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Case report

Pancreatic mixed serous neuroendocrine neoplasm with clear cells leading to diagnosis of von Hippel Lindau disease

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ABSTRACT

Mixed serous neuroendocrine neoplasms are extremely rare tumors that are usually seen in female patients and are often associated with von Hippel Lindau (VHL) disease. We describe the case of a 38-year-old male who presented with complaints of anorexia, weight loss, and abdominal pain. CT abdomen showed a mass in the head of the pancreas, multiple small nodules in the body of pancreas, and bilateral adrenal masses. Fine needle aspiration cytology (FNAC) from the mass showed features of a neuroendocrine tumor, with many of the cells demonstrating abundant clear cytoplasm. Histopathological examination of the pancreaticoduodenectomy specimen showed a mixed serous neuroendocrine neoplasm with two components viz. serous cystadenoma and neuroendocrine tumor (NET) World Health Organization (WHO) grade 2. In addition, he was diagnosed to have bilateral pheochromocytomas and a paraganglioma. The synchronicity of these tumors suggested the possibility of VHL disease. Thus, identification of a NET with clear cells or of a mixed serous neuroendocrine neoplasm should raise suspicion of VHL disease. In a mixed tumor, FNAC may identify only one of the two components. Thorough processing of all pancreatic serous tumors for pathological examination is recommended, as NET may occur as a small nodule within the serous cystadenoma.

1. Introduction

Neuroendocrine tumors (NETs) of the pancreas are rare and represent 1–2% of pancreatic neoplasms [1]. They usually occur in the 4th to 6th decades of life, with mean age at presentation being 50 years [1]. However, those occurring in patients with syndromic associations such as Multiple Endocrine Neoplasia (MEN1) and von Hippel Lindau (VHL) disease occur at a younger age. Although pancreatic NETs can harbour clear cells on occasion, this morphological feature is more frequent in VHL-associated tumors [2]. Pancreatic serous cystadenoma is a benign tumor composed of cystic spaces lined by cuboidal epithelial cells. It is as uncommon as NETs, accounting for 1–2% of all pancreatic tumors, but is seen in up to 90% of patients with VHL syndrome. We report the detailed cytological, histological and ultrastructural features of an unusual pancreatic neoplasm, of which only 16 cases have been reported in the English literature till date [3–15], which led to diagnosis of VHL disease in this patient.

2. Clinical summary

This 38-year-old male patient presented with complaints of anorexia and weight loss for eight months, on investigation of which he was diagnosed to have diabetes mellitus and was started on oral antidiabetic agents. He also complained of abdominal pain in the epigastric region and generalized itching for six months. Two months prior to presentation, he had a single episode of jaundice which was self-limiting, and associated with clay coloured stools. On examination, his vitals were stable; abdomen was soft, and no mass was palpable. Abdominal ultrasound showed a hypoechoeic mass in the head of pancreas. Computed tomography showed an enhancing mass in the head and uncinate process of the pancreas, abutting the second part of the duodenum, with dilatation of the main pancreatic and common bile ducts. Multiple small nodules were seen in the body and tail of pancreas. Bilateral enhancing adrenal masses were also seen. Hormone levels are shown in Table 1. MIBG scan showed increased radiotracer uptake in the

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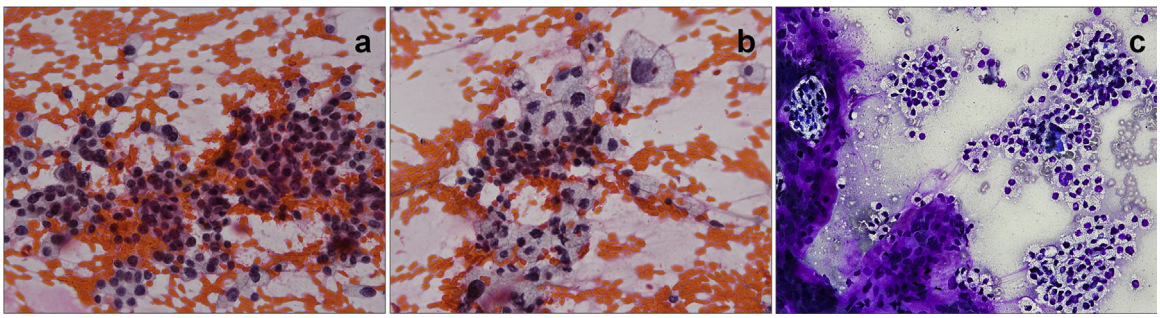

Fig 1. FNAC findings: Aspirate from pancreatic head mass showing cells from a neuroendocrine tumor with uniform round nuclei and salt-and-pepper chromatin (a; PAP, x200). Interspersed cells with abundant clear cytoplasm are seen (b; PAP, x400 and c; MGG, x200).

Table 1
Hormone levels of the patient.

Hormonal Tests	Levels	Normal Range
PTH	40.92 pg/ml	15–65 pg/ml
25 (OH) vit. D	< 4.0 ng/ml	15–80 ng/ml
HbA1c	9.6%	4%–6%
Insulin	3.1 μU/ml	2.6–24.9 μU/ml
PRL	4.93 ng/ml	4.6–21.4 ng/ml
DHEA	313.36 μg/dl	120–520 ug/dl
ACTH	4.67 pg/ml	7–60 pg/ml
Cortisol	26.89 μg/dl	6.2–19.4 μg/dl
Dexamethasone suppression test	4.1 s	
Chromogranin	527.66 ng/ml	<100 ng/ml
Urinary vanillyl mandellic acid	1.3 mg/24 h	0–13 mg/24 h
Plasma metanephrine	1024 pg/ml	<800 pg/ml
Plasma nor-metanephrine	2800 pg/ml	<2000 pg/ml
T4	10.08 mg/dl	5.1–14.1 mg/dl
TSH	2.18 mIU/L	0.27–4.2 mIU/L

adrenal masses, and identified a 1.5 cm right paravertebral lesion as well. DOTANOC scan demonstrated somatostatin expression by the pancreatic tumor. The patient did not have any family history of VHL disease. Fundoscopy and MRI brain were within normal limits. Endoscopic ultrasound (EUS)-guided fine needle aspiration cytology (FNAC) was performed from the pancreatic head mass, following which the patient underwent Whipple pancreaticoduodenectomy, and resection of bilateral adrenal tumors (partial on left side) and paraganglioma. Intraoperative frozen section examination from a nodule in body of pancreas was reported as serous cystadenoma.

3. Pathological findings

Papanicoloau and May-Grünwald-Giemsa stained smears prepared from the EUS-guided FNAC (Fig. 1) were cellular with a clean background. Tumor cells were arranged in clusters as well as singly, had moderate amount of cytoplasm, and uniform round nuclei with salt-and-pepper chromatin. Many of the cells had a plasmacytoid appearance. Interspersed large cells with abundant clear cytoplasm were also identified. The features were consistent with a clear cell NET.

The pancreaticoduodenectomy specimen showed a 5 × 5 × 3 cm tumor in the head of pancreas (Fig. 2). Microscopically, the tumor was composed of nests, cords and sheets of cells with moderate amount of eosinophilic cytoplasm and round nuclei with stippled chromatin (Fig. 3a). At places, the tumor cells had abundant clear cytoplasm (Fig. 3b). Abrupt nuclear pleomorphism was noted. Mitotic count was 3/10 high power fields. Tumor cells were immunopositive for synaptophysin, chromogranin, and CD56 (Fig. 3e-g) while they were negative for insulin, gastrin, somatostatin and glucagon. MIB-1 labelling index was 6% (Fig. 3h). The tumor was infiltrating into the muscularis propria of the duodenum. Immediately adjacent to this tumor, a lesion composed of numerous small cysts was identified (Fig. 3c). The cysts were lined by cuboidal cells with pale eosinophilic cytoplasm and uniform round nuclei with inconspicuous nucleoli. These cells showed granular PAS positivity in the cytoplasm (Fig. 3d) which was diastase-sensitive, and were immunopositive for cytokeratin and inhibin (Fig. 3i,j) but did not show positivity with neuroendocrine markers. Nuclear atypia and mitoses were absent. MIB-1 labelling index was less than 1%. Based on the above features, a diagnosis of pancreatic mixed serous neuroendocrine neoplasm: serous cystadenoma and NET World Health Organization (WHO) grade 2 was made. The former component accounted for approximately 60% of the tumor and the latter for 40%. Ultrastructural examination (Fig. 3k,l) showed dense-core neurosecretory granules in the cytoplasm of the NET cells, along with abundant glycogen and some intermediate filaments. Resected peripancreatic lymph nodes did not show metastases. However, one of them showed necrotizing granulomatous inflammation along with acid fast bacilli, consistent with tuberculosis. Bilateral pheochromocytomas and paravertebral paraganglioma showed typical histology. Postoperative period was uneventful. The patient was given anti-tubercular treatment for nine months and was doing well. However, one month later, he developed acute adrenal crisis and expired.

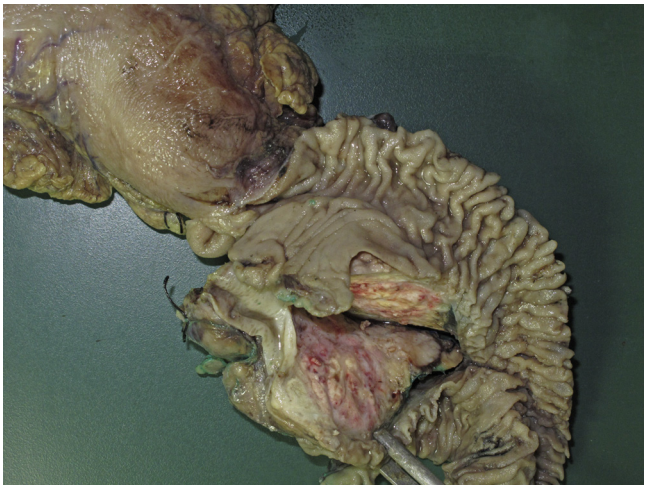

Fig. 2. Gross pathology: Pancreaticoduodenectomy specimen shows a mass in head of pancreas.

4. Discussion

VHL disease is an autosomal dominantly inherited genetic disorder with an incidence of 1:36,000 live births, and is characterized by presence of visceral cysts and markedly vascularised neoplasms in various organs, of which hemangioblastoma is the most com-

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