CASE REPORT / OLGU SUNUMU

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Renal Metastasis from a Primary Hepatic Neuroendocrine Tumor: A Case Report and Literature Review

Primer Karaciğer Nöroendokrin Tümörünün Böbrek Metastazı: Nadir Olgu ve Literatür Taraması

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Abstract

Neuroendocrine tumors (NET) are a diverse collection of neoplasms with varying biological characteristics, histologic patterns, and therapeutic responses. We present a rare case of a 41-year-old female who was diagnosed with a primary NET of the liver and had multiple kidney and bone metastases. Primary hepatic NETs are rare, and metastasis to the kidney makes this case one of the few in the literature. The patient was admitted to the hospital because of pain in the lower extremities. Several imaging examinations revealed multiple lesions in the bone, kidney, and liver. Sandostatin and Denosumab treatments are started against the tumor and bone metastases. At first, the team thought the case was a NET of the liver and synchronous renal cell carcinoma. However, after the total excision of the kidney, pathology was reported as the NET metastasis to the kidney. Despite showing regression in bone metastases, the lesion in the the liver has advanced. ^{177}Lu-DOTATATE treatment was added to the current treatment regimen. Renal metastasis from a primary hepatic NET can be challenging to diagnose and treat. Since there are no guidelines specifically designed for this type of case, multiple treatment modalities must be discussed with a multidisciplinary team to choose the best option for patients.

Keywords: Neuroendocrine tumor, primary hepatic neuroendocrine tumor, renal metastasis, sandostatin

Öz

Nöroendokrin tümörler (NET), değişen biyolojik özelliklere, histolojik yapılara ve terapötik yanıtlara sahip çok çeşitli neoplazmalar koleksiyonudur. Bu makalede karaciğerde primer NET tanısı alan, çok sayıda böbrek ve kemik metastazı bulunan 41 yaşında kadın hastayı sunuyoruz. Primer hepatik NET'ler nadirdir ve böbreğe metastaz olması durumu daha da nadir hale getirir. Hasta alt ekstremite ağrısı nedeniyle hastaneye başvurdu. Çeşitli görüntülemelerde kemik, böbrek ve karaciğerde çok sayıda lezyon ortaya çıktı. Tümör ve kemik metastazlarına karşı Sandostatin ve Denosumab tedavilerine başlandı. Ekip ilk başta vakanın karaciğerde nöroendokrin bir tümör ve senkron renal hücreli karsinom olduğunu düşündü. Ancak böbreğin total eksizyonu sonrasında patoloji, NET'in böbreğe metastazı olarak rapor edildi. Kemik metastazlarında gerileme görülmesine rağmen karaciğerdeki primer lezyonu ilerledi. Mevcut tedavi rejimine ^{177}Lu-DOTATATE tedavisi eklendi. Primer hepatik NET'ten kaynaklanan renal metastazın teşhis ve tedavisi zor olabilir. Bu tip vakalar için özel olarak tasarlanmış bir kılavuz bulunmadığından, hastalar için en iyi seçeneğin seçilebilmesi için birden fazla tedavi yönteminin multidisipliner bir ekiple tartışılması gerekir.

Anahtar Kelimeler: Nöroendokrin tümör, primer karaciğer nöroendokrin tümörü, böbrek metastazı, sandostatin

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Introduction

Neuroendocrine tumors (NETs) are a diverse collection of neoplasms with varying biological characteristics, histologic patterns, and therapeutic responses. NETs are commonly seen in the gastrointestinal system, especially in the small intestine and pancreas. Primary hepatic NETs (PHNETs) are exceedingly rare tumors that cause challenges in diagnosis (1). Kidney metastases are exceedingly rare in NET, especially if the primary site is the liver (2). Here, we present a rare case of a 41-year-old female who was diagnosed with a primary NET of the liver and had multiple kidney and bone metastases.

Case Presentation

The patient was admitted to the orthopedics department because of pain in the lower extremities. Magnetic resonance imaging (MRI) showed a 63 mm heterogenous lesion in the lower segment of the right kidney, a 24x36 mm heterogenous lesion with cystic structures was found in the left proximal femur, and a 42x76 mm similar lesion was detected in the right proximal femur (Figure 1H). Abdominal MRI with intravenous (IV) contrast showed multiple lesions in different segments of the liver, with the largest one being a 35 mm well-circumscribed hypervascular lesion in segment VIII (Figure 1D). In addition, the MRI revealed a semisolid lesion in the posterior part of the right kidney containing cystic structures with several retroperitoneal enlarged lymph nodes, which resembled renal cell carcinoma (Figure 1F).

Furthermore, fluorodeoxyglucose (FDG) positron emission tomography (PET) showed a 50x30 mm lesion with pathological FDG absorption in the proximal part of the right femur, liver, kidney and multiple lytic lesions in C7, TH5, TH11, and S1 vertebras (Figure 1A-C, E, G). Tru-cut biopsy was done for the lesions in the liver, and the results were consistent with a grade 1 NET. In the liver tru-cut biopsy sample, a neoplasm consisting of monotonous epithelial cells separated from the liver parenchyma with smooth borders is observed. Neoplastic cells, forming an organoid pattern, have oval or round nuclei with no visible nucleoli and eosinophilic granular cytoplasm (Figure 2). No mitotic figure is seen. No necrosis is observed. Immunohistochemical staining was done and demonstrated CK8/18 and Synaptophysin positive, PAX8, and GATA3 negative neoplastic cells (Figure 2). The proliferative index of the tissue provided by Ki-67 labeling was less than 2% (Figure 2). Furthermore, GA-68 DOTA PET was done to determine the possibility of Sandostatin treatment. GA-68 DOTA PET results showed high-level somatostatin receptor expression in lesions at the liver, vertebras, and femur (Figure 1). Denosumab 120 mg once in 4 weeks for bone metastases and Sandostatin 30 mg once in 4 weeks treatments were started. Palliative radiotherapy was done for the lesions on the proximal femur. After several

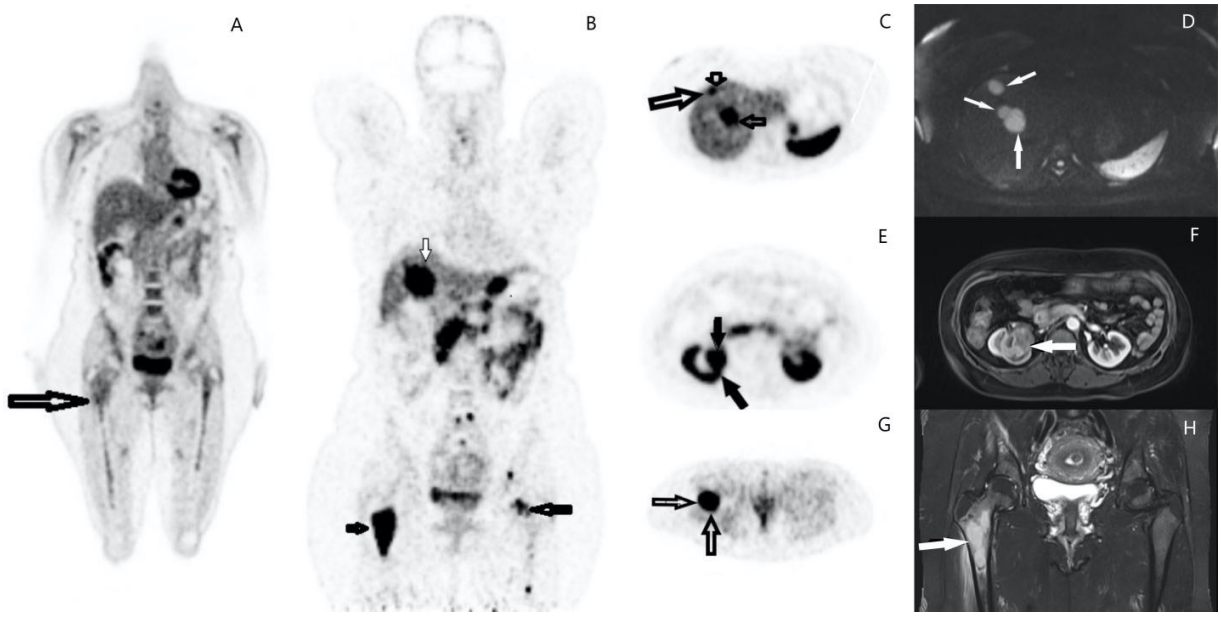

Figure 1: Tumoral masses in the liver, right renal cystic metastasis, and most of the bone metastasis are negative in FDG PET (A) and positive in ^{68}GA-DOTATATE PET (B). 2 Liver lesions in VIII segment showing intense ^{68}GA-DOTATATE uptake in axial Ga DOTATATE PET MIP image (C) and strongly restricted diffusion in diffusion-weighted axial MRI (D). Contrast-enhanced axial T1A FS MRI (F) images and axial MIP DOTA PET images (E) demonstrate a right renal cystic metastatic lesion with a great avidity for ^{68}GA-DOTATATE. The largest bone metastasis is located in the right femoral neck, causing surrounding soft tissue edema and cortical thinning; coronal T2A FS MRI (H). Intramedullary tumor showing metabolic activity both in FDG-PET/CT (A) and ^{68}Ga-DOTATATE PET/CT (B, G)

PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, MIP: Maximum intensity projection, FDG: Fluorodeoxyglucose

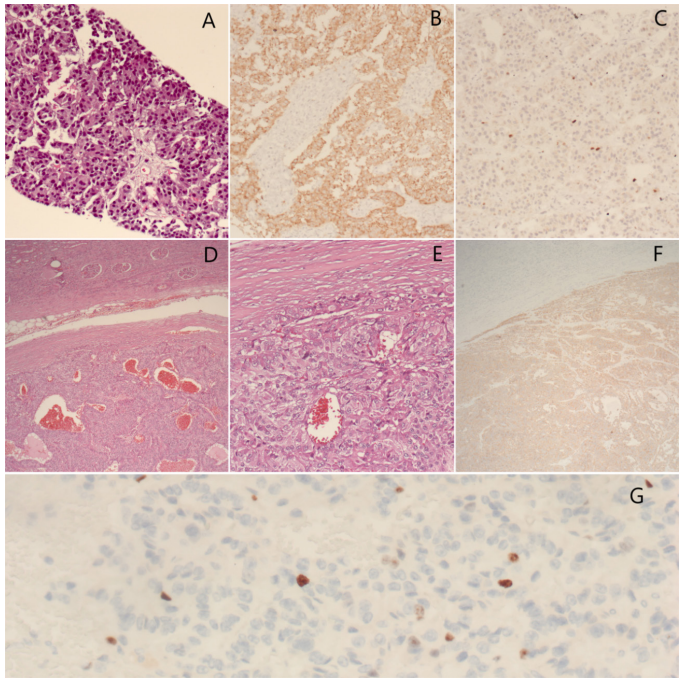

Figure 2: A) Tru-cut biopsy specimen, liver, hematoxylin eosin stain. B) Tru-cut biopsy specimen, liver, synaptophysin stain. C) Tru-cut biopsy specimen, liver, Ki-67 stain. D) Nephrectomy material, right kidney neuroendocrine tumor, hematoxylin-eosin stain 4x. E) Nephrectomy material, right kidney, neuroendocrine tumor hematoxylin-eosin stain 20x. F) Nephrectomy material, right kidney, neuroendocrine tumor synaptophysin stain. G) Nephrectomy material, right kidney, neuroendocrine tumor Ki-67 stain

months, laparoscopic right radical nephrectomy surgery was done with suspicion of renal cell carcinoma. Pathology reported a single Grade 1 NET. In the nephrectomy material, an intrarenal solid tumor with a diameter of 65 mm was observed in the lower pole. A neoplasm consisting of monotonous epithelial cells forming an organoid pattern, separated from the renal parenchyma by smooth borders, was observed (Figure 2). Neoplastic cells had oval or round nuclei with no visible nucleoli and large eosinophilic granular cytoplasm without necrosis (Figure 2). The mitotic index is counted as 0-1/10 HPF. Immunohistochemical staining was done and demonstrated CK8/18 and Synaptophysin positive, PAX8, and GATA3 negative neoplastic cells (Figure 2). The proliferative index of the tissue provided by Ki-67 labeling was less than 2%. Follow-up imaging demonstrated a heterogenous response to the treatment, a GA-68 DOTATAE PET/computed tomography (PET/CT) was obtained after seven months and showed an obvious enlargement noted in the high-grade somatostatin receptor-expressing lesions in the VIII segment of the liver (Figure 3A-C). In contrast, MRI showed partial regression in the dimensions, T2A signal intensity, and metabolic activity of right femoral metaphyseal metastasis (Figure 3A, D, E). ^{177}Lutetium-Dotatate treatment was added to the current drugs. The patient currently comes for control visits without any complications.

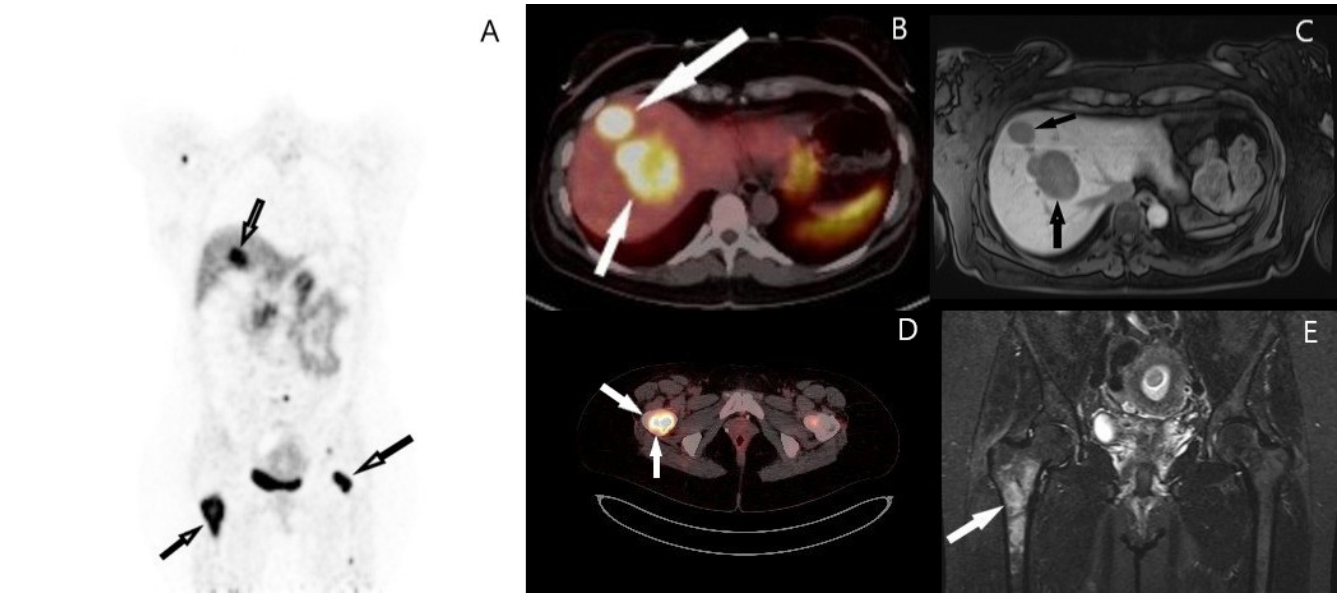

Figure 3: Heterogeneous metabolic response in ^{68}GA-DOTATAE PET/CT obtained 7 months after treatment. Obvious enlargement was noted in the high-grade somatostation receptor expressing lesions in the VIII segment of the liver; Coronary view DOTA PET (A), DOTA PET fused axial image (B), Late liver phase postcontrast T1W axial MRI obtained with hepatospecific contrast agent (C). Partial regression was observed in the dimensions, T2A signal intesivity and metabolic activity of right femoral metaphyseal metastasis; Fused posterior DOTA PET image (D), Coronal T2A FS MRI (E)

PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging

Discussion

PHNET are incredibly uncommon, and not many studies have been done to analyze the features and available treatments. PHNETs generally do not secrete hormones (2). The World Health Organization developed the NET categorization system in 2010, and it is based on pathological findings, including cell morphology, the number of mitotic cells found in ten high-power fields of view, and the Ki-67 index (3). NET tumors of the pancreas and gastrointestinal tract (GEP-NETs) can be divided into three categories based on this classification system: low malignancy (grade 1), moderate malignancy (grade 2), and high malignancy (grade 3). The tumor was grade 1 in our patient according to the classification.

With only around 200 reported PHNET cases globally, the diagnosis and treatment can be challenging.PHNETs can resemble other hepatic tumors radiologically so it is difficult to differentiate them preoperatively. CT with IV contrast and MRI with gadolinium can be helpful in showing tumor enhancement by featuring tumor vascularity (4). Immunostaining is one of the best tools to diagnose PHNETs since more than 70 percent of the tumors are positive for various hormones irrelevant of the functionality status (4). Neuroendocrine markers like hydroxyindoleacetic acid (5-HIAA) and serum chromogranin A can also assist to diagnose NET, but they are usually elevated in extrahepatic carcinoids rather than PHNETs (5). Although there are a few cases reported in the literature that show renal metastasis from rectal, ileal, and bronchial NETs, to our knowledge this is the first case that reports renal and bone metastasis from a PHNET (1,6-9).

Less than 1% of all NETs are found in the genitourinary tract, and the kidney is an incredibly uncommon location, accounting for 5-19% of them. Even less common are metastatic renal NETs from other main organs (1). Even though there is very little data regarding the management of renal metastasis of carcinoids because of their rarity, there are some papers regarding primary renal NET (PRNETs) that can give physicians some opinion. Romero et al. (10) investigated 56 reported cases and found that the median age of the patients with PRNETs was 49. 17.8% of the reported cases were present in horseshoe kidney. Only 12.7% of the cases showed classical neuroendocrine syndromes, and 45.6% of the cases were metastatic at the time of first diagnosis, which may suggest that there are challenges in early diagnoses of PRNETs. They found that significant negative prognostic factors are: age greater than 40 years, tumor size greater than 4 cm, purely solid tumors on the cut surface, mitotic rate higher than 1/10 high power fields, metastasis at initial diagnosis, and tumors extending throughout the renal capsule (10).

Most critically, renal NET need to be distinguished from renal cell carcinoma and from benign renal tumors such as oncocytoma, angiomyolipoma, or malacoplakia. The primary form of treatment for renal carcinoids, like with other carcinoids, is surgical resection (6). In our case, the lesion was thought of as renal cell carcinoma at first until the post-operative pathological report.

Treatment methods for NET are improving day by day. While surgery is counted as the best treatment option for solitary PHNETs, metastatic cases like ours are not the best candidates for resection (4,11). The 5-year survival rate was found 74% in patients who had undergone liver resection for the solid PHNET (4). Somatostatin analogs remain the first-line treatment for functional and non-functional NET because It has been demonstrated that somatostatin possesses all four regulatory roles: endocrine, paracrine, neurocrine, and autocrine (12). In addition, Stueven et al. (13) reported that while initially used in the treatment of carcinoid syndrome to inhibit the release of neuropeptides or bioactive amines, several trials meanwhile revealed an effect of somatostatin analogs on tumor cell proliferation. We used Sandostatin (octreotide) for the initial treatment of the patient.

GA-68 Dotatate PET/CT scan is widely used to detect the feasibility of somatostatin analog treatment in early-stage NET. Lee et al. (14) found that GA-68 DOTATATE PET/CT independently predicted early failure on SSA monotherapy in patients with well-differentiated grade 1-2 GEP-NET. Thus, Routine GA-68 DOTATATE PET/CT has excellent sensitivity for quickly identifying patients who are not expected to benefit from SSA therapy. We also used a GA-68 DOTATATE PET/CT scan before starting Sandostatin treatment.

In addition to Sandostatin, Denosumab treatment was added to the patient's treatment regimen to target the bone metastases. A helpful phase 3 trial done by Lipton et al. (15) reported that in individuals with advanced cancer and bone metastases, denosumab outperformed zoledronic acid in preventing skeletal-related events with favorable safety and convenience.

Novel approaches are emerging for the treatment of NET. ^{177}Lutetium-Dotatate treatment is one of them. ^{177}Lutetium-Dotatate approved by the FDA after the NETTER-1 trial and outcome data from a large European registry. The drug's mechanism is evident in its structure, which consists of a somatostatin analog (octreotide) that binds to only cells that express the somatostatin receptor and a chelated beta-emitting isotope called ^{177}Lu. Due to its potential to promote tumor cytoreduction, which is uncommon compared to other available treatments, and provide sustained disease control, ^{177}Lu-DOTATATE stands out as a unique addition to the treatment arsenal for gastroenteropancreatic NETs (16). We added ^{177}Lu-DOTATATE treatment to the patient's current treatment regimen after the treatment progression of the primary tumor.

There are other promising minimally invasive treatment modalities like trans-arterial chemoembolization, systemic chemotherapy, and local ablation, but none of them showed favorable results in terms of long-term survival (17).

Future research on the demographical, clinicopathological, and survival data with a large sample size of PHNETs would give a valuable understanding for clinicians.

Conclusion

To conclude, PHNETs are sporadic tumors, and metastasis to the kidney makes it even more uncommon. Renal metastasis from a PHNET tumor can be challenging to diagnose and treat. Since there are no guidelines specifically designed for these types of cases, multiple treatment modalities must be discussed with a multidisciplinary team to choose the best option for patients.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: A.A., T.H., N.A., G.A., A.H., E.S., Concept: A.I., A.A., E.S., G.A., Design: A.I., A.A., E.S., A.H., Data Collection and/or Processing: A.I., T.H., N.A., Literature Search: A.I., N.A., T.H., G.A., A.H., Writing: A.A., A.I.

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

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