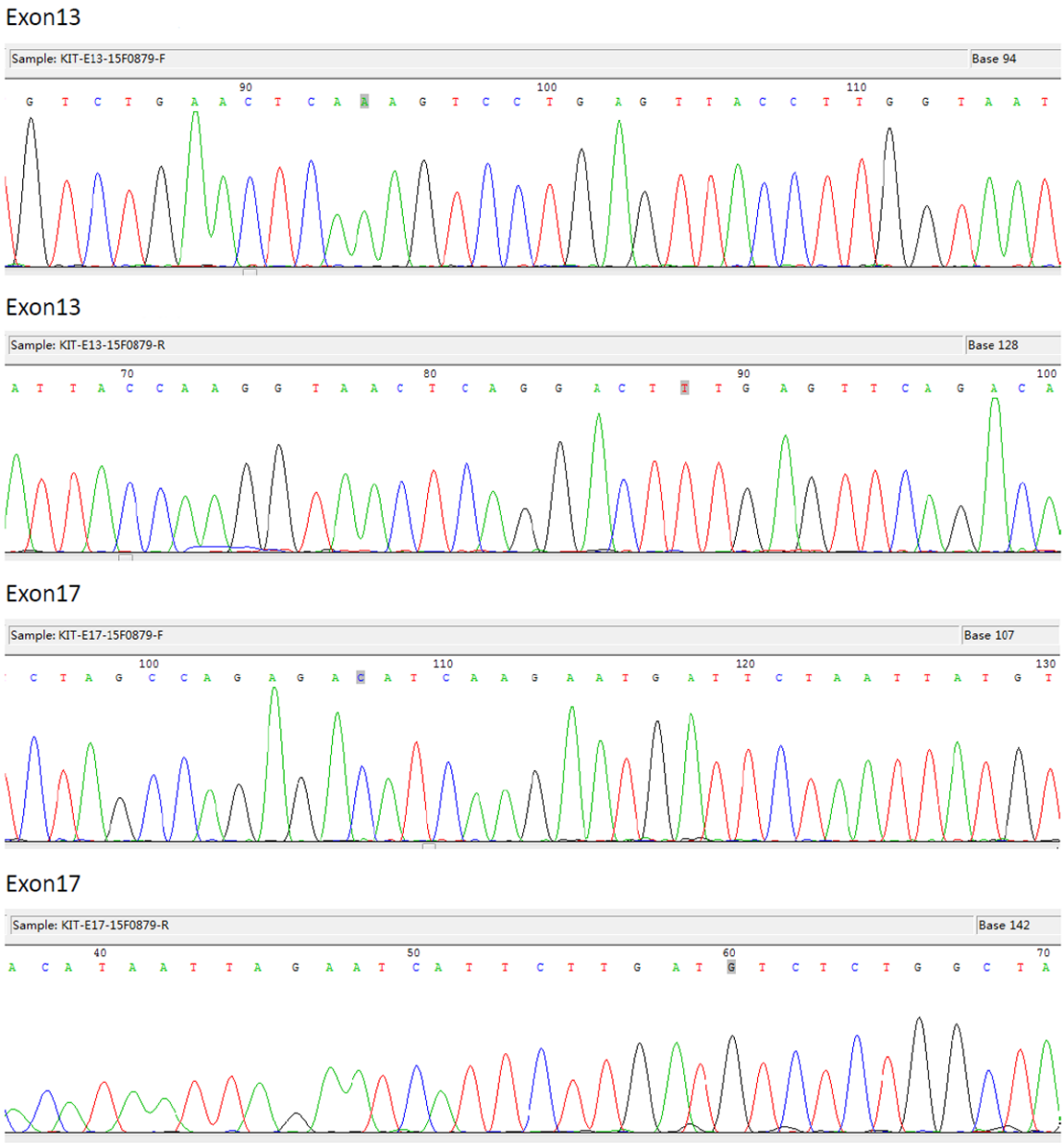

Figure 3. The forward and reverse sequences of Exon13 and Exon17.

ery without any remarkable symptoms. A postoperative 24-month's follow-up revealed no further recurrence or metastasis.

Discussion

Glomus tumors are rare mesenchymal neoplasms that are derived from glomus bodies, which generally develop in the peripheral soft tissues (e.g., dermis and subcutis) [2]. However, a small portion of these tumors can develop in the visceral organs (e.g., gastrointestinal tract, lungs, liver, and kidneys) [8]. A correct diagnosis is often deferred or even missed because the tumor is detected incidentally or the patient has vague symptoms. Most glomus tumors are detected in patients aged at 40-79 years, and a majority of patients are women (80%, 44/55) [8]. The most common gastrointestinal mesenchymal tumors are GISTs, while gastrointestinal glomus tumors are uncommon. More than 100 cases have been reported, which are estimated to be 100 times less common than GISTs. The tumors with minimal mitotic activity (1-3 per 50 HPF) have been found to metastasize

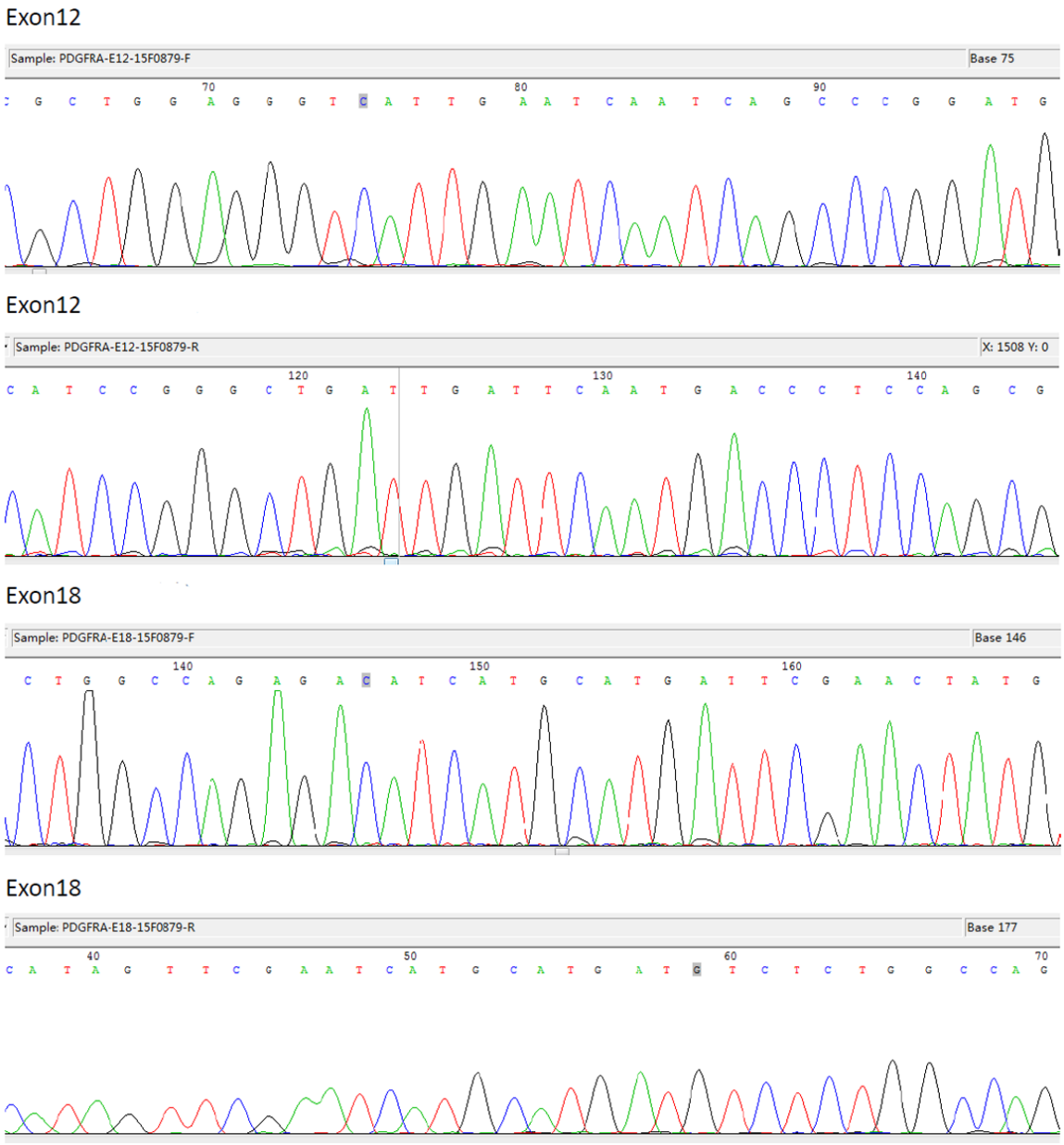

Figure 4. The forward and reverse sequences of Exon12 and Exon18.

[9]. The stomach antrum is the most frequent site of involvement, followed by the intestinal duodenum [6]. To the best of our knowledge, less than five malignant cases from the digestive system have been so far reported in the English literature (**Table 2**) [3, 10-12]. Among the reported cases, the longest follow-up period was 11 months. Owing to very limited cases, epidemiological data and prognosis for gastrointestinal malignant glomus tumor shave yet to be explored.

Gastrointestinal glomus tumors present with various symptoms, such as bleeding in the upper gastrointestinal tract (hemoptysis/hematemesis) or lower gastrointestinal tract (hematochezia/melena), when the tumor has ulcerated the overlying mucosa. This invasion can lead to varying degrees of anemia with cardiopulmonary complications [13]. Other symptoms may include non-specific ulcer-like symptoms (e.g., retrosternal epigastric discomfort), nausea, and bilious vomiting secondary to bowel obstruction, although many patients may remain asymptomatic [14]. The present case fits into this profile, as the patient was an elderly woman showing the most common

Table 2. Reported cases of malignant glomus tumor of the gastrointestinal tract

ID	References	Sex/age (years)	Symptoms	Site	Size (cm)	Treatment	Follow-up
1	Zhang Y, et al	M/47	progressive dysphagia	esophaus	5.8*4.5*4.0	SE	AWD at 11 months
2	Song SE, et al	F/65	Dizziness, dyspepsia	stomach	4.5	SE	DOD at 7 months
3	Abu-Zaid A, et al	F/29	abdominal mass, vomiting, melena	Intestinal	13.1*12.8*10.0	SE	AWD at 6 months
4	Bali GS ,et al	F/49	dysphagia	esophageal	5*4.5*3	SE	AWD at 6 months

SE, surgeryexcision; DOD, died of disease; AWD, alive with disease.

symptoms with anemia and digestive tract hemorrhage.

Glomus tumors can present as solitary or multiple lesions, with solitary tumors accounting for approximately 90% of all cases and generally involving adults [15]. According to the World Health Organization's 2013 classification of soft tissue and bone tumors, glomus tumors can be clinically classified as benign, malignant, or having uncertain malignant potential [2]. The following criteria were proposed by Folpe et al [7] to identify malignant glomus tumors: a deep location, a size of >2 cm, atypical mitotic figures, or combination of moderate-to-high nuclear grading and mitotic activity (5 mitoses per 50 high-powered fields). To the best of our knowledge, less than 5 such cases have been reported, and patients who fulfill those criteria have a high risk of metastasis and death. In the present case, the patient had a large lesion (>2 cm), very high mitotic activity, an intravascular tumor embolus, and distant metastasis to the brain. These findings were consistent with the diagnosis of a malignant glomus tumor. Multiple polyps in the transverse colon were inclined to be considered as primary lesions. Sequencing detection revealed no mutations in mismatch repair proteins. There has been no relevant literature reported so far.

A familial variant of glomangioma was associated with mutations in the *glomulin* gene located on chromosome 1p21-22. Truncating mutations generate 17 recognized inherited variants of glomulin [16]. Only a few molecular studies have been carried out to investigate the genetic phenotype of glomus tumors to date. One eminent study [17] collected 33 glomus tumors including 28 benign and 5 malignant tumors. Two of the malignant glomus tumors were located within gastrointestinal tract. The study identified MIR143-NOTCH2 fusion protein in a malignant gastrointestinal glomus tumor. Therefore, *NOTCH2* gene rearrangements detected by FISH may be used as a potential molecular diagnostic test in challenging cases.

Gastrointestinal malignant glomus tumors must be differentiated from other tumors with similar morphology, especially GISTs. The present case was misdiagnosed as GISTs prior to detection of *c-KIT* and *PDGFRA* gene mutations. Subsequently, direct sequencing of DNA extracted from the ileum tumor presented wild type sequences of *KIT* exons 9, 11, 13 and 17, as well as *PDGFRA* exons 12, 14 and 18. Therefore, a supplementary diagnosis of malignant glomus tumor was made. GISTs are almost always positive for CD117 (c-KIT) and very frequently (70%) positive for CD34. By contrast, gastrointestinal glomus tumors are positive for SMA, caldesmon and vimentin, occasionally positive for CD34, but negative for CD117 [8].

The genetic pathogenesis of glomus tumors has yet to be elucidated. There are very few studies regarding the molecular genetics of sporadic cases. Various numbers of BRAF V600E mutations exist in glomus tumors, especially in malignant ones [18-20]. This is of particular interest in tumors presenting clinically aggressive behavior. However, very few studies have been focused on examination of deeply located or visceral tumors. Our case showed a different finding of the absence of BRAF V600E, which could have potential therapeutic and prognostic implications for patients. This interesting result may explain the relatively favorable prognosis of the current case, in spite of distant extensive metastasis. The role of

BRAF mutation in the pathogenesis of glomus tumors is unclear, and the frequency of this mutation should be examined in a large cohort of glomus tumors systematically.

Here, we report a very unusual case of a primary malignant GT in the ileum that subsequently relapses and develops distant extensive metastasis. This type of tumor is very rare and extremely rarely metastasizes. Thus, timely clinical examination and careful histologic evaluation are essential for diagnosing malignant glomus tumors. Although the patient remains in good condition, it is difficult to accurately predict the prognosis of this malignant tumor. Therefore, both short-term and long-term follow-up are needed in patients with malignant glomus tumors.

Disclosure of conflict of interest

None.

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