

Pancreatic neuroendocrine tumor and renal cell carcinoma in a patient: Von Hippel-Lindau Disease

Pankreatik nöroendokrin tümör ve böbreğin şeffaf hücreli karsinomu: Von Hippel-Lindau Hastalığı

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Von Hippel-Lindau disease is an autosomal dominant multisystemic cancer syndrome due to a mutation of the Von Hippel-Lindau disease tumor suppressor gene on chromosome 3. The major lesions in Von Hippel-Lindau disease include hemangioblastomas in the central nervous system and retina, clear cell renal cell carcinomas, pheochromocytomas, pancreatic tumors, epididymal cystadenomas, endolymphatic sac tumors, carcinoid tumors, and multiple cysts of the kidney, pancreas and epididymis. Most patients have pancreatic involvement in Von Hippel-Lindau disease. Pancreatic disease of Von Hippel-Lindau disease includes benign cysts, microcystic adenomas, pancreatic neuroendocrine tumors, and pancreatic metastases of renal cell carcinoma. Pancreatic neuroendocrine tumors should be differentiated from other hypervascular tumors and especially with clear cell morphology, such as renal cell carcinoma and microcystic adenomas. Herein, we report a patient with the diagnosis of Von Hippel-Lindau disease who had malignant neuroendocrine tumor of the pancreas and renal adenocarcinoma.

Key words: Von Hippel-Lindau disease, pancreatic involvement, renal cell carcinoma

INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominant multisystemic cancer syndrome due to a mutation of the VHL tumor suppressor gene on chromosome 3, region p25-26, with an incidence of 1/36,000 in newborns (1). The major lesions in VHL disease include hemangioblastomas in the central nervous system and retina, clear cell renal cell carcinomas, pheochromocytomas, pancreatic tumors, epididymal cystadenomas, endolymphatic sac tumors, carcinoid tumors, and multiple cysts of the kidney, pancreas and epididymis (2). Metastases from renal cell carcinoma and neurological complications from cerebellar hemangioblastomas are the most common causes of death from VHL syndrome (1).

Pancreatic disease of VHL includes benign cysts, microcystic adenomas, pancreatic neuroendocrine tumors (NETs), and pancreatic metastases of renal cell carcinoma. Benign cysts and microcystic adenomas are the

Von Hippel Lindau hastalığı 3. kromozomdaki Von Hippel Lindau tümör supresör genindeki bir mutasyona bağlı olarak otozomal dominant (kalıtım –geçiş gösteren) multisistemik bir kanser sendromudur. Von Hippel Lindau hastalığında major lezyonlar santral sinir sisteminde ve retinadaki hemanjioblastomlar, böbreğin şeffaf hücreli (clear cell) karsinomu, feokromasitoma, pankreas tümörleri, epididimal kist adenomlar, endolenfatik kese tümörleri, karsinoid tümörler ve böbreğin, pankreasın, epididimisin kist adenomlarıdır. Von Hippel Lindau hastalarının bir çoğunda basit kistler, mikrokistik adenomlar, pankreatik nöroendokrin tümörler ve böbrek karsinomunun pankreas metastazları olmak üzere değişik pankreatik lezyonlar görülebilmektedir. Pankreatik nöroendokrin tümörlerin hipervasküler tümörler ve özellikle de böbreğin şeffaf hücreli karsinomu ve mikrokistik adenomlar gibi şeffaf hücreli tümörlerden ayırıcı tanısı yapılmalıdır. Burada pankreas nöroendokrin tümörü ile böbreğin şeffaf hücreli karsinomu olan bir Von Hippel Lindau hastalığı olgusu sunulmaktadır.

Anahtar kelimeler: Von Hippel Lindau Hastalığı, pankreas, böbreğin şeffaf hücreli karsinomu

most common lesions in pancreatic disease of VHL (3). The prevalence of pancreatic NET in VHL was reported as 10% to 17% in different series. It usually is multiple, asymptomatic and nonfunctional.

Herein, we report a patient with the diagnosis of VHL with malignant NET of the pancreas and renal adenocarcinoma.

CASE REPORT

A 28-year-old man was admitted to the hospital due to abdominal pain in the left lower quadrant. The pain had been present for 4 months and was periodic in nature, lasting for about half an hour and resolving spontaneously. He had been followed-up by the department of medical oncology as an outpatient with the diagnosis of malignant NET of the pancreas and renal adenocarcino-

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ma. His medical history revealed that he underwent Whipple operation because of malignant NET of the pancreas six years ago and partial right nephrectomy due to renal adenocarcinoma three years ago. Whipple operation was performed because of a 4 cm diameter mass with solid and cystic components in the head of the pancreas. The histopathologic examination of the specimen showed cells with clear cytoplasm and uniform nuclei without prominent atypia, which were organized as ribbons, cords or mostly trabeculae (Figure 1). The mitotic index and Ki-67 index were 11% and 25%, respectively. The tumor cells had positive staining with synaptophysin but were negative for chromogranin-A, vimentin and monoclonal carcinoembryonic antigen (Figure 2). Direct tumor invasion in peripancreatic lymph nodes and peri-

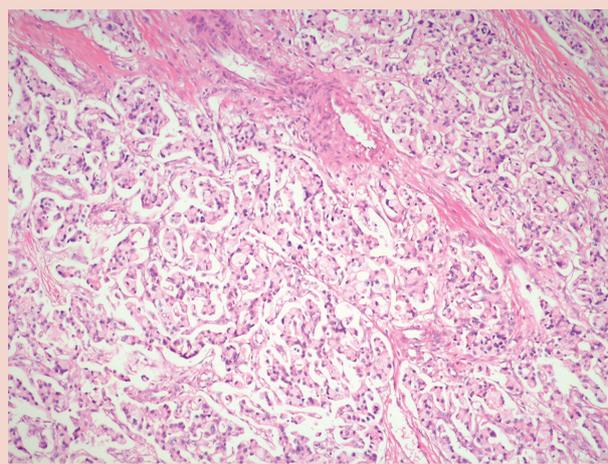


Figure 1. Histologic section from the pancreatic mass showing cells with clear cytoplasm and uniform nuclei without prominent atypia, and which were organized as ribbons, cords or trabeculae (Hematoxylin-eosin, x100).

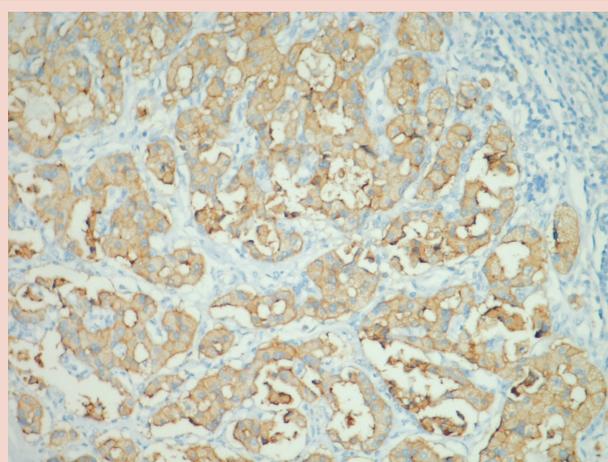


Figure 2. Immunohistochemical synaptophysin positivity (Hematoxylin-eosin, x100).

neural and vascular invasion within the tumor mass were noted (Figures 3, 4). He became diabetic after pancreatectomy. He had glaucoma and his left eye was enucleated as a result. Physical examination revealed incision scars on his abdomen and no abdominal tenderness or rebound. He had a prosthetic left eye. There was no other specific feature on physical examination. Laboratory parameters including hemogram, erythrocyte sedimentation rate and biochemical analysis were within normal limits. There was no pathologic finding on abdomen ultrasonography, upper gastrointestinal system endoscopy, small intestine passage imaging, abdominopelvic spiral computerized tomography (CT), and endosonographic examination except for a fibrous mass under the incision region. There was no new tumoral mass or metastatic lesion. Ophthalmology consultation was performed given the presence of glaucoma and diabetes mellitus. Ophthalmologic examination showed retinal angiomas lesions. In addition, cranial magnetic resonance imaging (MRI) detected a hemangioblastic lesion on the left side of the bulbus, although cranial CT was normal. Those lesions were confirmed with cranial angio CT. The patient was considered as type 1 VHL disease with the components of malignant pancreas NET, renal adenocarcinoma, and hemangiomas of the retina and central nervous system. He has been followed as an outpatient by the departments of medical oncology, neurology and neurosurgery for two months and is currently well.

DISCUSSION

Von Hippel-Lindau (VHL) disease is characterized by the presence of benign and malignant tumors and is associated with germ line mutation of the VHL gene of chromosome 3 (4). The diagnosis of VHL may be made in a patient with a family history of VHL based on a single retinal or cerebellar hemangioblastoma, renal cell carcinoma or pheochromocytoma, and possibly, multiple pancreatic cysts. In the absence of a family history of VHL, the presence of two or more retinal or cerebellar hemangioblastomas or of one hemangioblastoma with one visceral tumor is required for diagnosis (5). VHL disease is classified according to the presence of pheochromocytoma; VHL disease without and with pheochromocytoma is classified as type 1 or type 2, respectively (2). The present case was considered as type 1 VHL disease, and we could not perform genetic analysis.

Pancreatic involvement in VHL disease was reported as being between 17% to 77% in various imaging series (3,6,7,8). Different pancreatic lesions such as benign cysts, cystadenomas, adenocarcinomas, hemangioblas-

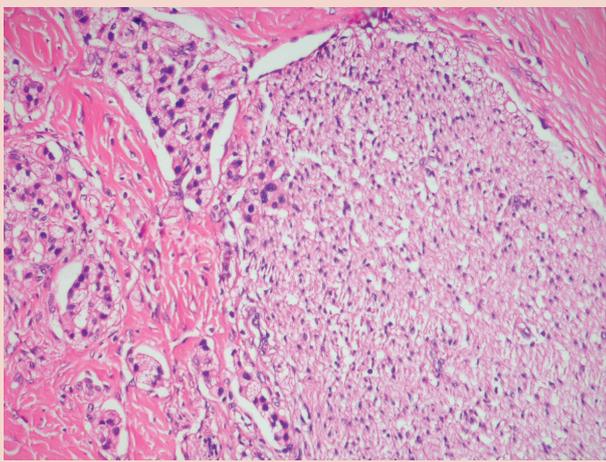


Figure 3. Perineural invasion in the pancreatic tumor (DAB, x400).

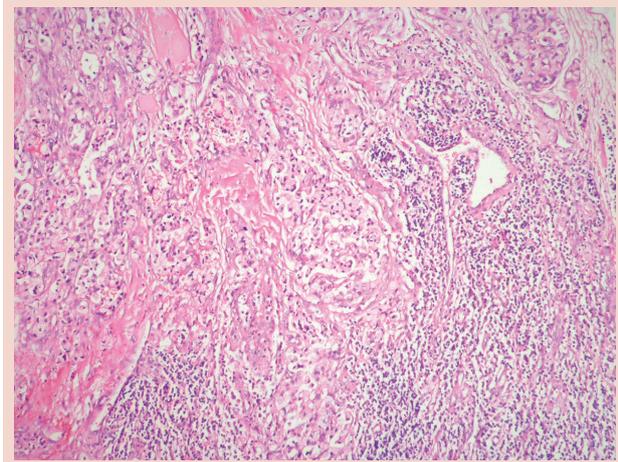


Figure 4. Direct invasion of the pancreatic tumor to the peripancreatic lymph nodes (Hematoxylin-eosin, x200).

tomas, NET, and metastasis of renal cell carcinoma have been reported. Pancreatic cysts are the most common lesion in the pancreatic involvement of VHL disease and are usually multiple, and almost 40% of them had calcification (6,9,10). Multiple pancreatic cysts should call to mind VHL disease as well as polycystic renal disease.

The prevalence of pancreatic NET has been reported as between 10% to 17% in different series (3,8). Pancreatic NET in VHL disease is usually nonfunctional (11). Pancreatic NET in VHL disease should be differentiated from other hypervascular tumors such as hemangioblastomas, vascularized microcystic (serous) adenomas and metastasis of renal cell carcinoma. Pancreatic hemangioblastomas can be seen rarely in VHL disease and immunohistochemistry analysis is also helpful in the differential diagnosis (12). Microcystic adenomas and renal cell carcinoma metastasis are the most common lesions that should be remembered in the differential diagnosis of pancreatic NET (3). Renal cell carcinoma is one of the most common tumors in VHL disease and can metastasize to the pancreas (13,14). Clear cell morphology is known as a distinguishing pathological feature of pancreatic NET

(8,14,15). Similarly, microcystic adenoma and metastatic renal cell carcinoma may have clear cell morphology. Histopathological and immunohistochemical features are the main factors for differentiating those tumors (11). Clear cell renal carcinomas usually have thin fibrovascular septae, and pancreatic microcystic adenomas are usually glycogen-rich; both of them show negative immunostaining for neuroendocrine markers (11). On the other hand, pancreatic NETs have broad collagen bands and are not glycogen-rich and show positive immunostaining for neuroendocrine markers. In the present case, pathologic examination of the pancreatic lesion showed clear cell tumor cells that were organized as ribbons, cords or mostly trabeculae with collagen bands, and tumor cells showed positive staining with synaptophysin.

In conclusion, most patients with VHL disease have pancreatic involvement. Pancreatic NETs in VHL disease are usually multiple and have malignancy potential. They should be differentiated from other vascular tumors and especially from metastasis of renal cell carcinoma since the therapeutic decision and management are not easy.

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