Case Report

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Malignant gastrointestinal neuroectodermal tumor: a case report and literature review

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Introduction and importance: A malignant gastrointestinal neuroectodermal tumor (GNET) is an extremely rare primary malignant mesenchymal tumor of the gastrointestinal tract characterized by EWSR1 gene rearrangement. An optimal systemic treatment strategy for advanced/recurrent GNET has not yet been identified.

Case presentation: A 24-year-old male patient was hospitalized with abdominal pain and underwent two operations for a tumor in his small intestine. Immunohistochemistry (IHC) showed strong expression of S-100 protein and SOX 10. Fluorescence in situ hybridization analysis and next-generation sequencing analysis indicated that there were *EWSR* gene rearrangements and the presence of *EWSR-ATP1* gene fusions, respectively. The diagnosis of GNET in the small intestine was confirmed by pathology. The young patient received the fifth-line of apatinib mesylate and the sixth-line of apatinib combined with temozolomide. The two apatinib-containing regimens showed stable disease and progression-free survival of 4.7 months and 3.1 months with single-agent apatinib or apatinib combined with temozolomide, respectively.

Clinical discussion: To our best knowledge, this is the first report of malignant GNET treated with apatinib and temozolomide. Apatinib-containing regimens might has antineoplastic activity against GNET. The authors reviewed the relevant reports of previous GNET treatment, summarized the clinicopathological characteristics of GNET, and found that there are no reports of apatinib for backline treatment of GNET.

Conclusion: Containing apatinib may provide an additional treatment option for patients with chemotherapy-resistant GNET tumors.

Keywords: apatinib mesylate, case report, malignant gastrointestinal neuroectodermal tumors, temozolomide, vascular endothelial growth factor receptor 2

Introduction

Malignant gastrointestinal neuroectodermal tumor (GNET) is an extremely rare primary malignant mesenchymal tumor of the gastrointestinal tract first described by Stockman *et al.* in 2012[1]. GNET was previously referred to as a clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLTGT) or 'osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma (CCS) of soft parts' because of its morphological and molecular similarity to conventional soft tissue or tendon and tendon membrane clear cell sarcoma (CCSTA), but lacks any specific markers of melanocytic differentiation[2,3]. Genetically, they were characterized by *EWSR1* gene rearrangements, including *EWSR1-ATF1* or *EWSR1-CREB1* fusions[1–3]. Apatinib mesylate (hereafter referred to as apatinib) is a tyrosine kinase inhibitor (TKI) that selectively targets vascular endothelial growth factor receptor 2 (VEGFR-2) and shows promising effects on prolonging progression-free survival (PFS) for a variety of advanced sarcomas after failure of standard multimodal therapy[4]. Here, we present a rare case of GNET and show the therapeutic effect of apatinib against this malignancy. This case has been reported in line with the Surgical CAse REport (SCARE) Criteria[5].

Case presentation

A 24-year-old man patient underwent resection of a small intestinal malignant tumor in a local hospital in April 2012

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without a clear pathological diagnosis and then was diagnosed with a small intestinal wild-type gastrointestinal mesenchymal stromal tumor with autonomic and rhabdomyolysis-like differentiation in a pathology consultation in another local hospital. The patient was not given adjuvant treatment such as radiotherapy after surgery and was regularly rechecked. In October 2014, the patient was sent to the Zhejiang Cancer Hospital for abdominal pain treatment, and abdominal and pelvic computed tomography (CT) scans showed multiple pelvic metastases. The recurrence of tumors after the resection prompted first-line chemotherapy of two cycles of mesna, adriamycin, ifosfamide, and dacarbazine (MAID), with efficacy evaluated as progressive disease (PD), followed by five cycles of second-line chemotherapy with modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6). Subsequent analysis of the patient determined PD. The patient refused further treatment and were followed up regularly.

The patient was again admitted to our hospital in June 2015 with complaints of abdominal pain, where a CT scan of the abdomen and pelvis showed multiple soft tissue masses located in the right lower abdomen as well as the left pelvic cavity. The patient underwent excision of the multiple masses in the pelvic and abdominal cavity in addition to partial resection of the small intestine, sigmoid colon, bladder wall, ileum, and ascending colon. Postoperative pathology diagnosed GNET, with tumors situated in both the pelvic cavity and mesocolon. Histopathological examination showed that the tumor cells were abundant and arranged in solid sheets with microcysts or hemorrhagic cysts of variable sizes. The cysts were covered with flat or cuboidal cells suggesting biphasic differentiation (Fig. 1A–H). IHC showed the neoplastic cells were diffusely positive for S-100 protein and SOX 10 (Fig. 1I–J). Fluorescence in situ hybridization (FISH) analysis for *EWSR1* showed evidence of rearrangement (Fig. 1K) and as determined by next-generation sequencing (NGS), a translocation between *EWSR1* intron 7 and *ATF1* intron 4 was found giving rise to an *EWSR1-ATF1* gene fusion comprised of *EWSR1* exons 1–7 and *ATF1* exons 5–7 (Fig. 1L).

Two months later, a whole-body positron emission tomography (PET)/CT scan revealed a metastatic soft tissue mass with increased glucose metabolism located in the right iliac fossa. The patient's tumor stage was grade IV and the prognosis was poor. He was initially treated with the traditional chemotherapy of gemcitabine plus paclitaxel. The patient developed allergic symptoms during the first cycle so paclitaxel was replaced with docetaxel. A CT scan was taken after every two cycles of treatment, which showed SD after two cycles of treatment and PD after four cycles. As a fourth-line chemotherapy, the patient was treated with a regimen of gemcitabine plus vinorelbine and showed SD after two cycles but PD after four cycles. After the patient provided written, informed consent, apatinib was administered as a fifth-line therapy at a dose of 425 mg/day on 6 May 2016. Following 4.7 months of targeted therapy, apart from mild fatigue and diarrhea, the regimen was well-tolerated. Enhanced CT revealed PD on 27 September 2016 (Fig. 2A–C). Considering the patient's young age and good Eastern Cooperative Oncology Group (ECOG) performance status (PS), after providing informed consent, he was given apatinib (425 mg/day) plus temozolomide (0.2 g/day, on days 1–5) as a sixth-line regimen on 29 September 2016. This sixth-line regimen was well-tolerated during 3.1 months of treatment. Pelvic enhanced CT scan suggested SD in the first and second months but PD on 2 January 2017 (Fig. 2D–E).

HIGHLIGHTS

- The most common part of a malignant gastrointestinal neuroectodermal tumor (GNET) is the small intestine, which is also more common in areas such as the stomach and colon.
- GNET can be positive for S-100 protein, SOX 10, Vimentin (+) and characterized by EWSR1 gene rearrangements, lack of expression of melanocyte-specific markers.
- GNET is a rare and aggressive malignancy for which there is currently no standard treatment guidelines.
- Containing apatinib may provide an additional treatment option for patients with chemotherapy-resistant GNET tumors.

The patient then discontinued targeted therapy and was transferred to a radiotherapy department for palliative radiotherapy, with an efficacy evaluation of SD. One year later, the patient underwent an emergency operation because of an intestinal perforation. He developed renal failure and a severe abdominal infection in September 2018, which led to his death on 3 February 2019. The overall survival of the young patient from the initiation of treatment with apatinib was 32.9 months. The main treatment timeline is shown in Figure 3.

Discussion

GNET was proposed by Zambrano *et al.*[6]. Currently, there are relatively few reports on GNET. A search of Pubmed, CKNI, and other databases for case report, malignant GNETs, apatinib mesylate, vascular endothelial growth factor receptor 2, EWSR1 and other keywords, we reviewed previous reports on GNET and found that only case reports and small series were published (Table 1), in which 38.5% (15/39) were male and 61.5% (24/39) were female; they occurred mainly in young and middle-aged adults with a mean age of 43 years (range: 17–70 years); the most common site of predilection was the small intestine, accounting for 43.6% (17/39), followed by the stomach 10.3% (4/39) and the colon 10.3% (4/39), which is consistent with our report. GNET is a rare and aggressive malignancy that differs from other primitive epithelioid and spindle cell tumors of the gastrointestinal tract, which can be positive for S-100 protein, SOX 10, Vimentin(+), and characterized by EWSR1 gene rearrangements (EWSR1-ATF 1 and EWSR1-CREB 1 fusion genes) (Table 1), lack of expression of melanocyte-specific markers. In our case, immunohistochemical staining showed positive for S-100 protein and Vimentin, melanocyte-specific markers HMB-45 (Melanoma) and MelanA negative. A final diagnosis of GNET was confirmed by a split-apart signal detected in *EWSR1* by FISH and NGS. It is consistent with another report from China[3]. However, there are also a few case reports in which EWSR1 gene rearrangements were not detected by FISH, suggesting that other genetic events may also be associated with GNET tumorigenesis[1,2,13]. EWSR1 gene rearrangements have been found in other specific tumors, including Ewing sarcoma, clear cell carcinoma of the salivary gland, and hemangioma-like fibrous histiocytoma[14]. Therefore, EWSR1 gene rearrangement is not a specific criterion for GNET, but can help confirm the diagnosis of GNET.

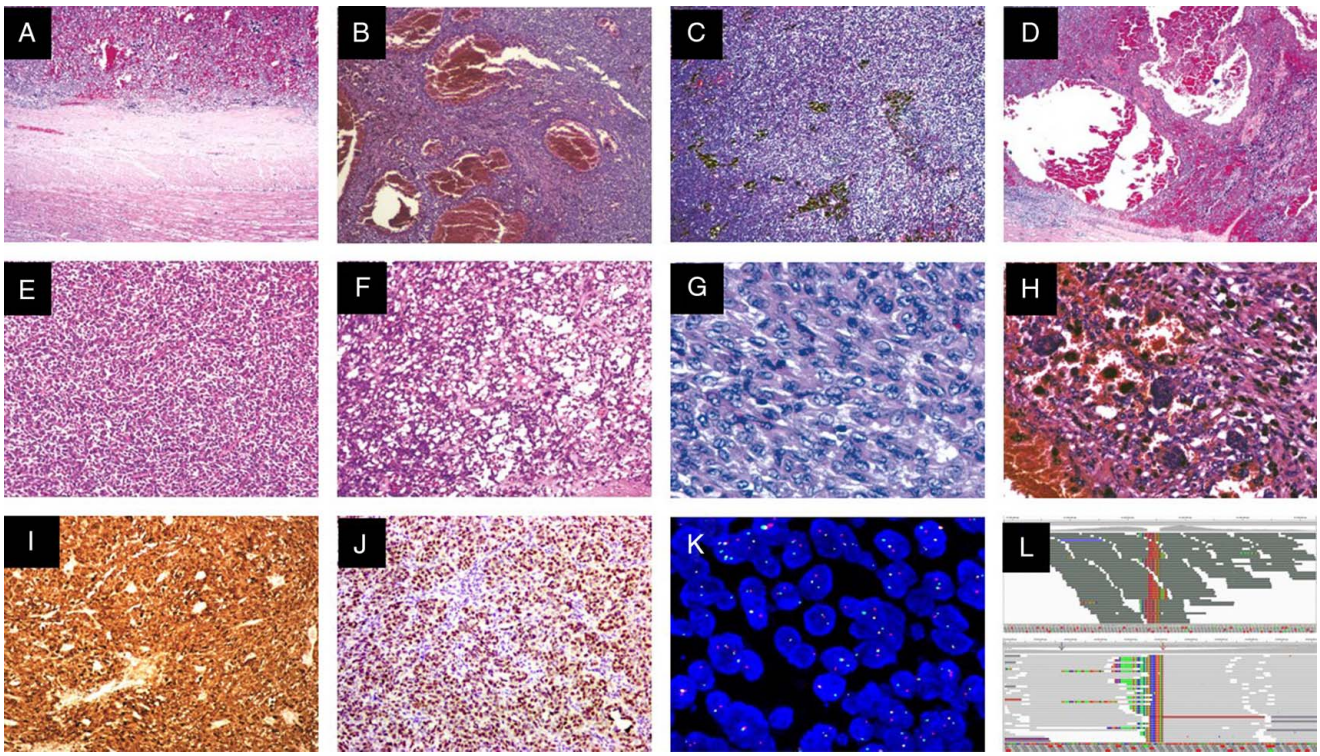

Figure 1. Histologic and molecular features. (A) The tumor was circumscribed but unencapsulated, and located in the serosa layer of the intestinal wall. (B) The tumor was cystic-solid with cystic areas showing extensive hemorrhagic cysts. (C) Solid areas were composed of sheets of small, round, blue cells. (D) The cysts were lining of single layer of flat or cuboidal cells that merged into the solid tumor areas. The tumor cells were oval to short spindle-shaped with sparse amphophilic (E) or clear (F)cytoplasm. (G) The nuclei were small with fine chromatin and inconspicuous nucleoli and scattered mitoses. (H) Osteoclast-like multinucleated giant cells were distributed randomly within the tumor stromas. (I,J) IHC staining showed that S-100 protein and SOX 10 was strongly and widely expressed in the tumor cells. (K) FISH analysis indicated EWSR1 gene rearrangement in tumor cells. (L) Partial enlargement of the fourth intron of ATF1. The common break region of the fourth intron of ATF1 was broken, and fusion occurred in two directions. Partial enlargement of the seventh intron of EWSR1 (IGV software). The red and blue arrows referred to the two breakpoint locations of the seventh intron of EWSR1.

GNET has a highly malignant phenotype and a poor prognosis due to limited therapeutic options[15]. There are no standard treatment guidelines for GNET because of its extreme rarity. We report the case of a 24-year-old man with GNET in the small intestine, and the failure of multiple chemotherapeutic regimens. Considering the toxicities of combined chemotherapy, apatinib, an oral small-molecule inhibitor of VEGFR-2 was administered. Apatinib has demonstrated antitumor activity through inhibiting angiogenesis in a variety of solid tumors and displays manageable toxicities in patients[16–18]. Apatinib also exhibits promising efficacy with a manageable safety profile in sarcomas[4,19]. In a small series of 19 patients with GNET, four patients with advanced GNET were treated with antivascular small-molecule targeted therapy, and two of them showed PR and SD to first-line treatment with apatinib, suggesting that apatinib may be effective in the treatment of advanced GNET[3]. The best response after fifth-line and sixth-line treatment with apatinib in our young patients was SD, PFS was total 7.8 months, and adverse effects could be tolerated. To our knowledge, this is the first report of malignant GNET treated with apatinib and temozolomide. There are no reports of apatinib for backline therapy of GNET. Overall, the regimen was well-tolerated with no drug-related severe adverse events reported.

Temozolomide is an oral prodrug exerting its antineoplastic effects through the formation of 5-(3-methyl-1-triazeno) imidazole-4 carboxamide (MTIC), the putative, active chemical metabolite of dacarbazine (DTIC)[20]. Temozolomide has shown activity against gliomas and melanoma in both Phase II and Phase III trials with acceptable toxicity[21,22]. Preclinical data suggests that temozolomide has activity in sarcoma cell lines[23]. In combination with irinotecan, temozolomide has been demonstrated to have activity in recurrent Ewing sarcoma[24]. A phase II trial evaluated the efficacy and toxicity of temozolomide in patients with unresectable or metastatic soft tissue sarcoma and showed modest activity and well-tolerated toxicity[25]. Why did the addition of temozolomide to apatinib prove more effective than single-agent apatinib? Preclinical models have shown that anti-VEGF therapy both maintains vascular normalization and promotes tumor invasion and migration through vascular co-option[26]. It demonstrates that effective blocking of the vascular component of the tumor is insufficient for tumor control. In an experimental human glioma model, apatinib exhibits efficient antitumor activity and enhances the effect of temozolomide, which was associated with decreased cell proliferation, colony formation, invasion and migration, and increased cell apoptosis[27]. A retrospective analysis of eight cases evaluated the feasibility of the addition of temozolomide to pazopanib (a multi-targeted receptor TKI that inhibits angiogenesis and blocks tumor growth) in patients with advanced sarcoma who had progressed on pazopanib. This combination showed a tolerable toxicity profile and passable response rate[28]. Inspired by the studies

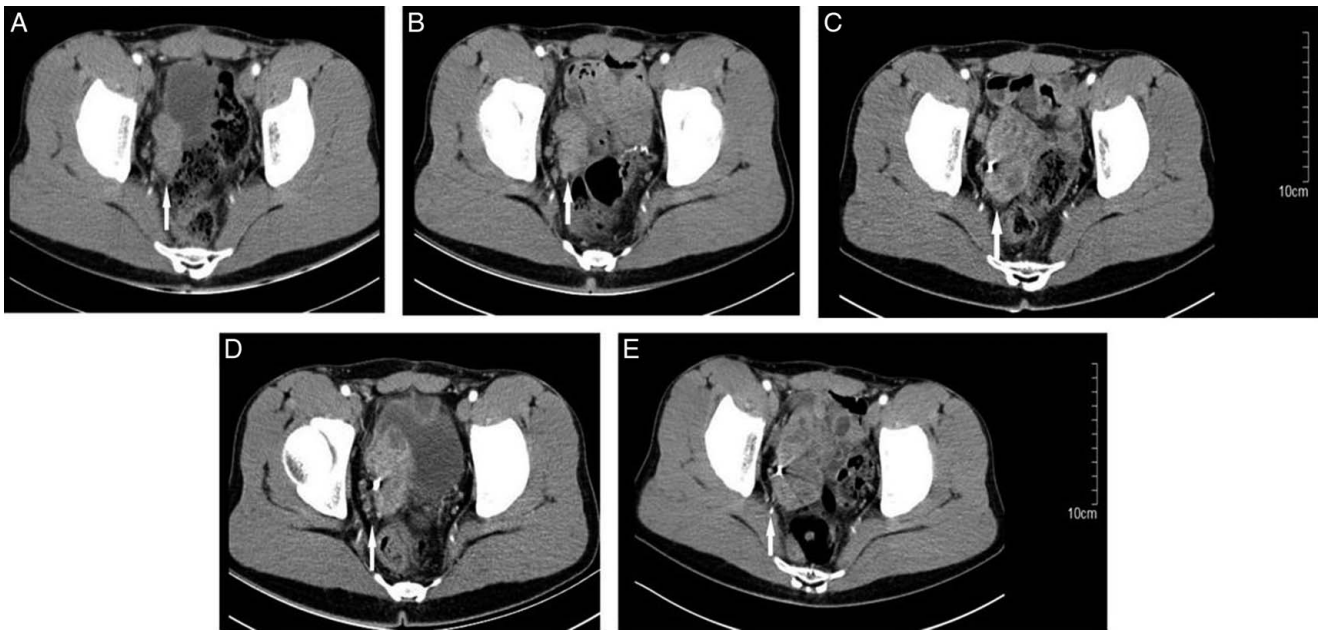

Figure 2. (A) Pelvic CT (2016.05.02) showed that the longest diameter (LD) of target lesion (TL) was ~4.5 cm. (B) Pelvic CT (2016.06.07) showed circa 4.6 cm of the LD and SD after apatinib treatment. (C) Pelvic CT (2016.09.27) showed the LD increased to 6.4 cm and PD after apatinib treatment. (D) Pelvic CT (2016.10.31) showed the LD was stable at 6.4 cm and SD after treatment with the combination of apatinib with temozolomide. (E) Pelvic CT (2017.01.02) showed that the LD of the TL was 9.1 cm and PD after treatment with the combination of apatinib with temozolomide.

above, at the time of PD, the patient continued to take apatinib and also initiated temozolomide. The combination therapy was well-tolerated and resulted in SD with a PFS of 3.1 months. Because of tumor progression, the patient died of abdominal infection caused by intestinal perforation and renal failure caused by urinary tract obstruction with an overall survival of 33 months.

There are still some limitations in our report. Firstly, only one patient was reported with limited data, and in the future we need more large-scale randomized controlled trials to study the efficacy and safety of apatinib-containing regimens in chemotherapy-resistant GNET patients. Secondly, the mechanism for the treatment of GNET with apatinib is not proposed, and appropriate basic research is needed to explore the potential mechanism of action of targeted therapy for GNET. Again, we could explore the efficacy of a triple regimen of antivascular combined with chemotherapy and immunotherapy. Moreover, additional insight into the efficacy, safety, and biologic mechanisms of the combination therapy warrants further investigation.

Conclusion

The paucity of historical data for the rare malignant tumor GNET leads to an absence of well-established systemic

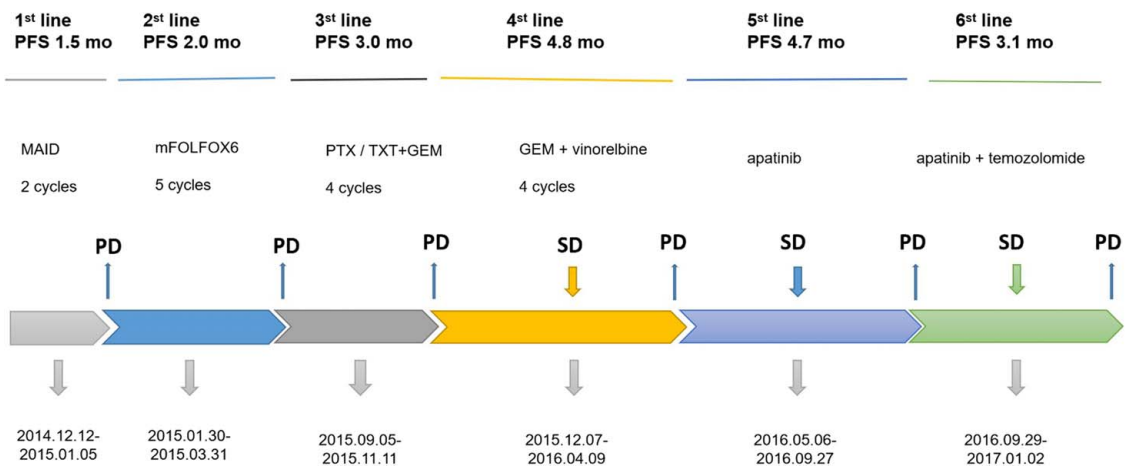

Figure 3. Review of treatment process Treatment process and effect evaluation of the patient. PFS, progression-free survival; SD, stable disease; PD, progressive disease, mo, months.

Table 1

Previous reports of treatments and Clinicopathologic features for GNET case reports/case series.

References	Case NO.	Age/ Sex	Location	Molecular pathological features	Treatment	Clinical outcome
Yagi T, *et al.*[7]	1	66 F	Small intestine	BRAF (V600 E) and EWSR1-ATF1.	Dabrafenib mesylate and trametinib dimethyl sulfoxide.	PR, OS was 23 months.
Harshavardhini *et al.*[8]	1	33 M	Small intestine	EWSR 1.	Adjuvant chemotherapy × eight cycles.	Lost to follow-up.
Ulici *et al.*[9]	11	14–70 (median 33 years), 3 M and 8 F	Neck (3/11), shoulder (1/11), buttock (2/11), orbit (1/11), and tongue/parapharyngeal space (1/11), bladder (1/11), and falciform ligament/liver (1/11).	EWSR1-ATF (7/11), EWSR 1-CREB (3/11), and EWSR 1- PBX (1/11).	Surgical resection (9/11), adjuvant radiation therapy (3/9), and adjuvant chemoradiotherapy(1/9).	Died (4/11), OS was 11months, 12 months, 25 months, and 64 months, respectively.
Li *et al.*[10]	2	17 M 62 F	Case 1: stomach Case 2: colon	EWSR1.	Case 1: partial gastrectomy. Case 2: laparoscopic right hemicolectomy.	Case 1: DFS was 10 months. Case 2: OS > 6 months.
Sugimoto *et al.*[11]	1	38 F	Primary retroperitoneum	EWSR1 and CREM.	Surgical removal	DFS was 7 months.
Huang*et al.*[12]	1	30 F	Ileum	EWSR1.	Adjuvant chemotherapy Ifosfamide and epirubicin × four cycles.	DFS was 6 months.
Chang*et al.*[3]	19	25–64 (median 43 years), 8 M and 11 F	Small intestine (11/19); stomach (3/19); large intestine (2/19); ileocecal (1/19); anal canal (1/19); lower esophagus (1/19).	EWSR1 (93.3%).	Four patients targeted therapy.	The ORR was 75% (3/4) with targeted therapy.
Kandler*et al.*[2]	3	49 M 62 F 49 M	Case 1: sigmoid colon Case 2: small intestine Case 3: ileum	Case 3: EWSR1-ATF1.	Case 1: Laparoscopic sigmoid resection. Case 2: small-bowel resection. Case 3:ileo-colic resection.	Case 1: disease free. Case 2: OS > 63 months. Case 3: OS was 36 months.

therapeutic options. In this report, our patient's best response after fifth-line and sixth-line treatment with apatinib was SD, with a total PFS of 7.8 months and tolerable adverse effects. This case suggests that regimens containing apatinib may provide an additional treatment option for patients with chemotherapy-resistant GNET tumors.

Ethical approval

This study was approved by the institutional Ethics Committee. Written informed consent was obtained from the patient.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

H.J.Y., T.W.Z., and D.S.: conception and design; M.Z., J.W., Z. K.Z., and J.G.Z.: resources; Q.X., J.S. and X.Y.L.: data curation; Y.P.H., H.J.Y., D.S. and H.Y.Z.: data analysis or interpretation; H.J.Y. and D.S.: writing – original draft; T.W.Z.: writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors have no conflicts of interest to disclose.

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Data availability statement

All the required data are available in the manuscript.

Provenance and peer review

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