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Periampullary Gangliocytic Paraganglioma: a Case Report

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Abstract. *A case of gangliocytic paraganglioma of the ampulla of Vater is reported. A 62-year-old female patient with abdominal discomfort and intermittent upper gastrointestinal bleeding was admitted for further diagnosis. Endoscopy revealed a broad-based periampullary polypoid mass. A mesenchymal neuroectodermal lesion of uncertain malignant potential of the intestinal submucosa was reported on frozen sections performed during exploratory laparotomy. Subsequently, a benign gangliocytic paraganglioma was diagnosed on paraffin-embedded tumour tissue. Gangliocytic paragangliomas are tumours of uncertain histogenesis. Entrapped intratumoural muscle fibres and artificially loosened accumulations of ganglion cells may potentially mimic malignancy, predominantly on frozen sections. It is important to recognise this rare, benign mesenchymal tumour in order to avoid possible surgical over-therapy.*

Gangliocytic paraganglioma (GP) is a rare tumour with a characteristic histology consisting of varying proportions of epithelioid cells with an endocrine growth pattern, spindle cells and ganglion or ganglion-like cells (1). The main histological features of GP are in accordance with those of a benign lesion, with the exception of the infiltrative growth pattern (2). The clinical course is usually benign, even though deep invasion into the duodenal wall, as well as cases with regional lymph node metastases and local recurrence, have been reported (3-6). One case has been published with distant metastasis (6). Dahl *et al.* (7) described this lesion in 1957 and Kepes and Zacharias (8) first used the term gangliocytic paraganglioma in 1971.

Macroscopically, the tumour generally presents as a submucosal tumour found mainly in the second portion of the duodenum with circumscribed, pedunculated or sessile lesions and a distinctive surface with a central shallow cleft (9).

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This paper reports on a single case of a 62-year-old woman with periampullary GP and discusses potential diagnostic difficulties associated with specific features of this tumour.

Case Report

A 62-year-old woman presented with pain in the hypochondrium that had started several weeks before presentation, followed by intermittent upper intestinal bleeding within the three days prior to presentation. An endoscopy of the duodenum revealed a 2 cm nodular periampullary intestinal wall mass. Because of a clinically suspected gastrointestinal stromal tumour, the patient underwent explorative laparotomy with perioperative biopsy of the lesion.

The frozen section (Figure 1) revealed a tumoural mass within the duodenal submucosa showing several entrapped muscle fibres but sparing the mucosa. Intestinal villi were normally structured and showed no epithelial atypia. Besides the spindle cell component of the tumour, multiple epithelioid islets were found. At higher magnification, many central areas of the latter structures appeared to be necrotic. Histopathological findings were suggestive of a neuroendocrine origin of the tumour, however, its origin remained uncertain. The surgery was terminated and the remaining tumoural tissue was fixed in formalin and subsequently embedded in paraffin. Immunohistochemical reactions (Table I) were performed along with haematoxylin-eosin (HE) staining and periodic acid Schiff reaction.

The tumour presented three distinct components characteristic of a gangliocytic paraganglioma (Figure 2): multifocal islands of carcinoid-like epithelioid cells, spindle cell proliferation and scattered ganglion cells present within both the spindle cell stroma and carcinoid-like portions. Ganglion cells were not pigmented. Several intestinal wall muscle fibres were found entrapped within the tumour. Neither cellular atypia nor tumour necrosis was present in the paraffin-embedded tissue.

Immunohistochemistry (Table II) confirmed the diagnosis of a gangliocytic paraganglioma, which is a benign gastrointestinal neuroendocrine tumour. More specifically, the epithelioid cells displayed strong AE1/AE3 positivity. Furthermore, both the epithelioid cells and some of the

Table I. *Immunohistochemical antibodies.*

Antibody	Clone	Dilution
AE1/AE3	Dako M3515	1:50
Synaptophysin	Dako M0076	1:20
Serotonin	Dako M 758	1:20
Ki-67	Mib-1, Dako M7240	1:400
NSE	Dako M7305	1:200
Chromogranin A	LK2H10+PHE5, Abcam	1:500
Somatostatin receptor	SSR2A, Gramsch Lab.	1:1000
Neurofilament	Dako M0762	1:50
GFAP	Dako Z334	1:1000
S-100	NeoMarkers	1:100

Table II. *Immunohistochemical analysis of each tumoral component.*

Primary antibody	Carcinoid-like	Gangliocytic	Spindle cells
AE1/AE3	+++	–	+
Synaptophysin	+++	+++	+
Serotonin	–	–	–
Ki-67	2%	–	2%
NSE	+++	+++	+++
Chromogranin A	+	–	–
Somatostatin receptor	++	–	–
Neurofilament	–	–	+++
GFAP	–	+	++
S-100	–	++	++

ganglion cells were immunoreactive for synaptophysin. All three cell lines were positive for neuron-specific enolase. Spindle cells were stained strongly with neurofilament. Interestingly, the epithelioid component displayed moderate reactivity against somatostatin receptor 2A. To summarise, the tumour was reported as a benign periampullary gangliocytic paraganglioma. No other neural tumours were found. The immediate postoperative course was unremarkable and the subsequent follow-up of 12 months was uneventful.

Discussion

In the gastrointestinal tract and pancreas, several neuroendocrine cell types can be distinguished producing different hormones but all expressing the general neuroendocrine marker synaptophysin (10). Both their functional diversity and non-random distribution in the gut and pancreas are probable reasons for the complexity of tumours derived from these cell types (11). Gangliocytic paragangliomas are found mainly in the second (periampullary) portion of the duodenum, and their size ranges from 1.5 to 7.0 cm (12-14). These tumours are composed of three characteristic mature cell types: (a) epithelial/endocrine cells, arranged in ribbons, solid nests and/or pseudoglandular structures; (b) S-100-positive neural spindle cells, which usually represent the major component; and (c) scattered or aggravated gangliocytic cells (3, 15). Reports on multifocal lesions of GP are rare (16). Despite their infiltrative growth, metastasis to the regional lymph nodes is rarely observed (3, 15, 17). The histological differential diagnosis of duodenal GP includes conventional paraganglioma, well-differentiated neuroendocrine carcinoma, ganglioneuroma, and spindle cell neoplasms (nerve sheath, smooth muscle, gastrointestinal stromal tumour) (18-20).

In the present case, a perioperative frozen section diagnosis was performed in order to clarify the origin and dignity of a periampullary tumoural mass found in the duodenum. Although cellular atypia was not found on perioperative frozen section biopsy, both the necrosis-like areas within the lesion and intralesional entrapped intestinal wall muscle fibres mimicked malignancy. Thus the lesion was preoperatively reported as a mesenchymal tumour of uncertain origin. Paraffin embedded tissue revealed a characteristic admixture of the three cellular components of GP: epithelioid carcinoid-like islands, spindle cell background and scattered ganglion cells. It is noteworthy that the formerly necrotic-appearing areas were reassigned as artificially loosened groups of both luminal epithelioid cells within partially trabecular structured epithelioid cells and ganglion cells. Immunohistochemical findings were typical of a GP and confirmed the conventional diagnosis. Interestingly, the epithelioid component showed a moderately positive reaction for somatostatin receptor 2A antibody. This finding has a several potential clinical implications. Recent literature has reported on using somatostatin receptor scintigraphy for detection and monitoring of head and neck paragangliomas and carcinoids (21). As with the potential diagnostic usefulness of somatostatin receptor expression (22), recent literature has also discussed data on peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor-positive tumours (23-25). Furthermore, there is strong evidence, that some mesenchymal tumours with somatostatin receptor expression may cause systemic oncogenic osteomalacia (26-29). In the present case of periampullary gangliocytic paraganglioma, however, possible systemic endocrine effects of the growing tumour were not observed.

Conclusion

Gangliocytic paraganglioma is a rare benign mesenchymal gastrointestinal tumour composed of three different cell types that may present with necrosis-like changes in portions with artificially loosened ganglion cells and entrapped intestinal wall muscle fibres during frozen section diagnosis, thus mimicking a malignancy. When reporting the results of a perioperative biopsy in cases with similar findings, every precaution should be taken to avoid possible over-therapy of this benign tumour.

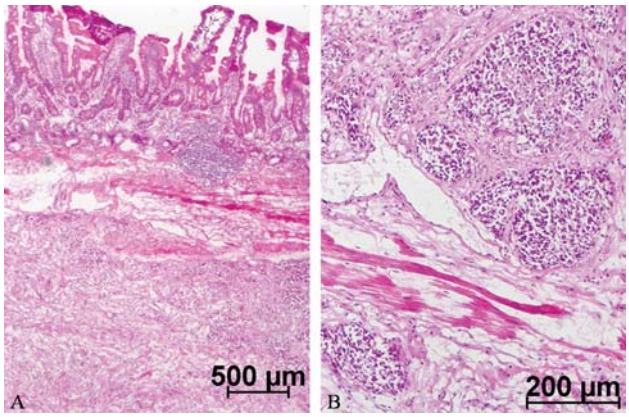

Figure 1. *Perioperative frozen section biopsy. A: Submucosal mesenchymal tumour was apparent under low magnification (HE, original magnification: ×25). B: At higher magnification, intralesional entrapped duodenal wall muscle fibres were found. Furthermore, epithelioid islands displayed eosinophilic central material, similar to necrosis (HE, original magnification: ×100).*

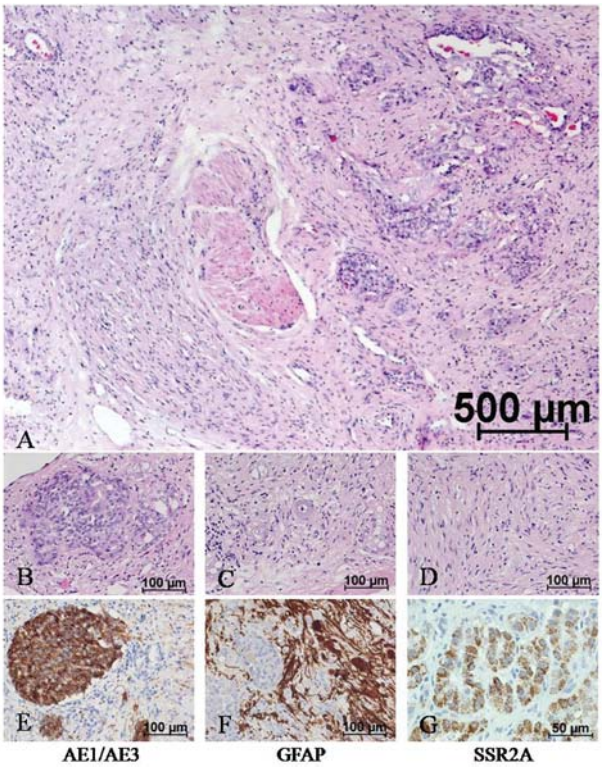

Figure 2. *Microscopic findings on paraffin-embedded material including immunohistochemistry. A: Submucosal tumour displayed spindle cell infiltration with multiple carcinoid-like islets and a few entrapped muscle fibres (HE; original magnification: ×25). B: Carcinoid-like portions of neoplasm contained solid infiltrates of small epithelioid cells with focal psedolumina or trabecular structure (HE; original magnification: ×200). C: Single ganglion cells or small groups of ganglion cells were apparent both within the spindle cell stroma and carcinoid-like proliferates (HE; original magnification: ×200). D: Spindle cell differentiated infiltrate bore some resemblances to schwannoma (HE; original magnification: ×200). E: Carcinoid-like infiltrates revealed strong AE1/AE3 reaction (original magnification: ×200). F: Both the ganglion cells and spindle cells were positive with GFAP (original magnification: ×200). G: Epithelioid cells showed positive reaction towards somatostatin receptor 2A (original magnification: ×400).*

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