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Gastric paraganglioma:
A case report and a review of the literature.

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Gastric paraganglioma: A case report and review of the literature.

AIM: *Paragangliomas are neural crest-derived neuroendocrine tumors, originating from paraganglia, which are dispersed neuroendocrine organs characterized by catecholamine and peptide-producing cells. With an annual incidence estimated at 1/100,000, paragangliomas represent 10% of catecholamine secreting tumors.*
MATERIAL OF STUDY: *We report a case of a 76-year-old man who was submitted to a subtotal gastrectomy with omentectomy and gastrojejunal anastomosis. The Hystologic exam has revealed an ulcerative polypoid gastric carcinoma with cell poorly cohesive and infiltration of the muscular gastric wall and an incidental parietal gastric lesion which was a paraganglioma with immunocytochemical investigations positive for NSE and negative for CD117, S100, CD34 e SMA.*
DISCUSSION: *Pheochromocytoma indicates exclusively tumors arising from the adrenal medulla, while the extra-adrenal paraganglioma suggests tumors of the chromaffin cells with other locations. Gastric or paragastric localization, as in our case, is very rare for these neoplasms, and in literature there are only isolated case reports. Genetical predisposition is observed in 30% of these tumors and can be responsible of hereditary disease characterized for differences in tumor distribution, catecholamine production, risk of metastasis, and association with others types of tumors.*
CONCLUSION: *In asymptomatic patients and when biochemical and clinical suspicion of neuroendocrine tumor is strong, you have to perform anatomical and functional investigations to detect these neoplasms. The first line treatment for resectable tumors is complete surgical resection, that can be performed with open surgery or laparoscopic technique. Surgical therapy is also indicated to palliative intent when a complete eradication of disease is not achievable for metastatic status of malignancies.*
KEY WORDS: Autonomic nervous system, Gastrectomy, Gastric cancer, Gastric paraganglioma

Introduction

Paragangliomas are rare neuroendocrine tumors arising from the embryonic neural crest. They may be located from the upper cervical region to the pelvis, related to the autonomic nervous system. The majority of paragangliomas appear to be sporadic but there are forms associated with genetic syndromes. The clinical presentation depends on secretion of catecholamines, malignancy or mass effect; paragangliomas may also be discovered incidentally and they are called "incidentalomas" [1,2]. Most paragangliomas are benign and are characterized by a strong vascularization; about 20% are malignant with poor survival. We report a rare case of parietal gastric paraganglioma fortuitously detected during intraoperative exploration on subtotal gastrectomy performed for gastric cancer endoscopically diagnosed. If this cancer is uncommon, gastric localization even more. Therefore, we briefly discuss the clinical and therapeutic approach for these tumors and the cytomorphological features which are important also for diagnosis.

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Case Report

A 76-year-old man with a notable medical history for polyglobulia, chronic obstructive pulmonary disease, peripheral vascular disease, benign prostatic hypertrophy. The patient undergoes gastroscopy to explain anemia arose during the follow-up for polyglobulia. Endoscopic examination revealed the presence of vegetative-ulcerated polypoid lesion of 4 cm between the gastric body and antrum. The histologic report demonstrated a gastric cancer, poorly cohesive, with areas of hepatoid differentiation, necrosis and intralesional extravasation of blood. TC chest-abdomen stadiation reported presence of no-specific pulmonary micronodules. No-radiological evidence of liver metastases or abdominal lymphadenopathy. The measurement of tumor markers showed CEA 2.84 ug/ml, AFP 107.40 ng/ml, CA19.9 (GICA) 23.22 UI/ml, CA50 11.20 U/ml. The patient did not present symptoms of diarrhea, flushing, palpitations or weight loss. We performed a subtotal gastrectomy with omentectomy and gastrojejunal anastomosis. Pathologic examination revealed, for the endoscopically diagnosed gastric lesion, an ulcerative polypoid gastric carcinoma with poorly cohesive cell and infiltration of the muscular gastric wall; chronic gastritis with calyciform metaplasia; free lymph nodes 12/12; no pathological omentum; pT3N0Mx R0. But the parietal gastric lesion revealed a surprising diagnosis: it was a localization gastric of paraganglioma with immunocytochemical investigations positive for NSE and negative for CD117, S100, CD34 e SMA.

Discussion

Paragangliomas are neural crest-derived neuroendocrine tumors, originating from paraganglia, which are dispersed neuroendocrine organs characterized by catecholamine and peptide-producing cells. With an annual incidence estimated at 1/100,000, paragangliomas represent 10% of catecholamine secreting tumors [1]. Males are affected slightly more commonly than females (1 to 1.8/1) and in terms of age at onset although the fifties are preferred, it has been encountered over an age range from 23 to 83 years [2].

According to World Health Organization classification, the term pheochromocytoma indicates exclusively tumors arising from the adrenal medulla, while the term extra-adrenal paraganglioma suggests tumors of the chromaffin cells with other locations [3].

Paragangliomas may be classified into two groups based on location into the autonomic nervous system: sympathetics and parasympathetics. The firsts arise from the sympathetic paraganglia located along the paravertebral and paraaortic axis relative to the cervical ganglia from the neck to the abdomen and pelvis; the seconds originate from paraganglia located in the head and neck proximal to the vascular structures that give rise to the carotid body, aorto-pulmonary septum, intravagal and jugulotympanic tumors, as well as those arising from the wall of some organs such as the urinary bladder. Gastric or paragastric localization, as in our case, is very rare for these neoplasms, and in literature there are only isolated case reports. However, our case was located on the posterior gastric wall while the other seven cases reported in the literature four were located on the gastric fundus, one on the anterior gastric wall, one on the lesser curvature and another on posterior gastric wall [4].

Sympathetic paragangliomas usually secrete catecholamines and are located in the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. In contrast, most parasympathetic paragangliomas are nonfunctional and located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull [5].

The most paragangliomas secrete norepinephrine and the clinical presentation is characterized by arterial hypertension, headache, sweating and palpitations. However, in the tumors not secreting catecholamines the symptoms can be vague: psychiatric disorders, anxiety, facial pallor, weight loss, polyuria/polydipsia, hyperglycemia, secondary erythrocytosis, stroke and cardiomyopathy [6]. The patients with paraganglioma can be asymptomatic and the diagnosis is fortuitous during testing for others clinical conditions not related to adrenal disease; the tumors so discovered are called "incidentalomas" and they are typical of paraganglioma genetically determined [7].

Also our patient was asymptomatic and the discovery was incidental, but the others case reported in the literature were discovered for a several clinical presentation: epigastric pain,

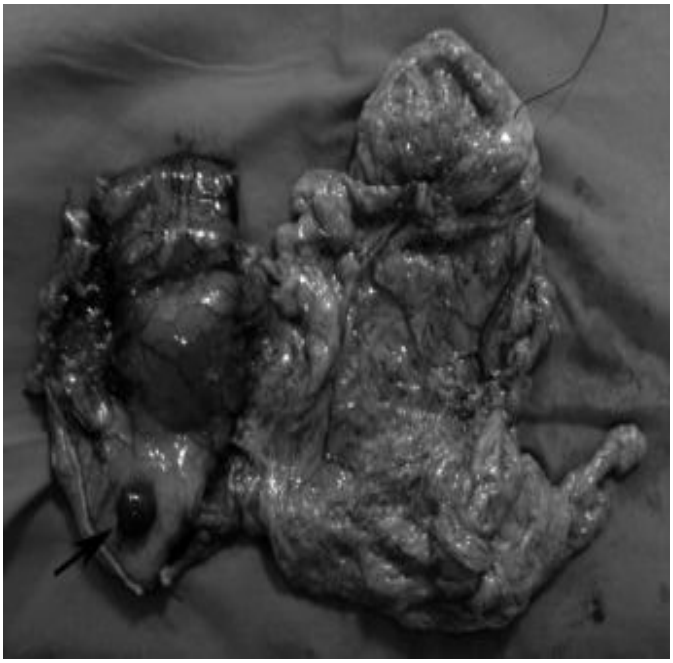

Fig. 1: Intraoperative image: subtotal gastrectomy with omentectomy; the arrow shows the incidental parietal gastric lesion.

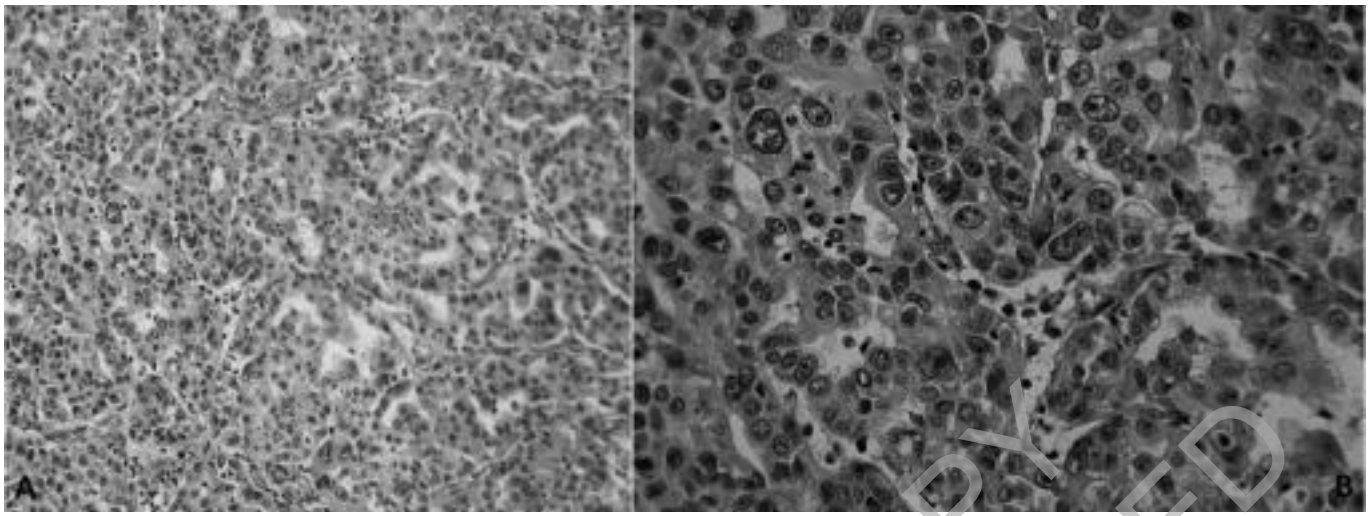

Fig. 2: A. E-E 10x, B E-E 40x: Gastric paraganglioma with immunocytochemical investigations positive for NSE and negative for CD117, S100, CD34 e SMA.

melaena, haematemesis, palpable mass or abdominal pain.
Genetical predisposition is observed in 30% of these tumors and can be responsible of hereditary disease characterized for differences in tumor distribution, catecholamine production, risk of metastasis, and association with others types of tumors. Three cancer predisposition syndromes are associated with the development of pheochromocytoma–paraganglioma: multiple endocrine neoplasia type 2 [men2(RETgene)], von Hippel–Lindau [vhl(VHL gene)], and neurofibromatosis type 1 [nf1(NF1gene)]. In addition to the syndromic forms, mutations in the succinate dehydrogenase (SDH) gene complex (SDHB, SDHC, and SDHD) have been linked to an increased risk of tumor development—namely, hereditary pheochromocytoma–paraganglioma. More recently, SDHA, SDHAF2, TMEM127, and MAX have been also associated with predisposition to these tumors [8]. Important new findings are that mutations of succinate dehydrogenase genes SDHA, SDHB, SDHC, SDHD, and SDHAF2 (collectively "SDHx") are responsible for a large percentage of hereditary pheochromocytoma–paraganglioma and that SDHB mutations are strongly correlated with extra-adrenal tumor location, metastasis, and poor prognosis [9]. Lefebvre et al. [8] proposed a screening recommendations and clinical follow-up for individuals who have a hereditary pheo–pgl syndrome, who have known disease-causing mutations in a pheochromocytoma–paraganglioma predisposing gene, who are at risk (based on their position in the pedigree), who have not yet undergone gene testing.
In patients with symptoms of secretory chromaffin tumour or in patients with a family history of pheochromocytoma–paraganglioma, who carry mutations and undergo screening for asymptomatic tumour, the first diagnostic investigation is determining levels of metanephrine, followed by anatomical and functional imaging. The determination of plasma or urinary metanephrine has a sensitivity and specificity of more than 95% [7]. According to catecholamine and their metabolites secretion these neuroendocrine tumors can be divided into three groups: noradrenergic (secreting mainly noradrenaline), adrenergic (secreting mainly adrenaline in addition to some varying amounts of noradrenaline), dopaminergic (secreting predominantly catecholamine). The catecholamine biochemical phenotype can be correlated to genotype and underlying mutation. Tumors with a RET or NF1 mutation show increased plasma concentrations of metanephrine, whereas VHL and SDHx related tumors do not secrete adrenaline and show increased plasma concentrations of normetanephrine. SDHB/D tumors demonstrate additional or solitary increases in plasma 3- methoxytyramine indicating dopamine production. Furthermore, the measurement of catecholamine metabolites, can be utilized as biomarkers of tumor size, location and malignancy. Adrenaline and metanephrine secretion is usually confined to adrenal tumors, whereas extra-adrenal tumors secrete predominantly or exclusively noradrenaline and normetanephrine. High levels of plasma free metanephrines are useful for estimating tumor size. Catecholamines and their metabolites could therefore be the potential biomarkers of malignant paraganglioma in addition to underlying SDHB mutation, a primary tumor size >5 cm and an extra-adrenal tumor [10]. Eisenhofer et al. showed that plasma 3-methoxytyramine level, also associated with SDHB mutation and extra-adrenal location of the primary tumor, is a more sensitive biomarker of malignant disease than plasma or urinary dopamine [11]. Furthermore, malignant transformation of tumor cells does not necessarily result in the loss of biochemical phenotype. Chromogranin A, when present in elevated levels, can be indicative of malignancy in both nonsecretory and secretory pheochromo-cytomas/paragan-gliomas.
Furthermore there is a proven correlation between chromogranin A levels and tumor mass as well as plasma

metanephrines. Chromogranin A also can be used to gauge tumor response and relapse [12].

In asymptomatic patient and when biochemical and clinical suspicion of neuroendocrine tumor is strong, you have to perform anatomical and functional investigations to detect these neoplasms. Computed tomography (CT) and magnetic resonance imaging are useful to determine features of tumor as the site, the number (single or multiple), the malignancy, the association with other neoplasms in context of hereditary syndrome [7]. Both CT and MRI have a sensitivity of 98%–100% for adrenal pheochromocytomas, but MRI is more sensitive (94% versus 90%) for extra-adrenal pheochromocytomas-paragangliomas. Still, these radiological investigations have aspecificity of approximately 70% because of the high incidence of adrenal incidentalomas [13].

Lowenthal et al. support that without histologic diagnosis and symptoms of cathecolamine excess, paragangliomas may be mistaken for GISTs because may have a similar radiographic appearance [6]. Large cathecolamine-secreting tumors can be detected by ultrasound scans, especially those with abdominal and cervical localization [14].

Functional imaging is an important step in the diagnostic approach of patients with pheochromocytomas and paragangliomas. The combination of anatomical imaging studies based on computed tomography (CT) or magnetic resonance imaging (MRI), and functional imaging studies (nuclear medicine) give a sensitivity of nearly 100% for the diagnosis of catecholamine-producing tumors [7]. With radionuclide imaging is possible to confirm diagnosis of neuroendocrine tumor through targeted tracer, to stage primary or metastatic disease, to watch patients at risk of recurrence, to select for targeted radionuclide therapy and to evaluate metabolic response to therapy [15].

The methods of nuclear medicine for localization of chromaffin tumors can be differentiated into specifics and non-specifics. The first, related to the synthesis, uptake or storage of catecholamines, should be sought as initial investigation, the latter, making use of the tumors' high glucose metabolism or expression of somatostatin receptors, should be used if recurrent, metastatic or malignant disease is suspected [16].

Between chromaffin-tumor-specific functional imaging, the radiolabelled MIBG (^{123}I e ^{131}I) scintigraphy is the most commonly used functional test for diagnosis of cathecolamine-secreting tumors in metastatic and primitive lesions [14]. Scintigraphic imaging using iodine-123 labelled MIBG (^{123}I-MIBG) has an overall sensitivity of 83%-100% and specificity of 95%–100%. However, the sensitivity in the SDHB mutated subgroup is as low as 65%-80% [12].

Then, in case of pheochromocytomas and paragangliomas associated with germline mutations in the SDHB gene, that have a high risk of extra-adrenal/malignant disease, PET with 18F-labelled fluoro-deoxy-glucose (18F-FDG) reported sensitivity of 97%–100% in tumor localization is by far superior to the sensitivity of 18F-DA PET (70%–88%) and 1^{13}I-MIBG scintigraphy (65%–80%).

Positron emission tomography (PET), performable with different tracers, generally considered to be superior to MIBG scintigraphy, may play a major role in the imaging of metastatic neuroendocrine tumors specifically for small tumors [13]. (68)Ga-DOTA-TOC PET may be superior to (18)F-DOPA PET and diagnostic CT in providing valuable information for pre-therapeutic staging of extra-adrenal PGL, particularly in surgically inoperable tumors and metastatic or multifocal disease [17].

The therapeutic modalities of paragangliomas include open or minimally invasive surgery, nuclear medicine, chemotherapy, radiotherapy and biological targeted agents. The choice of the type of treatment depends on various factors: location, size, extension, symptomatology, malignancy, status of somatostatin receptors.

According to the World Health Organization classification of tumors of the endocrine system, the presence of metastasis or tumor spread in sites normally devoid of chromaffin tissue define paragangliomas as malignant [19].

Recently, the size and the weight of the tumor, the presence of tumor necrosis, Ki-67 index > 4% and the absence of pS100 are considered as high risk factors for malignancy and recurrence [20].

About 30-40 % of paragangliomas are malignant and the overall 5-year survival is around 50%. Currently, the only validated risk factor for malignancy and poor prognosis is the evidence of a germline mutation in the succinate dehydrogenase subunit B (SDHB) gene [21].

The first line treatment for resectable tumors is complete surgical resection, that can be performed with open surgery or laparoscopic technique. In all cases of gastric paragangliomas reported in the literature was performed a total or subtotal gastrectomy, but even when the tumor is localized in another segment of gastroenteric tube the radical surgery is very important. Junsik Kwon et al. reported an extremely rare case of duodenal gangliocytic paraganglioma in the ampulla of Vater treated with pylorus preserving pancreaticoduodenectomy (PPPD)[22]. For the same principle, Lin Yu et al. have presented the first case of malignant paranganglioma of the low rectum; they have performed a radical surgery with laparoscopic rectectomy [23].

According to studies regarding the laparoscopic treatment of extra-adrenal intra-abdominal paragangliomas available in the literature, all tumors were less than 4 cm. In fact, Fotios Archontovasilis et al. have used open surgery to excise large paraganglioma of the greater omentum (15 cm x 15 cm), moreover extremely infrequent(second case reported) [18]. The choice between open or laparoscopic surgery depends on the experience of surgeon and findings, location and extension of tumor.

Surgical therapy is also indicated to palliative intent when a complete eradication of disease is not achievable for metastatic status of malignancies. The reduction tumor burden (debulking) can be helpful to the control of symptoms due to tumor size and cathecolamines secretion and to the improvement response to other therapeutic modalities [12].

In symptomatic patients for hypersecretion of cathecolamines, the preoperative management of blood pressure is important for reduce the incidence of perioperative complications. When possible, the mainstay of treatment are the alpha and beta blockers; but calcium blockers, angiotensin-converting enzyme inhibitors or alpha-methyl-para tyrosine are also effective [16].
Radionuclide treatment with somatostatin analogues is indicated in selected patients through scintigraphic examinations that demonstrate the presence of somatostatin receptors. The ^{90}Y- and ^{177}Lu-labelled somatostatin analogues showed encouraging results to size reduction of tumor. For this treatment is needed further studies to determine optimal doses, schedules and response criteria [12].
Radiotherapy is helpful to palliation in patients with painful metastases, not subject to other treatments [7].
Chemotherapy is indicated for tumour size reduction and control of symptoms related to hypersecretion of catecholamines in patients with local advanced and/or metastatic disease not accessible for surgery and resistant to treatment with radionuclide therapy. According to recent results the most effective chemotherapy regime is the CVD-protocol (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, and dacarbazine 600 mg/m2 on Day 1 and dacarbazine 600 mg/m^2 on Day 2; every 21 to 28 days). This combination showed partial or complete response (50-55% of the patients), as well as palliation of symptoms, without severe toxicity (haematologic, neurologic, and gastrointestinal) [12]. Other regimens include etoposide and cisplatin or etoposide and lomustine with 5-fluorouracil [16].
Recent studies demonstrated an over-expression of vascular endothelial growth factor (VEGF), endothelin receptor types A and B, and heat shock protein 90 (HSP90), that could represent targets for future therapies [12]. Buzzoni et al. according to genetic testing consider two cluster of patients with specific therapeutic targeting. CLUSTER 1 include patients with germ line mutations in VHL, SDH A/B/C/D, PHD or somatic mutations in VHL, that might benefit from antiangiogenic therapy (VEGF pathway). CLUSTER 2 include patients with germ line mutation in RET, NF1, TMEM127, MAX as well as most of sporadic tumors that may experience a benefit from TK, PI3K, AKT, mTOR, RAS, RAF, ERK inhibitors [21]. For this novel antineoplastic drugs, that currently are used for treatment of other neoplasms, future clinical trials are necessary to evaluate the efficacy and safety in the management of malignant paraganglioma.

Riassunto

I paragangliomi sono tumori neuroendocrini derivati dalla cresta neurale, provenienti dai paragangli, organi neuroendocrini dispersi e caratterizzati da cellule producenti catecolamine e peptidi. Presentano un'incidenza annuale stimata in 1 / 100.000, rappresentando il 10% dei tumori secernenti catecolamine. Riportiamo il caso di un uomo di 76 anni giunto alla nostra osservazione per la presenza di una lesione polipoide di 4 cm, vegetativa-ulcerata, tra il corpo e dell'antro gastrico rilevata durante una gastroscopia per la comparsa di anemia. Il paziente è stato sottoposto a gastrectomia subtotale con omentectomia e anastomosi gastrodigiunale. L'esame istologico ha rivelato un carcinoma gastrico polipoide ulcerato con cellule scarsamente aderenti con infiltrazione della parete gastrica muscolare e incidentalmente è stata identificata una lesione della parete gastrica posteriore incidentale che si rilevava essre un paraganglioma con la positività alle indagini di immunocitochimica per NSE e negatività per CD117, S100, CD34 e SMA.
Con il termine di feocromocitoma si indica esclusivamente i tumori derivanti dalla midollare del surrene, mentre il paraganglioma extra-surrenalico suggerisce tumori delle cellule cromaffini con altre posizioni. La localizzazione gastrica o perigastrica, come nel nostro caso, è molto rara per queste neoplasie, e in letteratura vi sono solo pochi case report. La predisposizione genetica si osserva nel 30% di questi tumori e può essere responsabile della malattia ereditaria caratterizzata da differenze nella distribuzione del tumore, nella produzione di catecolamine, nel rischio di metastasi, e nell'associazione con altri tipi di tumori.
In conclusione, nei pazienti con sintomi di tumore secernente cromaffini o in pazienti con una storia familiare di feocromocitoma-paraganglioma, che portano mutazioni e sottoposti a screening per il tumore asintomatico, la prima indagine diagnostica è determinare i livelli di metanefrina, seguita da immagini anatomiche e funzionali. In pazienti asintomatici e quando il sospetto biochimico e clinico di tumore neuroendocrino è forte, è necessario eseguire indagini anatomiche e funzionali per identificare queste neoplasie. La prima linea di trattamento per i tumori resecabili è la resezione chirurgica completa, che può essere eseguita con la chirurgia aperta o con la tecnica laparoscopica. La terapia chirurgica è indicata anche a scopo palliativo quando una completa eradicazione della malattia non è realizzabile per lo stato metastatico di tumori maligni.

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