Malignant triton tumor of the duodenum: report of a case

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Abstract

We report a case of malignant triton tumor of the duodenum, which is extremely rare. A submucosal malignant tumor was detected in the duodenum of a 49-year-old woman. The tumor was completely resected by performing pancreaticoduodenectomy. Pathological examination revealed that the lesion was a malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation, i.e., a malignant triton tumor. Long-term survival has been achieved with no recurrence at 8.5 years after surgery.

Keywords Malignant triton tumor · Malignant peripheral nerve sheath tumor · Duodenum · Rhabdomyoblastic differentiation · Osteogenic differentiation

Introduction

Malignant triton tumor is a malignant peripheral nerve sheath tumor (MPNST) with rhabdomyoblastic differentiation that rarely occurs in the duodenum. MPNST is a neuroectodermal neoplasm that either arises from a peripheral nerve or shows nerve sheath differentiation. MPNST includes several malignant tumors and is also known as malignant schwannoma, neurofibrosarcoma, neurosarcoma, malignant neuroma, malignant neurilemmoma, and neurogenic sarcoma [1, 2], with MPNST currently being the

recommended term. MPNST has an incidence as high as 4.6% in patients with neurofibromatosis type-1 (NF-1), but it is a rare disease in the general population, only occurring in 0.001% [3]. Epithelioid and heterologous differentiation are found in about 15% of MPNSTs [1]. Heterologous differentiation includes rhabdomyoblastic [4], cartilaginous [5], smooth muscle [6], and osteogenic components [7]. MPNST with rhabdomyoblastic differentiation was first reported by Masson in 1932 [8] and was reported in 1973 by Woodruff et al. as a ‘malignant triton tumor’ [4]. Malignant triton tumor (MTT) can develop at any site in the body [9] like

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MPNST [3, 10]. There have been some reports of MPNST involving the duodenum [10], but there have been no reports of MTT arising in the duodenum. Here, we report the first case of duodenal MTT in which the patient achieved long-term survival after surgery.

Case report

A 49-year-old woman was admitted to our hospital with the chief complaint of chest oppression on exertion for 5 months. The patient also had dizziness and palpitations, as well as vomiting after meals. Her past history included appendicitis treated by appendectomy. Her palpebral conjunctivae were pale. She had no abdominal tenderness, but a soft mass was palpable in the right epigastric region. The red blood cell count (RBC) was $3.10 \times 10^6/\text{dL}$, hemoglobin (Hb) was 4.5 g/dL, and hematocrit (Hct) was 18.1%. Total protein was 6.5 g/dL and tumor markers (CEA and CA19-9) were in the normal range. There were no abnormal gastrointestinal gas shadows on abdominal X-ray. Upper gastrointestinal endoscopy revealed a submucosal tumor covered by normal mucosa with ulceration in the second part of the duodenum (Fig. 1a). Biopsy of the tumor was performed and histopathological examination showed that it consisted

of eosinophilic spindle-shaped to oval cells accompanied by prominent vascular proliferation. A high Ki-67 labeling index suggested malignancy, but a definitive diagnosis could not be made. A barium study depicted a 50-mm filling defect in the second part of the duodenum (Fig. 1b). There was a depression at the center of the filling defect and the border of the defect was irregular at the anal side of the duodenum. Contrast-enhanced computed tomography (CT) depicted a 50-mm enhancing tumor in the second part of the duodenum at the oral side of the ampulla of Vater (Fig. 2a). The tumor had some calcified areas (Fig. 2b). Both the main pancreatic duct and the bile duct were dilated, and the gallbladder showed distension. There was no lymphadenopathy and no signs of distant metastasis from the duodenal tumor. Contrast-enhanced magnetic resonance imaging (MRI) demonstrated a 50-mm tumor with strong and heterogeneous enhancement in the second part of the duodenum. The patient underwent pancreaticoduodenectomy to remove the tumor. At operation, there were no signs of lymph node metastasis or distant metastasis. Macroscopically, a submucosal tumor was localized to the second part of the duodenum, at the oral side of the ampulla of Vater. The tumor did not invade into the ampulla of Vater. The lesion measured 5.5×5.0 cm and was white (Fig. 3). Histopathological examination of the tumor showed continuity of the tumor

Fig. 1 **a** Upper gastrointestinal endoscopy reveals a submucosal tumor covered by normal mucosa with ulceration in the second part of the duodenum. **b** Barium study shows a filling defect in the second part of duodenum

Fig. 2 **a** Contrast-enhanced CT of the duodenal tumor. The tumor is located in the second part of the duodenum, measures 50 mm in size, and shows enhancement. **b** Tumor contains some calcification

Fig. 3 Macroscopic appearance of the tumor. It is a white mass that measures 5.5 × 5.0 cm

with the muscularis propria of the duodenum and partial invasion into the muscularis mucosae (Fig. 4a). However, there was no invasion of the pancreas or the retroperitoneal fat (Fig. 4b). The tumor consisted of spindle-shaped cells that formed bundles or alveolar structures, or else showed random growth (Fig. 5a). These cells had enlarged nuclei with an irregular shape and increased chromatin, and the cytoplasm was eosinophilic to palely eosinophilic. Osteogenic components (Fig. 5b) and striated muscle components (Fig. 5c) were mixed with the background of spindle-shaped cells. There were 22 mitotic figures per 10 high power fields (HPF), and the Ki-67 labeling index was high at 64%. Immunostaining of large round tumor cells for myogenic markers (desmin and myogenin) was positive and alpha-SMA was also positive in a few tumor cells. Immunostaining for S-100 protein (Roche Diagnostics) was weakly positive for both nucleus and cytoplasm of the cells (Fig. 6a), but the tumor was negative for H3K27me3 (C36B11, 1:200, Cell Signaling Technology) (Fig. 6b), c-kit (1:100, Medical & Biological Laboratories), CD34 (QBEnd/10, Roche Diagnostics),

DOG-1 (K9, 1:100, Leica Biosystems) (Fig. 6c), MDM2 (1F2, 1:50, Calbiochem) (Fig. 6d), CDK4 (DCS-31, 1:50, Invitrogen) (Fig. 6e), cytokeratin AE1/AE3 (AE1/AE3/pck26, Roche Diagnostics), and EMA (E29, Roche Diagnostics). Based on the histological findings and the immunostaining profile, the final diagnosis was MPNST with rhabdomyoblastic and osteogenic components, i.e., malignant triton tumor. No lymph node metastasis was found by pathological examination.

Symptoms such as chest oppression on exertion, dizziness, and palpitations were relieved after surgery. No adjuvant therapy was performed. The patient was followed up with contrast-enhanced CT every 6 months for 5 years, after which contrast-enhanced CT was performed every 1 or 2 years. There is no sign of recurrence at 8.5 years after surgery.

Discussion

Malignant triton tumor (MTT) is a malignant peripheral nerve sheath tumors (MPNST) with rhabdomyoblastic differentiation. MPNSTs are otherwise known as malignant schwannoma, neurogenic sarcoma, or neurofibrosarcoma, and account for 5–10% of all soft-tissue sarcomas [11]. MPNSTs are frequently (24–52%) associated with NF-1 [3, 12–14]. NF-1 is a congenital condition that was first described in detail by von Recklinghausen in 1882. It is characterized by the presence of café-au-lait spots, cutaneous neurofibromas, and neoplasms of the peripheral or central nervous system [15]. In addition, almost 10% of MPNSTs arise secondary to radiation therapy [3]. Sporadic MPNSTs are rare, occurring in only 0.001% of the general population [3]. MTT is also associated with NF-1 in 69% of cases [16], and, otherwise, arises secondary to radiation therapy [17] or is sporadic [18]. The present patient had a sporadic MTT, since there was no history of NF-1 or radiation therapy.

Fig. 4 **a** Histopathological examination shows that the tumor mainly exists in the duodenal muscle layer (original magnification ×40). **b** Continuity between the tumor and the muscularis propria (original

magnification ×40). **c** Tumor does not invade the pancreas or the retroperitoneal fat (original magnification ×40)

Fig. 5 **a** Tumor is mainly composed of spindle-shaped cells (H–E stain, original magnification $\times 400$). **b** Osteogenic differentiation in the tumor (H–E stain, original magnification $\times 400$). **c** Rhabdomyoblastic differentiation in the tumor (H–E and desmin stain, original magnification $\times 400$)

Fig. 6 **a** Immunostaining for S-100 protein was weakly positive in tumor cells (H–E stain, original magnification $\times 200$). **b** Immunostaining for H3K27me3 was negative. Internal positive control: vascular endothelial cells and infiltrating lymphocyte are indicated by arrows. (H–E stain, original magnification $\times 200$). **c** Immunostaining

for DOG-1 was negative (H–E stain, original magnification $\times 200$). **d** Immunostaining for MDM2 was negative (H–E stain, original magnification $\times 200$). **e** Immunostaining for CDK4 was negative (H–E stain, original magnification $\times 200$)

Immunostaining for S-100 protein is positive in up to half of all MPNSTs, and S-100 is the marker most

closely associated with this tumor; it was weakly positive in the present case. Schaefer et al. reported that loss

of H3K27me3 immunostaining is a useful diagnostic marker for distinguishing MPNSTs from other spindle cell neoplasms, because 51% of MPNSTs were negative for H3K27me3, while all other spindle cell neoplasms showed positive staining [19]. H3K27me3 was also reported to be a sensitive marker for sporadic and post-radiation MPNSTs [20]. Gastrointestinal stromal tumor (GIST) and liposarcoma are other submucosal tumors that may occur in the duodenum [21, 22]. In the present case, negative staining for c-kit, CD34, and DOG-1 [23] led to exclusion of GIST, while liposarcoma was excluded by negative staining for MDM2 and CDK4 [24]. Approximately 15% of MPNSTs show histological evidence of divergent differentiation [3, 19] which can produce rhabdomyoblastic, cartilaginous, osseous, smooth muscle, glandular, liposarcomatous, and epithelioid components. MPNST with rhabdomyoblastic differentiation was first reported by Masson in 1932 [8]. It was later reported as ‘malignant triton tumor’ in 1973 by Woodruff et al., who proposed three diagnostic criteria for MTT [4]: (1) The tumor arises along the course of a peripheral nerve, or in a patient with NF-1, or at a typical location for peripheral nerve tumors, or else is a metastasis from such a tumor. (2) It largely shows the growth characteristics of Schwann cell tumor. (3) Rhabdomyoblastic differentiation occurs within the body of the tumor. Today, MTT can be diagnosed without fulfilling criterion 1) [25]. The term ‘triton’ is derived from the discovery that supernumerary limbs containing neural and muscular elements can be induced to grow on the backs of triton salamanders by transplantation. Osteogenic differentiation is also not uncommon in MTT and was found in the present case [4, 24].

In the present case, the tumor showed no continuity with the pancreas or the retroperitoneal fat, but there was continuity with the muscularis propria of the duodenum, confirming duodenal origin of the MTT. Because of the rarity of MTT, the most frequent primary site for MTT differs among reports, with the extremities [26] or the head, neck, and trunk [16] being mentioned previously. There have been no previous reports of MTT arising in the duodenum, although there have been some cases of duodenal MPNST. Lee et al. [10] reviewed the literature on gastrointestinal tract MPNSTs in 2006 and listed only four cases of duodenal MPNST [27–29]. Another case report on duodenal MPNST was published in 1997 [30]. These reported cases of duodenal MPNSTs are summarized in Table 1. Symptoms of MPNST depend on the site of the tumor. The present patient had symptoms such as chest oppression on exertion, dizziness, and palpitations. Laboratory tests revealed anemia related to the bleeding from the tumor, and this presumably caused our patient’s symptoms. Other symptoms that may be associated with duodenal MPNSTs include dyspepsia and abdominal pain [28].

Table 1 Previously reported cases of duodenal MPNSTs

	Sex	Age	NF-1	Size (cm)	Divergent differentiation	Treatment	Outcome	Year	Author	References
1	F	60	+	NA	–	Palliative operation	Died 9 days	1971	Clapp	[27]
2	F	64	+	NA	–	Tumor excision, Jejunal serosal patch	Died 5 days	1979	Thomson	[28]
3	M	34	+	8	–	Tumor excision, Jejunal serosal patch	Alive 2 years	1979	Thomson	[28]
4	M	47	NA	8	–	Pancreaticoduodenectomy	Disease-free 5 years	1995	Melissas	[29]
5	M	64	–	4.2	–	Pancreaticoduodenectomy	Alive 3 years 6 months	1997	Tanaka	[30]
Present case	F	49	–	5.5	+	Pancreaticoduodenectomy	Disease-free 8 years 6 months			

NA information not available

The main treatment strategy for MTT and MPNST is complete removal of the tumor by surgical resection. Routine lymph node dissection is not indicated for MPNST [3, 31]. Compared to the tumors of the extremities, complete surgical excision of the tumors arising in the trunk (including abdomen) is harder to achieve [3, 32]. One reason for the relatively poor local control of abdominal tumors is that they arise closer to vital structures than tumors of the extremities. Another reason is that abdominal tumors tend to be diagnosed later than those of the extremities, because detection is more difficult [32]. There have been reports about adjuvant therapy for MTT such as postoperative chemotherapy and radiation therapy [26, 33], but no definitive adjuvant therapy has been found that can improve the overall survival of MTT patients. Moreover, the majority of trials of adjuvant chemotherapy for MPNST have failed to show a significant response [31]. There are some reports, suggesting that radiation therapy may be useful for achieving local and symptomatic control, but it does not improve survival [34]. Thus, large-scale clinical studies are needed in the future to develop better therapy for MPNST and MTT. In the present case, complete resection with a negative surgical margin was accomplished and adjuvant therapy was not performed. The prognosis of MTT is reported be worse than that of MPNST, with a 5-year survival rate 10–20% for MTT and 34–44% for MPNST [9]. However, the present patient has been recurrence-free for 8.5 years after surgery, and is now being followed by annual CT. As shown in Table 1, there is only one previous case report of duodenal MPNST with survival for more than 5 years.

In conclusion, we experienced a rare case of MTT of the duodenum. The tumor was successfully removed by pancreaticoduodenectomy and the patient has been disease-free for 8.5 years after surgery.

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