Case Report

A Diagnostic Dilemma of Hormone-Secreting Paraganglioma Presenting as Secondary Diabetes

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Abstract

Paragangliomas are rare neuroendocrine neoplasms that arise from chromaffin cells. They most commonly arise in adrenal medulla and are called as pheochromocytoma. About 10% of paragangliomas arise at extra-adrenal sites. Of the functioning extra-adrenal paragangliomas, majority present with intermittent hypertensive attacks. Very rarely, paragangliomas secreting other hormones including adrenocorticotropic hormone, endorphins, pancreatic polypeptide, androgens, and insulin have been reported. Patients should be evaluated with imaging studies along with appropriate hormonal assays keeping in mind the variety of hormones paragangliomas may secrete in turn leading to diagnostic dilemmas. This case report describes a patient with uncontrolled high blood glucose levels and an abdominal mass initially suspected for a glucagonoma which was later discovered to be a functioning retroperitoneal paraganglioma.

Keywords: *Catecholamines, paraganglioma, retroperitoneal mass, secondary diabetes*

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Introduction

Paragangliomas are neoplasms of neuroendocrine cells. Paragangliomas which arise in adrenal medulla are known as pheochromocytomas and account for <0.1% of hypertensive population. Ten percent of paragangliomas are extra-adrenal with an incidence of 2–8/million.[1,2] Of these, a majority are nonfunctioning. Functioning paragangliomas are rare lesions which present most commonly with hypertension and account for 0.05%–0.2% of hypertensive population.[3] These tumors constitute surgically correctable forms of hypertension. Exceptionally, paragangliomas may present a diagnostic dilemma presenting with hyperglycemia.

Case Report

A 34-year-old female presented with pain abdomen for 6 months. There is no past or family history of diabetes. At admission, the patient's blood pressure was 120/60 mmHg. On examination, a firm, tender, ill-defined, nonmobile mass was palpable in the umbilical region. Investigations revealed a fasting blood glucose of 206 mg/dl, postprandial blood glucose of 370 mg/dl, and a glycated hemoglobin of 12%. Urine glucose was 2% with the presence of ketone bodies.

Computed tomography (CT) abdomen [Figure 1] revealed two well-defined, oval-shaped masses measuring 48 mm × 41 mm and 30 mm × 32 mm, interconnected with each other, inferior to the head of pancreas. The lesion was compressing and displacing the second part of the duodenum, abutting the uncinate process of the pancreas and right proximal ureter. Clinically, differential diagnosis of paraganglioma, glucagonoma, and gastrointestinal stromal tumor (GIST) was made.

Intraoperatively, a highly vascular capsulated mass was noted at the root of the mesocolon abutting the pancreas and second part of duodenum. The mass was excised completely [Figures 2 and 3]; imprint smears were taken and were sent for histopathological examination. Postoperatively, blood sugar levels

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returned to normal limits within 2 days and remained so even at discharge.

Imprint cytology [Figure 4] revealed moderate cellularity with atypical pleomorphic cells arranged in loose clusters and singly scattered. Individual cells had round-to-oval vesicular nuclei, stippled chromatin, and moderate amount of pale eosinophilic cytoplasm. Few bi-and multinucleate forms were also noted. Background had plenty of red blood cells.

On histopathology, an encapsulated tumor tissue [Figure 5] arranged in Zellballen, trabecular, and organoid pattern separated by delicate fibrovascular septae was noted. Individual cells were round to oval with stippled nuclear chromatin, prominent nucleoli in few, and moderate granular eosinophilic cytoplasm [Figure 6]. Foci of hemorrhage [Figure 7] and calcification were also noted. Reticulin stain showed excellent delineation of nesting pattern [Figure 8]. Further, immunohistochemistry showed diffuse cytoplasmic positivity for chromogranin [Figure 9] and focal positivity for synaptophysin [Figure 10] thus confirming the diagnosis of paraganglioma. The final diagnosis of retroperitoneal hormone-secreting paraganglioma was made.

Discussion

Paragangliomas are neoplasms of paraganglia or chromaffin neuroendocrine cells. Paraganglia are distributed symmetrically near about the autonomic nervous system migrating from neural crest to various sites during embryogenesis.[4]

Paragangliomas may be sympathetic or parasympathetic. Sympathetic paraganglia are commonly found in adrenal medulla (pheochromocytoma), axial regions of the trunk along pre and paravertebral sympathetic

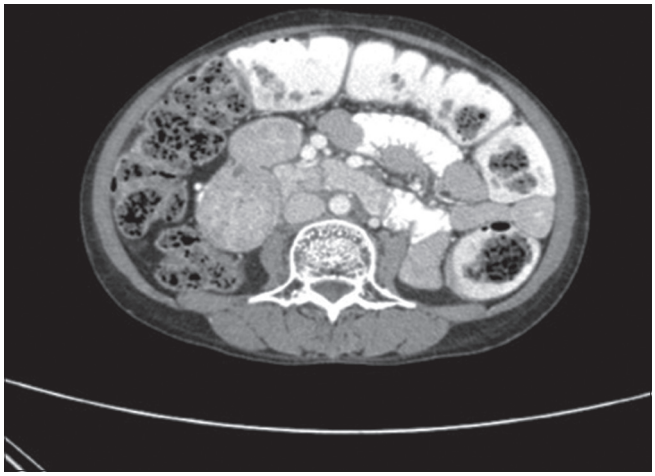

Figure 1: Computed tomography abdomen showing two well-defined, oval-shaped masses measuring 48 mm × 41 mm and 30 mm × 32 mm, interconnected with each other, inferior to the head of pancreas

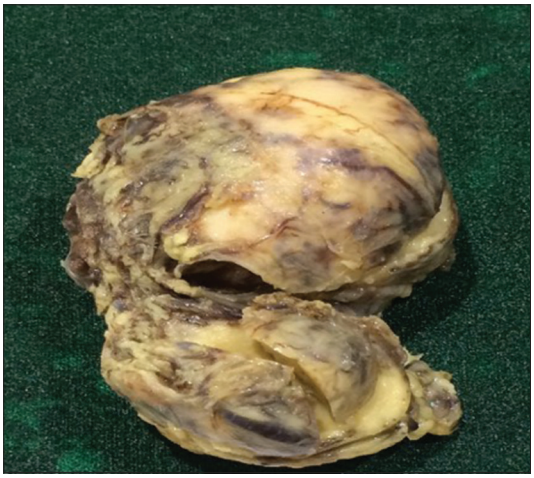

Figure 2: Gross appearance of excised tumor showing two interconnected encapsulated pale yellow masses with prominent blood vessels over the surface

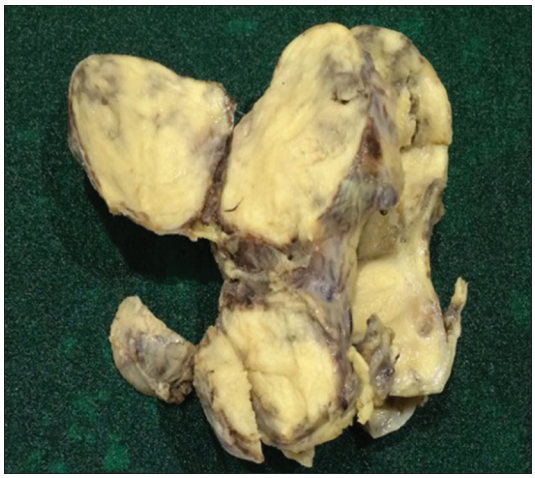

Figure 3: Cut surface of the mass showing homogenous solid pale-yellow appearance with areas of hemorrhage

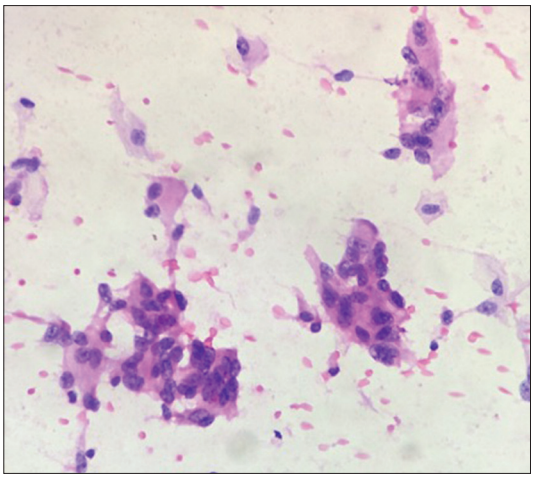

Figure 4: Imprint cytology showing loose clusters of atypical cells with nuclei showing stippled chromatin. Also seen a binucleated cell

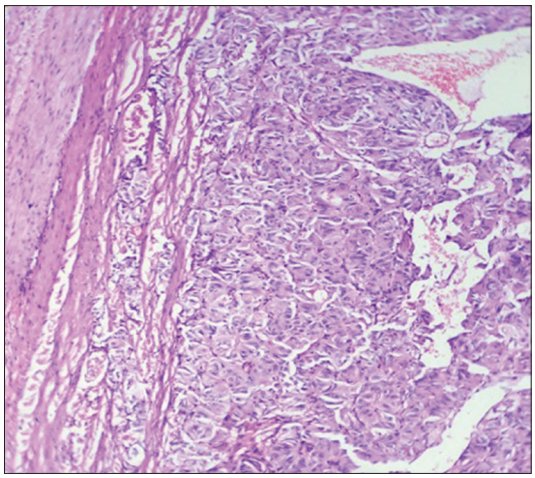

Figure 5: Microphotograph (H and E, ×40), an encapsulated tumor tissue arranged in Zellballen and organoid pattern

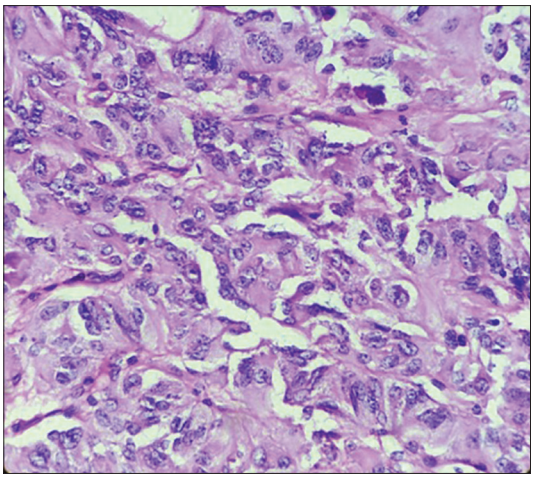

Figure 6: Microphotograph (H and E, ×400). Individual cells are round to oval with stippled nuclear chromatin, prominent nucleoli in few, and moderate granular eosinophilic cytoplasm

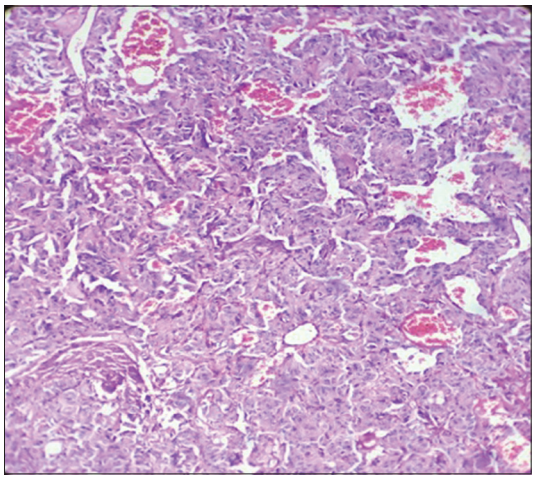

Figure 7: Microphotograph (H and E, ×100). Showing increased number of blood vessels, few are congested

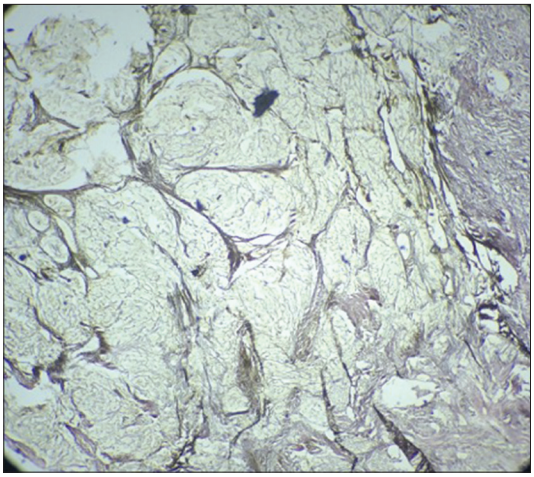

Figure 8: Microphotograph ×100. Reticulin stain showed excellent delineation of nesting pattern

chains, and in connective tissue within/near pelvic organs. Parasympathetic paraganglia are almost exclusively confined to head and neck in the vicinity of major arteries and nerves.[5] Paragangliomas which arise from sites other than adrenals are known as extra-adrenal paragangliomas or extra-adrenal pheochromocytomas (EAP) seen in 10%–20% of patients.[6,7]

Most sympathetic paragangliomas are functional and commonly secrete catecholamines – epinephrine, norepinephrine, and dopamine. Pheochromocytomas account for 85%–90% of functioning paragangliomas.[5] About 10%–15% of EAPs are nonfunctional and in 10% hormonal symptoms are not manifested.[8] Frequently, nonfunctioning paragangliomas are an incidental finding, detected as "incidentalomas" on imaging.[3,7]

Clinical presentation is varied and frequently present with triad of headache (72%), sweating (69%), and palpitations (51%) which commonly occur as paroxysms and provides a cornerstone for the diagnosis. Abdominal tumors usually present with pain and mass per abdomen.[7]

In our case, the patient had persistently elevated glucose levels and blood sugar returned to normal within 2 days of surgery and remained so without any medication. Disappearance of hyperglycemia after resection is suggestive hormone-secreting EAP. To the best of our knowledge, this is only the second case of an EAP presenting with hyperglycemia which resolved after surgical resection of the tumor, a rare condition with little documentation. A probable explanation for the hyperglycemia would be the action of catecholamines which are known to increase blood glucose levels.[3]

Other hormones that may be secreted by functioning EAPs include adrenocorticotropic hormone, endorphins,

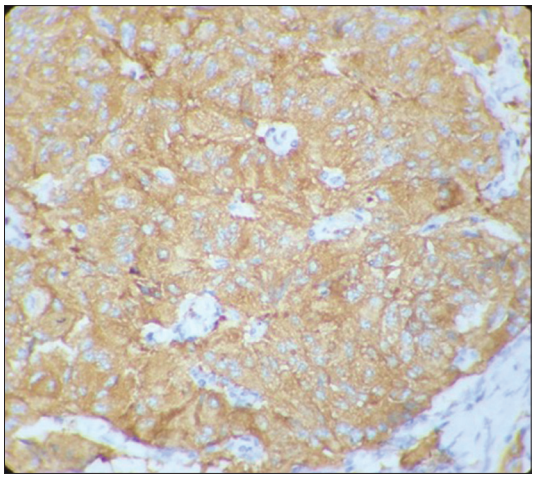

Figure 9: Microphotograph ×400 immunohistochemistry showing diffuse cytoplasmic positivity for chromogranin

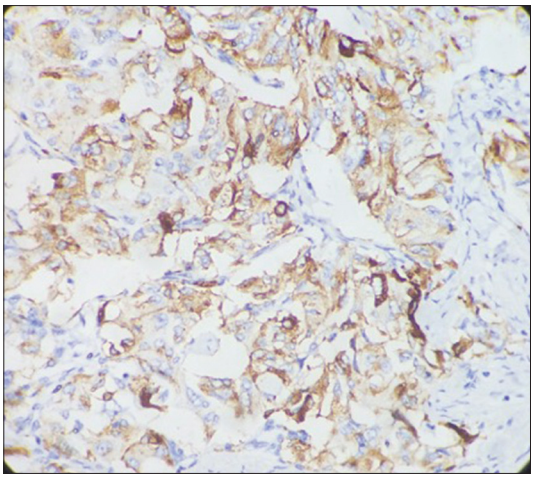

Figure 10: Microphotograph ×400 magnification immunohistochemistry showing focal positivity for synaptophysin

pancreatic polypeptide, and androgens. Rarely, patients may present with hypoglycemia due to insulin-secreting EAPs.[9]

Among primary imaging modalities, CT is the imaging investigation of choice for retroperitoneal lesions and is important for tumor evaluation and staging with 90% sensitivity.[10]

Grossly, paragangliomas present as encapsulated solid, rubbery, firm tumors and vary in size from few millimeters to 22 cm. Cut section is pale yellow to tan, and foci of hemorrhage, fibrosis, or cystic degeneration may be seen.[4,6]

Intraoperative imprint cytology for EAPs is valuable for preliminary diagnosis of paragangliomas. A wide range of cytomorphological features can be seen which include round to oval, plasmacytoid, or spindle-shaped tumor cells with varying degrees of anisokaryosis. Bi-and multinucleation, naked nuclei, nuclear grooves, inclusions, membrane irregularity, budding, nucleoli may be seen. "Salt and pepper" chromatin pattern due to vesicular nuclei with fine chromatin is typical.[1,2]

Pheochromocytomas and paragangliomas are similar on histopathological examination. Neoplastic chief cells show finely granular cytoplasm arranged in characteristic "Zellballen" pattern of surrounded by sustentacular cells and fibrovascular septae.[6]

On immunohistochemistry, chief cells express neuroendocrine markers chromogranin, synaptophysin, and neuron-specific enolase. Sustentacular cells express S-100 and glial fibrillary acidic protein.[6]

Based on clinical and radiological findings, differential diagnoses include glucagonoma, GIST, pancreatic masses including islet cell tumor, adrenal cortical tumor, carcinoid tumor, renal cell carcinoma, and metastatic adenocarcinoma.[1,4] Histopathology with ancillary techniques can differentiate EAP from other entities and offer a confirmatory diagnosis.

Retroperitoneal functioning paragangliomas are unusual tumors and may rarely present with secondary diabetes. Since paragangliomas are benign in nature, they account to a curable cause of diabetes. Hence, this entity must be kept in mind during the evaluation of retroperitoneal lesions presenting with endocrine abnormalities.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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