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Subject Review:

Malignant Gangliocytic Paraganglioma: Case Report and Review of the Literature

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## ABSTRACT

Gangliocytic paraganglioma is a rare tumor which occurs nearly exclusively in the second portion of the duodenum. Generally, this tumor has a benign clinical course, although rarely it may recur or metastasize to regional lymph nodes. Only one case with distant metastasis has been reported. We present a case of duodenal gangliocytic paraganglioma treated first by local resection followed by pylorus-preserving pancreaticoduodenectomy. Examination of the first specimen revealed focal nuclear pleomorphism and mitotic activity, in addition to the presence of three characteristic histologic components: epithelioid, ganglion and spindle cell. In the subsequent pancreaticoduodenectomy specimen, there was no residual tumor identified in the periampullary area, but metastatic gangliocytic paraganglioma was present in 2 of 7 lymph nodes. This case confirms the malignant potential of this tumor. We review the published literature on gangliocytic paragangliomas pursuing a malignant course. We conclude that surgical therapy of these neoplasms should not be limited to local resection, as disease recurrence, lymph node involvement and rarely distant metastasis may occur.

## **INTRODUCTION**

Gangliocytic paraganglioma (GP) is a rare tumor which occurs nearly exclusively in the second portion of the duodenum (1, 2). The lesion was first described by Dahl et al in 1957, and further characterized as a benign nonchromaffin paraganglioma by Taylor and Helwig in 1961 (3,4). Kepes and Zacharias coined the term “gangliocytic paraganglioma” in 1971, recognizing the features in common with both paraganglioma and ganglioneuroma (5). Generally, this tumor has a benign clinical course, although rarely it may recur or metastasize to regional lymph nodes (6-9). There has been one report of distant metastases (10). We report a case of a 38 year old female with a periampullary gangliocytic paraganglioma with lymph node metastases, and review the published literature on GPs pursuing malignant course

## **CASE PRESENTATION**

A 38 year old woman with thalassemia trait presented to a local hospital with right upper quadrant pain. A presumptive diagnosis of hiatal hernia with ulcers was made, and the patient was started on a proton pump inhibitor. Upon further workup, an upper endoscopy revealed a mass in the duodenum, near the ampulla of Vater. After several negative biopsies, she underwent endoscopic excision of the mass, which proved to be a gangliocytic paraganglioma, with extension to the margin. Due to the positive margin status, the patient was referred for surgical opinion and

regional resection was recommended. Three months following endoscopic resection, the patient underwent pylorus-preserving pancreaticoduodenectomy with standard reconstruction. Following an uneventful recovery, she was discharged from the hospital on the 8th postoperative day.

Pathologic evaluation of the endoscopic ampullectomy specimen showed a 1.5 cm polypoid tumor in the submucosa with extension to the muscularis propria (Figure 1A). The lesion was non-encapsulated and had an infiltrative margin. The tumor was composed of 3 morphologically distinct cell populations: epithelioid cells, spindle cells and scattered ganglion cells (Figure 1B). The epithelioid cells were arranged in nests and trabeculae, and had granular eosinophilic cytoplasm and nuclei showing mild to moderate atypia (Figure 1C). The spindle cells formed slender fascicles wrapping around nests of epithelioid cells. The ganglion cells had round nuclei with prominent nucleoli and abundant eosinophilic cytoplasm. The mitotic count was 2 per 10 high power fields. Necrosis was not present. In the subsequent pancreaticoduodenectomy specimen, there was no residual tumor identified in the periampullary area, but metastatic gangliocytic paraganglioma was present in 2 of 7 lymph nodes (Figure 1D). The metastatic foci show the presence of the 3 cellular components identified in the primary tumor. Immunohistochemical stains were performed on the metastatic tumor. The chromogranin stain showed positivity in the epithelioid cells, while synaptophysin highlighted epithelioid

and ganglion cells. The spindle cells stained with S100 and neurofilament. Cytokeratin and glial fibrillary acidic protein were negative in all 3 cell populations.

## **DISCUSSION**

Gangliocytic paraganglioma (GP) is usually seen in the periampullary region of duodenum, with rare cases reported in the jejunum, pylorus (1,2), esophagus (11), pancreas (10) and appendix (12). Recently, three cases of pulmonary GP have been reported (13, 14, 15). The age at presentation ranges from 15-82 years (mean 54), and there is slight male predominance.

Clinically, GPs arising in the gastrointestinal tract present with bleeding, abdominal pain or obstruction; some cases are found incidentally at endoscopy or autopsy (2). In the largest reported series of 51 GPs, abdominal pain was the most common presenting symptom and was usually attributed (like in our case) to ulcer disease (1). The three cases of pulmonary GP reported to date presented with chest pain, pneumonia and Cushing's syndrome, respectively (13,14,15). The tumor is usually unrelated to other diseases although an association with von Recklinghausen disease has been reported (2, 16).

GP has three characteristic histologic components: epithelioid, ganglion and spindle cell. Recognition of this triad aids diagnosis on routine hematoxylin and eosin sections. The proportion of the three cell types varies in each tumor, but each component shows characteristic immunohistochemical staining similar to those observed in our case (17).

Theories on the origin of GPs are widely divergent. Studies have not been able to reconcile the combination of endocrine, ganglion, and spindle cells observed in a single tumor. The tumor components are of different embryologic origins, the first being of endodermal origin and the other 2 originating from neural crest tissue. Initially, it was suggested that these tumors were of ectodermal origin, from pluripotent stem cells derived from the neural crest, which were found in Lieberkühn's glands or the celiac ganglion during fetal development (3). Given the presentation of GPs in various sites in the duodenum and its variable histology, some authors have proposed that it originated from an endodermal pluripotent progenitor or stem cell that has the potential for divergent differentiation (16). It was also proposed that GPs were hamartomas of endodermal (epithelial cells) and neuroectodermal (ganglion and spindle cells) origin (17). However, evidence conflicting with the hamartoma theory includes cases such as ours of lymph node and distant metastasis. Most authors consider GPs to be variants of gastrointestinal tract paragangliomas (18). Paragangliomas may differentiate to other neuroectodermal elements, including neurons and Schwann cells (19). Further evidence of potential for divergent differentiation of neoplastic neuroendocrine cells includes the observation that, when stimulated by nerve growth factor, cell cultures from carcinoid tumor or small cell carcinoma differentiate toward neurons (20).

Most GPs are benign and are amenable to local resection (2). However, rare instances of recurrence, lymph node involvement, and distant metastases have been previously reported (6-10, 21-26). Twelve cases of GPs with malignant features are summarized in Table 1. In eleven cases, lymph node metastases were identified. One patient treated initially by local resection developed bone and liver metastasis 3 months later (10). Outcomes of these twelve cases clearly indicate the rare malignant potential of GP. Furthermore the incidence of malignant cases could be underestimated since majority of the reported as benign GPs cases underwent local resection only, which does not allow examination of lymph nodes. In addition most cases have been published as single case reports, without long term follow up data.

To date, histologic features predicting malignant potential has not been defined, although the presence of nuclear pleomorphism, mitotic activity and infiltrative margin, as seen in our case, raises the concern for aggressive behavior. Since GP may recur or metastasize, pancreaticoduodenectomy with lymph node dissection may be indicated for large lesions with infiltrative margin or lesions with pleomorphism and mitoses.



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**Table 1. Gangliocytic Paragangliomas with Lymph Node or Distant Metastasis**

Author	Treatment	Tumor site	Nodal Spread	Distant Spread	Follow up
Burke et al. (1)	Whipple procedure	Duodenum	Yes	No	NED 91 mo
Buchler et al (21)	Local resection	Ampulla of Vater	Yes	No	NED 20 mo
Korbi et al (22)	Whipple procedure	Duodenum	Yes	No	Not known
Tomic et al (23)	Whipple procedure	Head of pancreas	Yes	No	NED 19 mo
Bucher et al (24)	Whipple procedure	Ampulla of Vater	Yes	No	NED 40 mo
Dookhan et al (8)	Local resection	Duodenum	Yes	No	Not known
Inai et al (7)	Local resection*	Ampulla of Vater	Yes	No	NED 30 mo
Hashimoto et al (9)	Whipple procedure	Ampulla of Vater	Yes	No	NED 14 mo
Ljungberg et al (25)	Local resection	Ampulla of Vater	Yes	No	Not known
Sundararajan (6)	Whipple procedure	Duodenum	Yes	No	NED 9 mo
Wong (26)	Whipple procedure	Ampulla of Vater	Yes	No	Not known
Henry et al(10)	Whipple procedure	Not known	No	Liver Bone	Not known

\*Whipple procedure after recurrence. NED indicates alive with no evidence of disease; Mo, months.

## Figure Legends

Figure 1. (A) Submucosal location of the tumor in the periampullary region (H&E, 10X). (B) The tumor consists of epithelioid cells forming nests, fascicles of spindle cells (arrow) and ganglion-like cells (arrowhead) (H&E, 20X). (C) Nuclear pleomorphism and mitosis (arrowhead) are present (H&E, 40X) (D) Metastatic tumor in a lymph node retrieved at pancreaticoduodenectomy, composed of epithelioid and spindle cells(arrowhead) (H&E, 20X).