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Non-Functional Pancreatic Paraganglioma: A Diagnostic Masquerade

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ABSTRACT:

Background: Primary pancreatic or peri-pancreatic paragangliomas are exceedingly rare extra-adrenal neuro-endocrine tumours, with fewer than 60 well-documented cases reported [1]–[3]. Because most are non-functional and radiologically mimic pancreatic neuro-endocrine tumours or complex cystic lesions, pre-operative diagnosis is notoriously difficult [4],[7],[11].

Case presentation: We describe a 63-year-old man who presented with six months of worsening chronic epigastralgia and unquantified weight loss. Routine laboratory tests, including CA 19-9 and CEA, were normal. Cross-sectional imaging (ultrasound, contrast-enhanced CT and MRI) demonstrated a 4-cm, well-circumscribed, mixed cystic–solid, hyper-vascular mass in the duodeno-pancreatic groove compressing—but not invading—the inferior vena cava. Endoscopic ultrasound clarified the multilocular cystic architecture, yet fine-needle aspiration was deferred because of vascular proximity and low diagnostic yield. The patient underwent pancreas-preserving en bloc excision via midline laparotomy; intra-operative haemodynamics remained stable.

Histopathology: Microscopy revealed classic "Zellballen" nests of uniform chief cells within a rich vascular stroma. Immunohistochemistry showed strong, diffuse expression of chromogranin A and CD56, with negative cytokeratin AE1/AE3, DOG1 and CD117, and a Ki-67 index < 1 %, confirming non-functional paraganglioma [2],[7]. Resection margins were clear (R0) and no metastatic lymph-nodes were identified. The patient remains disease-free 18 months post-operatively.

Discussion: This case underscores the diagnostic challenges posed by pancreatic paragangliomas, which often lack catecholamine-related symptoms and display non-specific imaging features. Differentiation from pancreatic neuro-endocrine tumours relies on a keratin-negative immunoprofile [7]. Complete surgical excision with negative margins is the treatment of choice [8],[2]; however, because malignant potential cannot be predicted histologically, prolonged surveillance is recommended [2],[4],[8].

Conclusion: Pancreatic paraganglioma, though exceptionally uncommon, should be considered in the differential diagnosis of well-vascularised cystic-solid pancreatic masses with normal tumour markers. Awareness of this entity facilitates timely surgical management and appropriate long-term follow-up.

INTRODUCTION

Paragangliomas are rare neuroendocrine tumors arising from neural crest-derived chromaffin cells located outside the adrenal medulla [12]. While pheochromocytomas refer to tumors developed within the adrenal medulla, paragangliomas can occur along the sympathetic and parasympathetic chains, from the base of the skull to the pelvis. Pancreatic or peri-pancreatic localization of paragangliomas is exceptionally rare, with a limited number (< 60) of well documented cases described in the worldwide scientific literature [1]–[3]. These tumors are most often non-functional, meaning they do not secrete excess catecholamines, unlike their adrenal counterparts or those in other more common extra-adrenal locations [4],[9],[11]. Their clinical presentation is therefore often non-specific, dominated by symptoms related to mass effect or discovered incidentally during imaging studies performed for other reasons [7],[12]. Preoperative diagnosis is challenging, as radiological features can mimic other pancreatic lesions, particularly pancreatic neuroendocrine tumors (PNETs) or complex cystic lesions [7],[11]. Histology, coupled with immunohistochemistry, confirms the diagnosis, but assessing malignant potential remains difficult in the absence of metastases [4],[5]. We report here the case of a 63-year-old patient presenting with a paraganglioma of the pancreatic head, discovered during the investigation of chronic epigastralgia, and discuss the diagnostic and therapeutic aspects of this rare entity in light of the literature data.

CASE PRESENTATION

A 63-year-old man with a history of hypertension and pulmonary tuberculosis treated three years prior, reported long-standing epigastric discomfort that had intensified over 6 months, resulting in unquantified weight loss without jaundice, flushing or paroxysmal spells. Physical examination was unremarkable. Laboratory tests showed normal liver chemistry, fasting glucose and

tumour markers (CA 19-9 14 U mL^{-1}, CEA 5.3 ng mL^{-1}). Abdominal ultrasound visualised a 43 × 35 mm mixed cystic–solid lesion anterior to the inferior vena cava (IVC) and contiguous with the pancreatic head. Triple-phase CT confirmed a 34 × 55 × 40 mm well-circumscribed, heterogeneously enhancing mass in the duodenopancreatic groove, compressing but not invading the IVC; no ductal dilatation or lymphadenopathy was seen. Contrast-enhanced MRI demonstrated a hyper-vascular capsule, central fluid signal and low T1/high T2 areas compatible with cystic degeneration. Endoscopic ultrasound identified a multilocular cystic mass but fine-needle aspiration was deferred because of vascular proximity and the decision for upfront resection.

Via a midline laparotomy on 14 October 2024, the encapsulated 4-cm tumour was meticulously dissected from the IVC and uncinate process and excised with a cholecystectomy; pancreatic parenchyma and bile duct were preserved. The postoperative course was uneventful and the patient was discharged on day 7.

Histology showed nests (Zellballen) of uniform polygonal cells in a vascular stroma with focal cystic change. Immunohistochemistry revealed strong, diffuse CD56 and chromogranin-A expression; cytokeratin AE1/AE3, DOG1 and CD117 were absent. Ki-67 index was < 1 %. These findings favoured a **paraganglioma**. Resection margins were clear, and no lymph nodes were identified. At 6-month and 18month surveillance MRI, the patient remains disease-free.

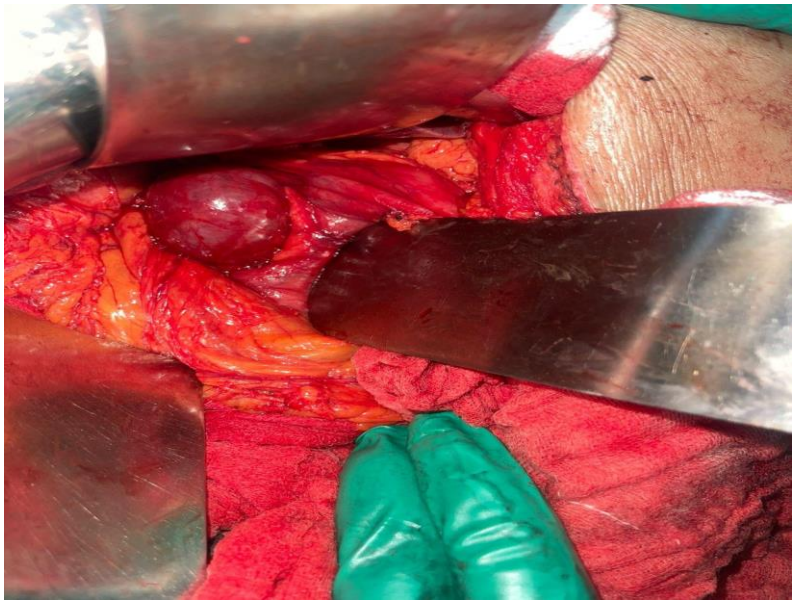

Figure 1: Intraoperative view of the encapsulated, hypervascular paraganglioma in the pancreatic head.

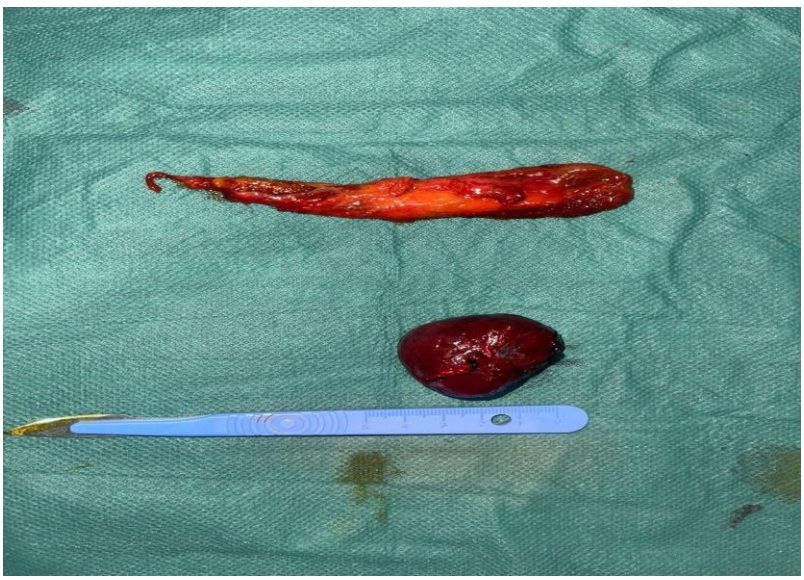

Figure 2: Gross specimen showing the resected paraganglioma alongside the gallbladder.

DISCUSSION

Pancreatic or peri-pancreatic paraganglioma represents an extremely rare pathological entity [1]–[3]. Arising from ectopic neural crest-derived chromaffin cells, these neuroendocrine tumors are much less common than their adrenal counterparts (pheochromocytomas) or paragangliomas located in other classic sites [12]. The scientific literature includes only a very limited

number of cases, often in the form of isolated case reports or small series [1]–[3]. Nevertheless, it appears that these tumors occur preferentially in adults, typically between the fourth and fifth decades, with no clear gender predilection [3],[9], which is consistent with our patient's age (63 years). A major characteristic of pancreatic paragangliomas, found in our case, is their most often non-functional nature [4],[9],[11]. Unlike pheochromocytomas, which are frequently associated with catecholamine hypersecretion leading to the classic triad (headaches, palpitations, sweating) and arterial hypertension, pancreatic paragangliomas are rarely symptomatic from an endocrine perspective [9],[11],[12]. Our patient had recent hypertension, but no other symptoms suggestive of catecholamine excess were reported, and hormonal workup was not performed preoperatively due to the lack of clinical suspicion. The clinical presentation is therefore dominated by non-specific symptoms related to mass effect, such as abdominal pain (chronic epigastralgia in our case), a feeling of heaviness, or a palpable mass, or the discovery is purely incidental during an imaging examination [7],[12]. The absence of jaundice in our patient is also typical, as these tumors rarely invade or significantly compress the main bile duct [6].

The preoperative diagnosis of pancreatic paraganglioma remains a major challenge. Conventional imaging (ultrasound, CT, MRI) typically shows a well-limited, often encapsulated, hypervascular mass, enhancing intensely and early after contrast injection [6],[7],[11]. Cystic changes, calcifications, or areas of necrosis may be present, conferring a heterogeneous appearance, as observed in our patient on CT and MRI, which described a solid-cystic lesion with heterogeneous enhancement of the solid component. However, these radiological characteristics are not specific and can mimic other pancreatic tumors, particularly non-functional pancreatic neuroendocrine tumors (PNETs), which constitute the main differential diagnosis [6],[7],[11]. Other diagnoses such as cystic tumors (serous or mucinous cystadenoma, IPMN), solid pseudopapillary tumors, or even hypervascular metastases or an aneurysm, can also be considered. Endoscopic ultrasound (EUS) can refine the characterization of the lesion and its relationships, showing a hypoechoic, well-limited mass, sometimes cystic, with internal vascularity on Doppler [7]. However, EUS-guided fine-needle aspiration (EUS-FNA) is often disappointing for diagnosing paraganglioma. Samples may be paucicellular, hemorrhagic, or show non-specific cellular atypia, leading to erroneous or inconclusive diagnoses [7],[10]. Furthermore, biopsying a potentially secreting tumor carries a theoretical risk of hypertensive crisis if not anticipated [7]. Functional imaging with MIBG scintigraphy or DOTATATE-PET could be useful in cases of suspected PNET or paraganglioma but was not performed here due to the absence of functional signs and the initial diagnostic uncertainty.

The definitive diagnosis relies on the anatomopathological examination of the surgical resection specimen.

Histologically, paragangliomas exhibit a characteristic nested or lobular architecture (so-called "Zellballen" pattern), composed of polygonal chief cells with granular eosinophilic cytoplasm, surrounded by spindle-shaped sustentacular cells at the periphery of the nests, all within a rich fibrovascular stroma [2],[7]. Immunohistochemistry is crucial to confirm the diagnosis and differentiate it from PNETs. Paragangliomas typically express neuroendocrine markers such as chromogranin A and synaptophysin, as well as CD56; they are classically positive for S100 protein in the peripheral sustentacular cells and negative for keratins [7],[9]. The Ki-67 proliferation index is usually low in benign paragangliomas [7]. This immunohistochemical profile (CD56+, chromogranin A+, CKAE1/AE3-, DOG1-, CD117-, low Ki-67) is entirely consistent with the diagnosis of paraganglioma.

Assessing the malignant potential of paragangliomas remains problematic. No reliable histological or immunohistochemical criteria can formally distinguish benign from malignant forms [5]. Malignancy is defined by the presence of metastases, either in regional lymph nodes or at distant sites (liver, lung, bone) [4]. The reported malignancy rate for extra-adrenal paragangliomas varies from 10 % to over 40 % depending on the series and locations [4],[5]. For pancreatic paragangliomas specifically, the rarity of cases makes estimation difficult, but malignant cases have been described [5]. Factors such as large tumor size, presence of necrosis, high mitotic activity, or vascular invasion might be associated with increased risk, but their predictive value is limited. The absence of metastases at the initial exploration and the deemed complete excision are good prognostic factors for our patient, but long-term surveillance remains necessary [4],[8].

The treatment of choice for pancreatic paragangliomas, whether functional or not, is complete surgical resection [8],[2]. The goal is to achieve clear resection margins (R0), which maximizes the chances of cure and minimizes the risk of local recurrence or metastases [8]. The extent of pancreatic resection depends on the tumor's location and size. For tumors in the pancreatic head, like in our case, a pancreaticoduodenectomy (Whipple procedure) is often necessary, although local excisions or enucleations have been described for well-encapsulated tumors without close contact with the Wirsung duct or bile duct [2]. In our case, excision of the inter-duodeno-pancreato-caval mass was performed, combined with cholecystectomy for gallstones. The lack of need for a Whipple procedure suggests a rather peri-pancreatic location or a cautious excision considering the suspected benign nature. R0 resection was confirmed by pathology. In cases of proven or suspected functional tumors, preoperative medical preparation with alpha-blockers (and possibly beta-blockers) is essential to prevent an intra-operative hypertensive crisis during tumor manipulation [7],[11]. For malignant metastatic or unresectable forms, therapeutic options are limited and may include systemic chemotherapy, metabolic radiotherapy (iodine-131 MIBG), or targeted therapies, but their effectiveness is variable [7],[11].

The prognosis for pancreatic paragangliomas after complete resection is generally good for benign forms. However, due to the unpredictable malignant potential and the risk of late recurrence or metastases, prolonged clinical and radiological surveillance is recommended for all patients [2],[4],[8],[12]. The frequency and modalities of this surveillance are not standardized due to the rarity

of the disease but might include clinical examination, plasma or urinary metanephrine levels (even if the initial tumor was non-functional, recurrence can become functional), and annual abdominal imaging (CT or MRI) for several years, then spaced out.

CONCLUSION

Pancreatic paraganglioma is an exceptionally rare neuroendocrine tumor, posing significant diagnostic challenges preoperatively due to its often non-specific clinical presentation and imaging features that can mimic other lesions, particularly pancreatic neuroendocrine tumors. The presented case perfectly illustrates these difficulties, with a long history of non-specific symptoms, multiple imaging examinations, and an inconclusive EUS with FNA, ultimately leading to an indication for surgical exploration for diagnostic and therapeutic purposes. The diagnosis was only confirmed after anatomopathological and immunohistochemical analysis of the resection specimen. Although complete surgical excision is the standard treatment and offers a good prognosis for benign forms, the inability to formally predict malignant potential based solely on histological criteria necessitates prolonged clinical and radiological surveillance.

PROVENANCE AND PEER REVIEW

Not commissioned, externally peer reviewed.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONFLICTS INTERESTS

Authors have declared that no competing interests exist.

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None

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