

REVIEW ARTICLE

Gangliocytic paraganglioma: A case report



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Abstract Paragangliomas (PGLs) are rare and encapsulated neuroendocrine tumors (NET), located in the adrenal gland or the extra-adrenal paraganglia. Extra-adrenal PGLs may develop a gangliocytic component with ganglion cells which are called gangliocytic paragangliomas (GPs). The most common location is the duodenum, and they appear with digestive symptoms or as an incidental finding.

We described a 43 years old patient, with epigastric pain, nausea and vomiting. The CT-scan reveals a nodular image in the duodenum. An ultrasound-guided FNA was performed and the pathological report revealed neuroendocrine cell groups and neural tissue. Surgery was the chosen treatment. As the patient did not present lymphatic or pancreatic parenchyma invasion, radiotherapy (RT) was not administered.

The management of GPs is not well established and multidisciplinary team approach is recommended to lead to therapeutic options. Surgical resection is still key in the treatment, and adjuvant RT may be considered in cases of lymph node invasion.

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PALABRAS CLAVE

Gangliocítico;
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Neuroendocrino;
Duodeno;
Linfático

Paraganglioma gangliocítico: a propósito de un caso

Resumen Los paragangliomas (PGL) son tumores neuroendocrinos (TNE) raros y encapsulados, localizados en la glándula suprarrenal o en los ganglios extraadrenales. Los PGL extraadrenales pueden desarrollar un componente gangliocítico con células ganglionares, denominados paragangliomas gangliocíticos (PGs). La localización más frecuente es el duodeno, apareciendo con síntomas digestivos o como hallazgo incidental.

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Describimos a un paciente de 43 años, con dolor epigástrico, náuseas y vómitos. El TAC informó de una imagen nodular en el duodeno. Se realizó una PAAF ecoguiada, describiéndose grupos de células neuroendocrinas y tejido neural en el informe anatomopatológico. La cirugía fue el tratamiento elegido. Dado que no presentaba invasión linfática ni del parénquima pancreático, no se administró radioterapia (RT).

El manejo de los PGs no está adecuadamente establecido y se recomienda el enfoque de un equipo multidisciplinar, para guiar las opciones terapéuticas. La resección quirúrgica sigue siendo el tratamiento principal, considerándose RT adyuvante en caso de invasión linfática.

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Case report

A 43-year-old patient with no relevant personal history presented to the ER with a few-day history of epigastric pain radiating to the back and worsening with food intake, along with nausea and vomiting. The patient was referred to the Digestive unit, where a computerized axial tomography (CT) scan revealed the presence of a 1.6 cm nodule in the second portion of the duodenum, likely related to a neuroendocrine tumor (NET). A fine-needle aspiration biopsy (FNAB) was requested, and the pathological result revealed the presence of neuroendocrine cell groups and neural tissue. Magnetic resonance (MRI) cholangiography suggested GI stromal tumor (GIST) and NET as differential diagnoses. However, the duodenal lesion did not show uptake in the octreoscan study. Additionally, the catecholamine and metanephrine values in urine were normal.

We decided to perform surgical intervention through tumor enucleation, along with biliary tract stenting using a T-tube. The pathological results of the sample were consistent with gangliocytic paragangliomas (GP) with 3 differential histological patterns (Figs. 1 and 2). Each presented a different immunohistochemical staining. The neuroendocrine component tested positive for synaptophysin, chromogranin, and enolase (Fig. 3), while the Schwann cell component tested positive for S100 (a protein present in crest-derived cells [Schwann cells and melanocytes] used as an immunohistochemical marker),

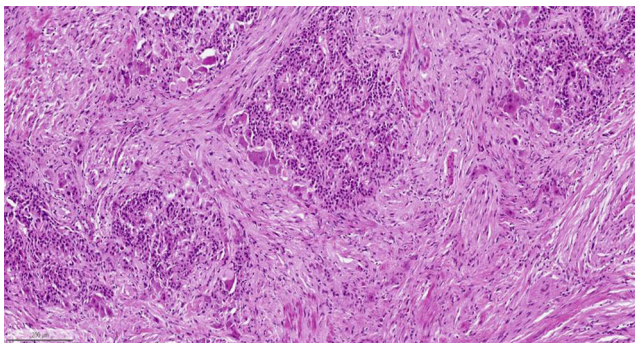


Figure 1 Hematoxylin and eosin staining (× 100): gangliocytic paraganglioma.

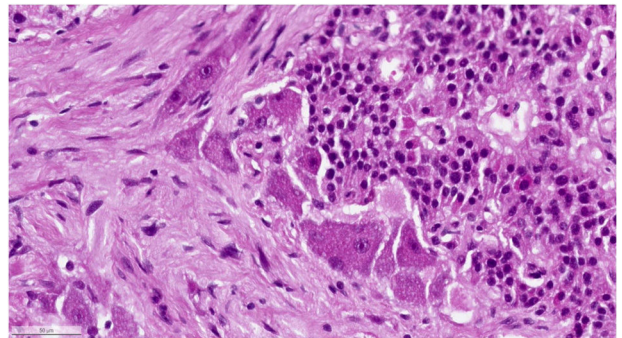


Figure 2 Hematoxylin and eosin staining (× 400): gangliocytic paraganglioma.

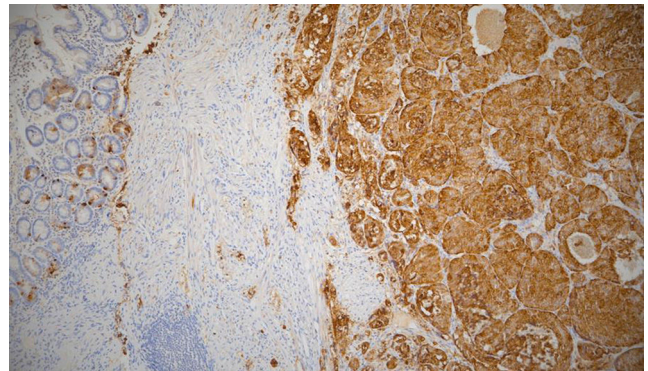


Figure 3 Immunohistochemistry: chromogranin A+ for the neuroendocrine component, – for Schwann cells.

synaptophysin, and enolase. Ganglion cells also tested positive for synaptophysin, enolase, and neurofilaments. The sample showed a Ki67 index < 1%, without infiltration of the intestinal submucosal layer, lymphatic system, or pancreatic parenchyma. The genetic study of the sample tested negative. Next-generation sequencing (NGS) was performed, including mutation hotspots, copy number variations (CNV), and fusion mutations (both inter- and intragenic). However, mutations in hypoxia-inducible factor-2 alpha (HIF-2 α) were not included. Given the absence of lymphatic involvement, radiotherapy (RT) was ill-advised.

Management

Paragangliomas (PGL) are encapsulated and rare NETs which can be found in the adrenal medulla or extra-adrenal ganglia.

In some cases, PGL develops a gangliocytic component with ganglion cells, known as GP.¹ This unusual tumor includes 3 characteristic components: epithelioid neuroendocrine cells, spindle cells with Schwann cell differentiation, and ganglion cells² (Figs. 1–3).

The lesion was first described by Dahl et al. back in 1957.³ It was characterized as a non-chromaffin benign PGL by Taylor et al. in 1961.⁴ Later, in 1971, Kepes et al. began using the term “gangliocytic paraganglioma”, recognizing the characteristics of both paraganglioma and ganglioneuroma.⁵

The most common location is the duodenum—referred to as duodenal gangliocytic paraganglioma (DGP)—followed by the respiratory system, spinal cord, jejunum, esophagus, and appendix.

Although DGPs clinically show abdominal pain, digestive bleeding, or obstructive jaundice, they are also diagnosed as incidental findings. Abdominal pain occurs in one-third of the patients and can be of epigastric etiology with dyspeptic characteristics.⁶ Although most are sporadic, an association with type I neurofibromatosis (NF1) has been reported.⁷

HIF-2 α mutations are responsible for the syndrome of multiple PGLs and duodenal somatostatinomas, associated with polycythemia (Pacak-Zhuang syndrome). This type of mutation was found in 20% of GPs in the series by Zhuang et al.⁸ Most cases were considered non-functioning, except for somatostatin-producing ampullary NETs, also associated with NF1. Of note that these tumors are often confused with other GI neoplasms on the imaging modalities and/or endoscopies.⁹

DGPs have a good prognosis, with recurrence being unusual. Few cases with lymphatic and/or hepatic metastases have been described,^{10–15} representing 5% up to 7% of diagnosed patients.¹⁶ However, periaampullary GP should be considered a tumor with higher malignant potential, as metastases have been reported in 26.3% of cases.¹⁷ Interestingly, there seems to be a higher risk of lymphatic metastasis when they extend beyond the intestinal submucosal layer, as well in younger patients.^{7,9,16} This lymphatic involvement appears to influence treatment modality, but not prognosis.⁷

Surgical resection is the standard therapy, varying according to the extent of the lesion. It can range from endoscopic submucosal resection to duodenopancreatectomy.^{12,15}

Areas of uncertainty

Although the etiology of GPs remains unclear, 2 theories have been proposed trying to explain it. The first one suggests an ectodermal origin, arising from pluripotent cells derived from the neural crest. These cells are found in Lieberkühn's glands or celiac ganglia during fetal development. The second one suggests an epithelial cell origin derived from the endoderm in the ventral pancreatic primordium and neuroectodermal ganglion or spindle cells.⁶ Ganglion cells express synaptophysin,

neuron-specific enolase, and neurofilament, indicating their neuronal differentiation.¹

Three cases have shown that adjuvant external RT may be useful in the management of regional lymph node metastases.^{7,13,14} These patients remain recurrence-free to date, with the maximum follow-up time recorded being 8 years.¹⁴ In general, chemotherapy (CT) is not recommended due to the low likelihood of distant metastasis and the poor response to CT these tumors have. One case was described without recurrence at a 3-year follow-up after 5 cycles of CT.¹⁶

Clinical practice guidelines

Currently, since there are no specific guidelines on the management of GPs, PGL protocols are used in these cases. As all PGLs are potentially metastatic, the distinction between benign and malignant has been withdrawn from the World Health Organization (WHO) classification of endocrine tumors.¹⁸ The clinical presentation of PGLs is extremely variable and depends on many factors such as anatomical location, tumor size, extent, functionality, hereditary or sporadic cause, malignancy potential, and time elapsed from symptom onset to diagnosis.

CT or MRI are the most widely used imaging modalities for localization. Although they have similar sensitivity and specificity rates, the former provides better anatomical details.¹⁹ PGLs are typically solid, hypervascular, and well-demarcated masses.²⁰ Treatment options depend on the extent of the disease, with surgery being the cornerstone for most patients.^{18,21}

Conclusions and recommendations

PGL is an extremely rare tumor. Anatomopathological diagnosis is essential, as there may be discordance between the different imaging modalities used. Infiltration beyond the intestinal submucosal layer could be considered a risk factor for lymphatic metastasis.

Given its very low prevalence, joint evaluation by a multidisciplinary team is recommended to guide the best therapeutic option. Surgical resection remains the standard therapy, with adjuvant RT being considered in cases of lymphatic invasion. There is insufficient evidence to recommend the use of CT.

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Conflicts of interest

None declared.

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