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EDITORIAL

Plexiform angiomyxoid myofibroblastic tumor of the stomach

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Abstract

Plexiform angiomyxoid myofibroblastic tumor of the stomach is a unique mesenchymal tumor that we first described in 2007. The tumor is very rare, and to date, only 18 cases confirmed by immunohistochemistry have been reported in the literature. The patients' ages ranged from 7 to 75 years (mean, 43 years), and the male-to-female ratio was approximately 1:1. Representative clinical symptoms are ulceration, associated upper gastrointestinal bleeding (hematemesis), and anemia. The tumors are located at the antrum in all cases, and grossly, the tumor is whitish to brownish or reddish, and forms a lobulated submucosal or transmural mass. Microscopically, the tumor is characterized by a plexiform growth pattern, the proliferation of cytologically bland spindle cells, and a myxoid stroma that is rich in small vessels and positive for Alcian blue stain. Immunohistochemically, the tumor cells are positive for α-smooth muscle actin and negative for KIT and CD34. Differential diagnoses include gastrointestinal stromal tumor and other mesenchymal tumors of the gastrointestinal tract. Some authors proposed that this tumor should be designated as "plexiform fibromyxoma", but this designation might cause confusion. The tumor is probably benign and thus far, neither recurrence nor metastasis has been reported.

Key words: Plexiform angiomyxoid myofibroblastic tumor; Stomach; Gastrointestinal stromal tumor; Plexiform fibromyxoma; Myofibroblast; Fibroblast

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INTRODUCTION

The majority of gastrointestinal mesenchymal tumors are gastrointestinal stromal tumors (GISTs) that are characterized by a high frequency of positive immunohistochemical reactivity for KIT and mutations of the *KIT* gene[1-6]. Mutations of the platelet-derived growth factor receptor α (*PDGFRA*) gene have been reported in GISTs that are negative for mutations in *KIT*[7,8]. The effect of molecular target therapy by imatinib mesylate was reported for GIST[9,10], and in recent times, the accurate pathological diagnosis of GIST has been gaining more importance.

Mesenchymal tumors other than GIST occur in the stomach although their frequency is very low. In 2007, we reported 2 cases of a unique gastric mesenchymal tumor that had not been previously described and designated it as "plexiform angiomyxoid myofibroblastic tumor (PAMT)" of the stomach. The tumor was characterized by a plexiform growth pattern, the proliferation

of bland spindle cells that were separated by an abundant intercellular myxoid matrix, and a myxoid stroma that was rich in small vessels and histochemically positive for Alcian blue stain[11]. Since then, several similar cases have been reported[12-14]. Some authors reported cases with more obvious smooth muscle differentiation of the tumor cells, and used the term "plexiform angiomyxoid tumor" removing the "myofibroblastic" designation[14]. Furthermore, Miettinen *et al*[15] recently reported 12 cases of the same tumor under the diagnostic name of "plexiform fibromyxoma".

In this article, we review the clinicopathological features of PAMT cases, including an unpublished case that we recently examined, and discuss differential diagnoses, the nature of the tumor cells, and the appropriate nomenclature.

CLINICAL FEATURES

Epidemiology

PAMT of the stomach is a very rare tumor. To date, only 18 cases of PAMT of the stomach confirmed by immunohistochemistry have been reported in the medical literature[11-15]. Miettinen *et al*[15] estimated that the frequency of PAMT is less than 1/150 compared with that of gastric GIST. Table 1 shows the clinicopathological features of the reported cases and our new unpublished case of PAMT. The patients' ages ranged from 7 to 75 years (mean, 43 years). Ten cases were male and 9 cases were female; thus, the male-to-female ratio is approximately 1:1.

Symptoms and signs

The representative clinical symptoms are ulceration, associated upper gastrointestinal bleeding (hematemesis), and anemia. Other clinical symptoms include nausea, emesis, weight loss, gastric mass, and pyloric obstruction. One case was found by acute abdominal pain due to perforation[11], and one case was incidentally found during a cholecystectomy[11].

Endoscopic and radiographic findings

The tumor is detected as a submucosal tumor-like elevated lesion by endoscopy and is often ulcerated. The tumor was also detected as a multinodular hypoechogenic lesion[13] or as an infiltrating mass[14] using ultrasonography. In one case with a very large tumor, it was detected as a solid and cystic tumor using abdominal computed tomography (unpublished case).

PATHOLOGICAL FEATURES

Gross appearance

The size of PAMT of the stomach ranges from 1.9 cm to 15 cm, with a mean value of 6.3 cm. Interestingly, the tumor was located in the antrum in all 19 cases. The tumor often involves the pylorus, and extends to the duodenal bulb in approximately one-third of cases. The tumor is whitish to brownish or reddish, and forms a lobulated submucosal or transmural mass. It is not encapsulated and protrudes from the serosa (Figure 1A) in many cases, which often has a granular or nodular appearance. The surface of the tumor is ulcerated in approximately two-thirds of cases, and is perforated in one case (Figure 1B)[11]. Cystic degeneration was observed in the case with a very large tumor mass (unpublished case).

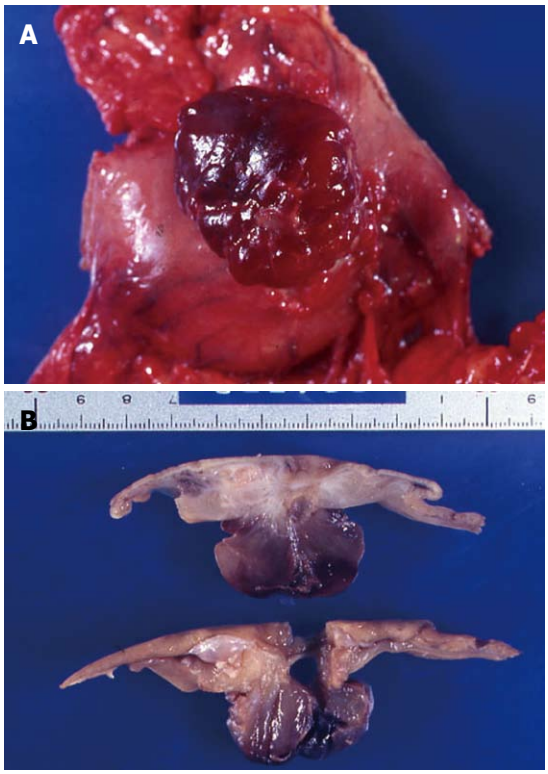

Figure 1 Gross appearance of a case of plexiform angiomyxoid myofibroblastic tumor (PAMT). A: A reddish and lobulated tumor protrudes from the serosa; B: The cut section of the tumor. The tumor causes ulceration and perforation.

Microscopic findings

PAMT shows a characteristic multinodular plexiform growth pattern in the gastric wall (Figure 2A). However, the extragastric tumor component does not show a plexiform pattern. The mucosa is often ulcerated. Spindle-shaped bland tumor cells are separated by an abundant intercellular myxoid or fibromyxoid matrix (Figure 2B). Fascicular or palisading arrangements of tumor cells are not usually observed. The tumor cells possess oval nuclei and a slightly eosinophilic cytoplasm. The nucleoli are inconspicuous and the cell borders are indistinct (Figure 2C). In the cases reported by Yoshida *et al*[14], a small number of tumor cells had morphological features reminiscent of smooth muscle cells (blunt nuclear ends and thin long eosinophilic cytoplasmic extensions). Mitoses are usually not detected (at most 4/50 high-power fields). The stroma is positive for Alcian blue stain (Figure 2D), and rich in small and thin-walled blood vessels. Dilated and arborizing blood vessels were also observed, and thrombi were formed in one case (unpublished case). Stromal collagenization was inconspicuous in some cases, but conspicuous in others (Figure 2E). The tumor cells

Table 1 Clinicopathological data of plexiform angiomyxoid myofibroblastic tumor of the stomach

Case	Age (yr)	Sex	Clinical presentation	Location	Tumor size (cm)	Mitoses	Ki-67 index	Operation	Prognosis	Ref.
1	50	M	Acute abdominal pain (due to perforation)	Antrum	4.0 × 4.0 × 2.5	None	< 1%	Distal gastrectomy	No data	[11]
2	68	M	None (incidental finding at cholecystectomy)	Antrum	4.5 × 3.5 × 3.0	None	< 1%	Partial gastrectomy	Alive without tumor (12 mo)	[11]
3	50	F	Morning nausea	Antrum	1.9 × 1.8 × 0.8	None	2%	Local excision (wedge resection)	Alive without tumor (3 mo)	[12]
4	61	M	Hematemesis	Antrum	3.7	None	Not stated	Partial gastrectomy	Alive without tumor (3 mo)	[13]
5	19	F	Mass in the stomach	Antrum	4.5 × 3.5 × 3.0	None	Not stated	Distal gastrectomy	Alive without tumor (9 mo)	[14]
6	46	M	Upper gastrointestinal bleeding	Antrum	3.5	< 1/50 HPF	< 1%	Distal gastrectomy	Alive without tumor (4 mo)	[14]
7	38	F	Upper gastrointestinal bleeding, ulcer	Antrum	3 × 2	1/50 HPF	Not stated	Distal gastrectomy	No data	[15]
8	62	M	Weight loss	Antrum	4 × 4	0/50 HPF	Not stated	Partial gastrectomy, omentectomy	No data	[15]
9	75	F	Unknown	Antrum	5	0/50 HPF	Not stated	Subtotal gastrectomy	Died of unknown cause (2 mo)	[15]
10	65	F	Weight loss, gastric ulcer	Antrum, duodenal bulb	5.0 × 4.5 × 2.5	4/50 HPF	Not stated	Partial gastrectomy	Died of unknown cause (14.5 yr)	[15]
11	33	M	Anemia, weakness	Antrum	5.5 × 3.5 × 3.5	0/50 HPF	Not stated	Distal gastrectomy	Alive without tumor (19.7 yr)	[15]
12	43	M	Gastrointestinal bleeding	Antrum	5.5 × 4.5 × 4.5	0/50 HPF	Not stated	Partial gastrectomy	Alive without tumor (18.4 yr)	[15]
13	56	F	Unknown	Antrum, duodenal bulb	5.5 × 3.0	0/50 HPF	Not stated	Partial gastrectomy	Alive without tumor (19.9 yr)	[15]
14	50	M	Gastric outlet obstruction	Antrum, duodenal bulb	7 × 6 × 6	2/50 HPF	Not stated	Distal gastrectomy	Died of unknown cause (25.5 yr)	[15]
15	21	M	Syncope, anemia	Antrum, duodenal bulb	9 × 6 × 5	0/50 HPF	Not stated	Antrectomy	Alive disease status unknown (22 yr)	[15]
16	16	F	Hematemesis	Antrum	10 × 9 × 6	2/50 HPF	Not stated	Distal gastrectomy	Alive disease status unknown (3 yr)	[15]
17	30	F	Gastric ulcer	Antrum	10 × 9 × 6	1/50 HPF	Not stated	Distal gastrectomy	Alive disease status unknown (24 yr)	[15]
18	7	F	Emesis, diarrhea, abdominal mass	Antrum, duodenal bulb	15 × 11 × 8	4/50 HPF	Not stated	Excision of tumor	No data	[15]
19	23	M	Abdominal pain and discomfort, tarry stool	Antrum, duodenal bulb	14 × 14 × 7	None	< 1%	Partial gastrectomy	Alive without tumor (12 mo)	Unpublished

HPF: High power fields.

are sometimes surrounded by a pseudovacuolar lacunar space limited by a fibrous matrix network. Mast cells are scattered in the stroma, but infiltration of lymphocytes, plasma cells, or eosinophils is inconspicuous. Tumor necrosis is not usually observed, but hemorrhage, necrosis, and cystic degeneration were observed in one case (unpublished case).

Immunohistochemical staining

In all cases examined, the tumor cells were positive for vimentin and muscle actin, and negative for KIT (Figure 3A), CD34, S-100 protein, neurofilament, cytokeratin, epithelial membrane antigen, and ALK. Tumor cells were positive for α-smooth muscle actin (SMA) in 15 of the 17 cases examined (Figure 3B), but a significant SMA-negative component was found in 3 cases. Focal or partial immunoreactivity for desmin and caldesmon was occasionally observed. Tumor cells were focally positive for CD10 in 1 of the 4 cases examined. The Ki-67 labeling index is usually less than 1% (at most 2%).

Mutation analysis of the KIT and PDGFRA genes

Sequence analysis was performed for mutational hot spots in the *KIT* and *PDGFRA* genes in GISTs (i.e. exons 9, 11, 13, and 17 of *KIT* and exons 12 and 18 of *PDGFRA*) in 8 cases, and no mutations were found in any case[11,12,14,15].

Differential diagnosis

The primary histological differential diagnoses include GIST, leiomyoma, leiomyosarcoma, schwannoma, desmoid fibromatosis, solitary fibrous tumor (SFT), inflammatory fibroid polyp, and inflammatory myofibroblastic tumor.

GISTs consist of spindle and/or epithelioid cells. In tumor areas composed of spindle cells, these cells are arranged in short fascicles in several architectural patterns including storiform, herringbone palisades, and broad sheets. Conversely, epithelioid cells are arranged in organoid clusters or sheets. Approximately 90% of GISTs are immunohistochemically positive for KIT, and muta-

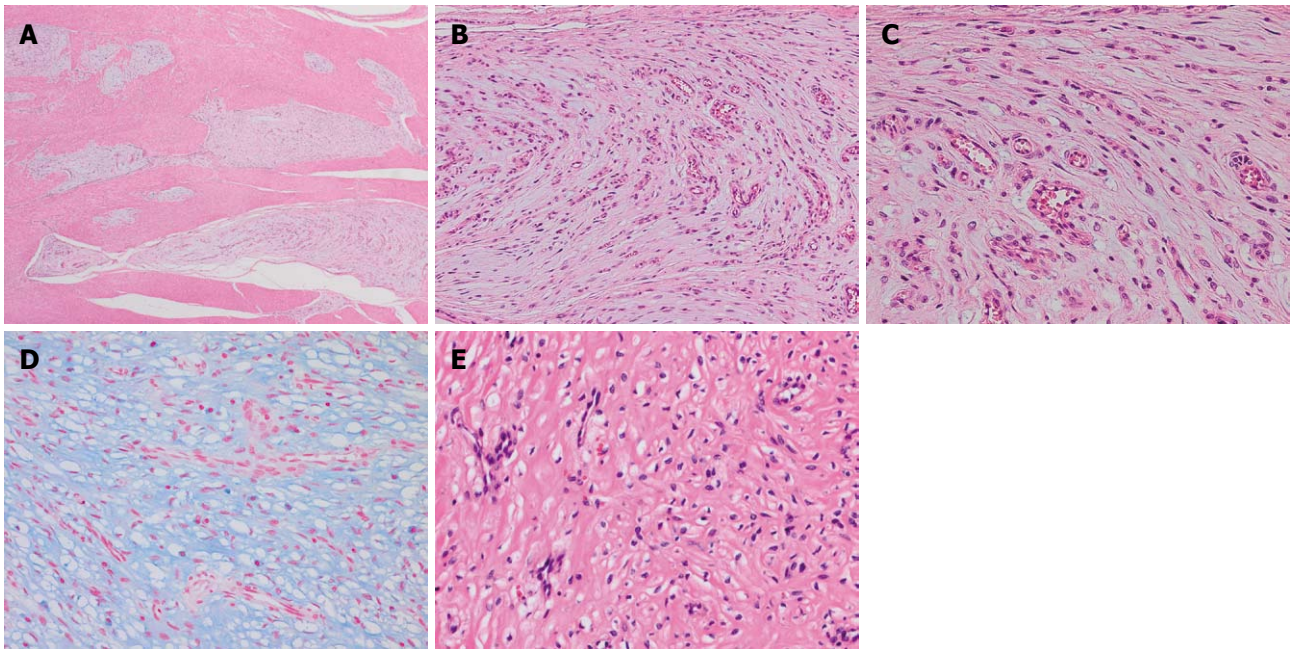

Figure 2 Histological appearance of PAMT. A: The tumor shows a multinodular plexiform growth pattern (HE stain, × 20); B: Spindle-shaped bland tumor cells are separated by an abundant intercellular myxoid matrix. The stroma is rich in small vessels (HE stain, × 100); C: Tumor cells possess oval nuclei and a slightly eosinophilic cytoplasm. The nucleoli are inconspicuous and the cell borders are indistinct (HE stain, × 200); D: The stroma is positive for Alcian blue stain (× 200); E: Stromal collagenization is occasionally observed (HE stain, × 200).

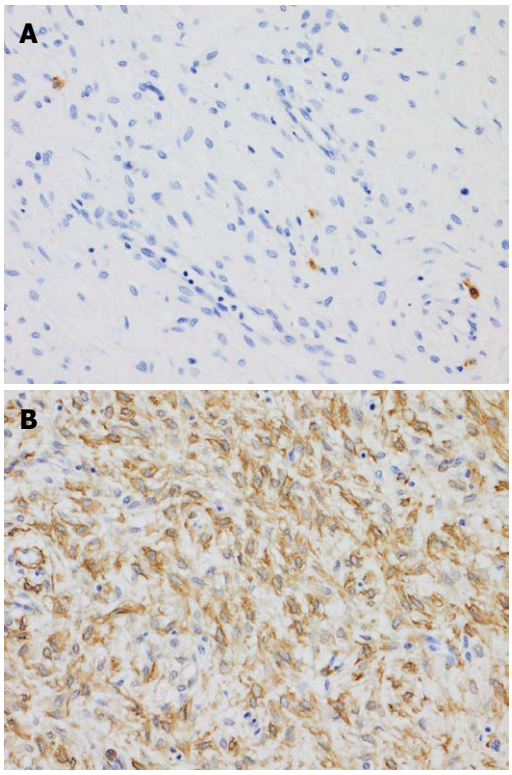

Figure 3 The results of immunohistochemical staining. A: The tumor cells are negative for KIT. The scattered KIT-positive cells are mast cells (× 200); B: The tumor cells are diffusely positive for smooth muscle actin (× 200).

tions of the *KIT* gene have been found in most of these KIT-positive GISTs[1-6]. *PDGFRA* gene mutations have been reported in some GISTs in the absence of *KIT* gene mutations[7,8]. In addition, immunohistochemical staining for CD34 is often positive in GISTs[16]. Accordingly, the histological appearance, negative immunoreactivity for KIT and CD34, and wild-type sequences of the *KIT* and *PDGFRA* genes differentiate PAMT from GIST.

Leiomyoma is characterized by the fascicular arrangement of tumor cells that possess spindle-shaped nuclei and markedly eosinophilic cytoplasm. Leiomyosarcoma shows high cellularity, cellular atypia, and remarkable mitoses. Gastric schwannoma is histologically characterized by wavy and palisading arrangements of spindle cells, lymphoid cuffing, and S-100 protein immunostaining. Desmoid fibromatosis shows long fascicular arrangements of spindle cells and dense collagen deposits. The alteration of hypercellular and hypocellular areas, deposition of dense keloid-type collagen, occurrence of hemangiopericytoma-like areas, and positive immunohistochemical staining for CD34 are the most distinguishing features of SFT. An inflammatory fibroid polyp is usually a small submucosal lesion characterized by bland spindle-cell proliferation in an onion skin-like pattern around vessels with eosinophilic infiltrates. Prominent lymphocyte and plasma cell infiltration, and positive immunoreactivity for ALK are the distinguishing features of inflammatory myofibroblastic tumors.

CELL NATURE AND NOMENCLATURE

In general, myofibroblasts are immunohistochemically positive for SMA, and negative for desmin and caldesmon[17]. Conversely, fibroblasts are negative and smooth muscle cells are positive for these three markers. Accordingly, the abovementioned immunohistochemical

characteristics of PAMT suggest that myofibroblastic tumor cells are predominant in most cases. The myofibroblastic nature of the tumor cells was also confirmed by ultrastructural analysis of PAMT[11]. However, the facts that focal immunoreactivity for desmin and caldesmon is occasionally observed in PAMT and the presence of a small number of tumor cells showing morphological features reminiscent of smooth muscle cells observed in some PAMT cases[14] suggest that PAMT may contain tumor cells with smooth muscle differentiation. Furthermore, Miettinen *et al*[15] confirmed the presence of tumor cells with fibroblastic traits. Accordingly, it is conceivable that PAMT is mainly composed of tumor cells with a myofibroblastic nature, but may also contain tumor cells with fibroblastic or smooth muscle characteristics.

We designated this tumor as "plexiform angiomyxoid myofibroblastic tumor" based on the plexiform growth pattern, a myxoid stroma that is rich in small vessels, and the myofibroblastic nature of the tumor cells[11]. Yoshida *et al*[14] reported cases with focal smooth muscle differentiation and used the term "plexiform angiomyxoid tumor", because the "myofibroblastic" designation might not be totally accurate. As mentioned above, we agree that this tumor is not a pure myofibroblastic tumor and may contain tumor cells with a fibroblastic or smooth muscle nature. However, we think that the "myofibroblastic" designation is not necessarily inappropriate, because myofibroblastic tumor cells are predominant in the majority of the reported cases. For example, inflammatory myofibroblastic tumors may also contain fibroblastic components as determined using ultrastructural analysis[18,19], and focally express desmin and calponin in 60%-70% of cases[18,20]. Miettinen *et al*[15] proposed that this tumor should be designated as "plexiform fibromyxoma" based on the plexiform architecture and combination of myxoid and fibromyxoid elements. However, most of the cases reported under the designation of "gastric fibromyxoma" or "gastric myxofibroma" were reported before the development of immunohistochemical techniques, and most of these cases are probably examples of other types of mesenchymal neoplasms with secondary regressive changes[21]. Currently, the term "gastric fibromyxoma" or "gastric myxofibroma" is used only in the case of pure fibroblastic tumors[22,23], and some different features from PAMT, such as positive immunoreactivity for CD34, are observed[22]. Superficial acral fibromyxomas possess different immunohistochemical features from those of PAMT, such as positive staining for CD34 and negative staining for SMA[24]. Thus, in using the designation "plexiform fibromyxoma", it is necessary to be careful to avoid confusion.

BIOLOGICAL BEHAVIOR AND PROGNOSIS

Follow-up data were obtained for 15 cases. The follow-up period ranged from 2 mo to 25.5 years (median, 3 years), and 12 patients were alive while 3 had expired. These 3 patients died 2 mo, 14.5 years, and 25.5 years after surgery, and the cause of death was unknown. Nine patients were alive without disease after 3 mo to 19.9 years (median, 12 mo), and 3 were alive for 3, 22, and 24 years with an unknown tumor status. Thus, neither recurrence nor metastasis was confirmed in any case.

CONCLUSION

PAMT of the stomach is a very rare mesenchymal tumor with a unique histological appearance, and it needs to be distinguished from GIST and other gastrointestinal mesenchymal tumors. It is very interesting that all of the reported PAMT cases were located at the gastric antrum, implying that this tumor might originate from a cell that is specifically distributed at this location. The absence of atypia of the tumor cells and a very low Ki-67 labeling index suggest the benign nature of this tumor, and neither recurrence nor metastasis was observed in any case. The clinicopathological features of the tumor should be elucidated by examination of a larger number of cases, and analysis of pathogenesis should be performed in the future.

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