

Primary hepatic neuroendocrine tumor: Five cases with different preoperative diagnoses

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Neuroendocrine tumors, also known as carcinoid tumors, behave like benign tumors; however, they show the characteristics of carcinoma. While more than 80% of the neuroendocrine tumors found in the liver are metastatic, primary hepatic neuroendocrine tumors are very rare. Five patients with hepatic mass who admitted to our clinic between August 2003 and July 2007 were treated surgically. Ultrasonography, computerized tomography and magnetic resonance imaging were performed in all patients. Endoscopy and colonoscopy were conducted to exclude malignancy of other sites. Hepatectomy was carried out in all patients. Diagnosis was confirmed with immunohistochemical examination. The five patients treated surgically were diagnosed as primary hepatic neuroendocrine tumor histopathologically. Abdominal pain was the most common complaint of all patients. Hepatectomy was conducted in all patients due to tumors originating from the liver lobes. Only one patient (Case 2) underwent transarterial chemoembolization before hepatectomy to reduce tumor bleeding. Owing to tumor recurrence on the left lobe of the liver in Case 2, transarterial chemoembolization was performed four years after hepatectomy. R0 resection was achieved in two patients (Cases 1 and 3). In conclusion, primary hepatic neuroendocrine tumors are very rare and asymptomatic tumors. Thus, high-sensitive laboratory and imaging examinations are required. At present, hepatectomy remains the main treatment for primary hepatic neuroendocrine tumor.

Key words: Carcinoid, primary hepatic neuroendocrine tumor, liver

Primer hepatik nöroendokrin tümör: Ameliyat öncesi farklı tanı 5 olgu

Karsinoid tümör olarak bilinen nöroendokrin tümörler aslında iyi huylu tümör gibi davranan fakat karsinom karakteri gösteren tümörlerdir. Karaciğerde yerleşmiş olan nöroendokrin tümörlerin %80 kadarı metastatik iken karaciğerin primer nöroendokrin tümörleri oldukça nadir görülür. Karaciğerde kitle tanısı ile Ağustos 2003 – Temmuz 2007 tarihleri arasında kliniğimize başvuran 5 hasta cerrahi yöntem ile tedavi edildi. Ultrasonografi, bilgisayarlı tomografi ve manyetik rezonans görüntüleme tüm hastalar için yapıldı. Diğer malign odakları tespit ve ekarte edebilmek için endoskopi ve kolonoskopi planlandı. Tüm hastalara hepatektomi yapıldı. Histopatolojik tanı immünohistokimyasal yöntem ile doğrulandı. Cerrahi yöntem ile tedavi edilen beş hasta histopatolojik olarak hepatik nöroendokrin tümör tanısı aldı. Karın ağrısı en sık gözlenen şikayet idi. Hepatektomi tümörün yerleşim yerine göre yapıldı. Sadece bir hastaya (olgu 2) hepatektomi öncesi tümörün kanlanmasını azaltmak için transarteriyel kemoembolizasyon yapıldı. Aynı hastaya gelişen tümör nüksü nedeniyle hepatektomiden 4 yıl sonra tekrar transarteriyel kemoembolizasyon işlemi uygulandı. R0 rezeksiyona yalnız iki hastada ulaşıldı (olgu 1 ve 3). Primer hepatik nöroendokrin tümörler çok nadir görülen ve asemptomatik seyreden tümörlerdir. Halen daha yüksek duyarlılıkta laboratuvar ve görüntüleme tetkiklerine ihtiyaç duyulmaktadır. Günümüzde hepatektomi primer hepatik nöroendokrin tümör için hala asıl olan tedavi yöntemidir.

Anahtar kelimeler: Karsinoid, primer hepatik nöroendokrin tümör, karaciğer

INTRODUCTION

Neuroendocrine tumors (NETs), also known as carcinoid tumors, behave like benign tumors; however, they show the characteristics of carcinoma. They have been referred to as carcinoid or carcinoma-like tumors in the past. The development of

these tumors occurs as a consequence of the neoplastic proliferation in neuroendocrine cells (enterochromaffin or Kulchitsky cells). Although there has been an increase in the frequency of the tumors in recent years, they are seen in six cases out

of 100,000 people on average. These tumors are seen most frequently (2) in the small intestines (45%) in the gastrointestinal system, and they show frequent incidence of metastasis in the liver. Whereas more than 80% of the NETs found in the liver are metastatic, primary hepatic neuroendocrine tumors (PHNETs) are very rare (1). The first case of PHNET was reported by Edmondson in 1958 (3). While progressing asymptotically in general, pain and palpable mass in PHNET are the most frequent symptoms in symptomatic cases.

In the literature, terms such as carcinoid or NET are still used for these tumors. With the decision taken by the World Health Organization (WHO) in 2000, WHO found it more appropriate to use the term NET for these tumors (6).

This study aims to review PHNET with the clinicopathological features of five patients who were admitted to our clinic with their extraordinary historical examinations and underwent liver resection.

CASE REPORTS

Five patients with the diagnosis of hepatic mass were admitted to our clinic between August 2003 and July 2007. Three of the five patients (Cases 2,

4, 5) were operated initially at other hospitals with the preoperative diagnosis of acute abdomen due to tumor rupture originating from the liver, amoebic abscess and giant hemangioma of the liver; however, two of these three patients (Cases 2 and 5) were sent to our hospital due to intraoperative massive bleeding, and Case 4 applied to our clinic because of no recovery in his clinic in the postoperative period. Case 1 and Case 3 were operated with the preoperative diagnoses of hemangioma and hepatocellular carcinoma. Ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients. Case 1 and Case 3 were evaluated additionally with upper gastrointestinal system endoscopy and total colonoscopy in the preoperative period.

The diagnosis was confirmed by histopathological examination in the five patients, and all were treated surgically. The clinical characteristics of patients are summarized in Table 1. There were 2 females and 3 males, with a mean age of 42 (range 34-50) years. Abdominal pain was the most common complaint in all patients. Serological tumor markers [alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA)19-9] were within normal ranges except in one pati-

Table 1. Clinical characteristics of five patients with PHNET

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex / Age	F/43	M/34	F/50	M/41	M/42
Main complaint	Abdominal pain	Acute abdomen due to tumor rupture	Abdominal pain	Abdominal pain and high fever	Abdominal pain
US findings	Hyperechoic hepatic mass in left lobe	US, not performed	Hyperechoic hepatic mass in right lobe	Solid surfaces with non-smooth center mass, compatible with abscess	Hyperechoic giant hepatic mass in left lobe
CT findings	8x10 cm diameter mass in left lobe	CT, not performed	10x8 cm mass in right lobe segment VI-VII	15x10 cm diameter mass in right lobe	20x11 cm diameter mass in left lobe
MR findings	Hypervascular mass in segment II-III	18x10 cm diameter, hypervascular mass in right lobe	Similar to CT findings, compatible with HCC	Central necrosis and contrast involvement (+)	Similar to CT findings, no main vascular invasion
AFP, CEA, CA19-9	Normal	Normal	Moderate-high AFP level	Normal	Normal
Preoperative diagnosis	Hemangioma	Hemangioma	HCC	Liver abscess or angiosarcoma	Hemangioma
Surgical treatment	Left lateral segmentectomy	Right hepatectomy	Right hepatectomy	Right hepatectomy	Left hepatectomy
Tumor size	10x7x4 cm	18x14x7 cm	9x8 cm	19x12,5x7 cm	20x11x10 cm
Status	Alive	Unknown	Alive	Died of lung and brain metastasis	Died of liver metastasis

F: Female. M: Male. AFP: Alpha fetoprotein. CEA: Carcinoembryonic antigen. CT: Computed tomography. HCC: Hepatocellular carcinoma. MR: Magnetic resonance. US: Ultrasound.

ent (AFP: 11.6 ng/ml, Case 3). Endoscopy and colonoscopy were performed in all patients to search for other sites of the disease. No abnormal findings were observed with endoscope screening. Hepatectomy was carried out in all patients due to tumors originating from the liver lobes. Right hepatectomy was performed on on 2nd case (Figure 2), 3rd case (Figure 3) and 4th case (Figure 4). Case 5 (Figure 5) underwent left hepatectomy and Case 1 (Figure 1) underwent left lateral segmentectomy. Only one patient (Case 2) underwent transarterial chemoembolization (TACE) before hepatectomy in order to reduce tumor bleeding. Diagnosis was confirmed with immunohistochemical examination in all patients. Chromogranin A (CgA) was positive

in all cases. While synaptic membrane protein (SYP) was positive in all patients except Case 1, neuron-specific enolase (NSE) was positive except in Cases 4 and 5 (Table 2). Somatostatin receptor scintigraphy was not performed due to the unavailability of this technique in our center. R0 resection was achieved in two patients (Cases 1 and 3), and they are still alive. Three patients (Cases 2, 4 and 5) received palliative chemotherapy on the grounds of tumor rupture in their first operation. Due to tumor recurrence on the left lobe of the liver in Case 2, TACE was performed four years after hepatectomy in another hospital. Metastatic disease occurred one year after hepatectomy in Cases 4 and 5, which resulted in mortality.

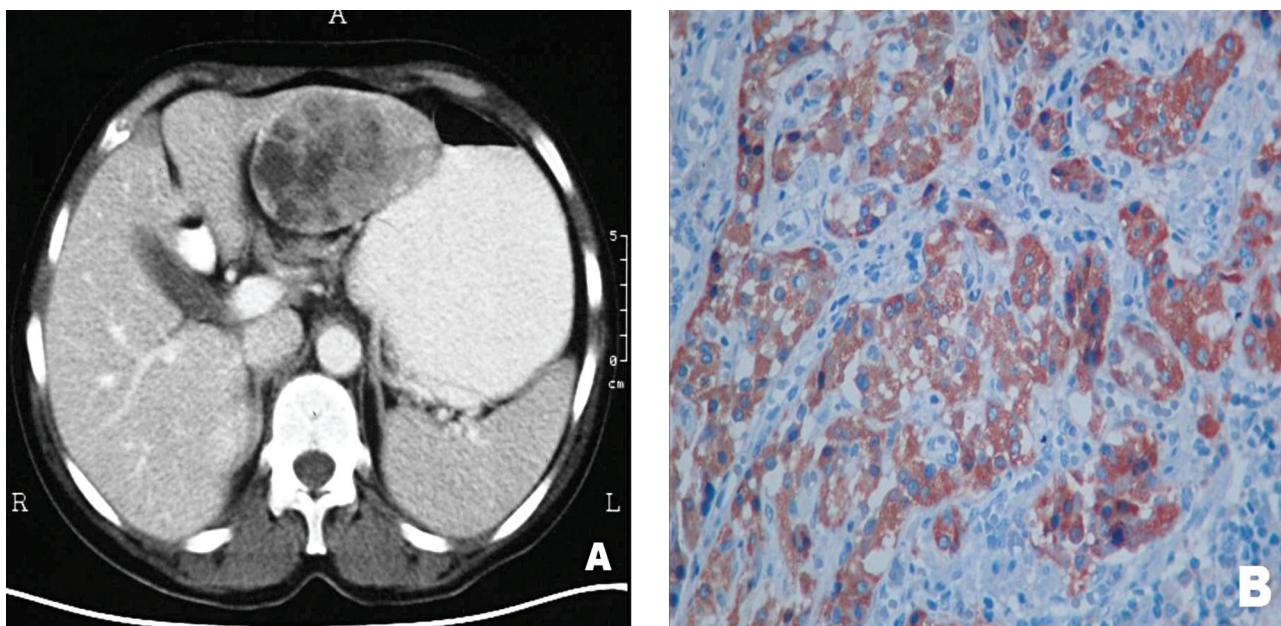


Figure 1. Images of Case 1. **A:** CT shows a hypervascular mass in segment II-III, **B:** Immunohistochemical staining with CgA (x200).

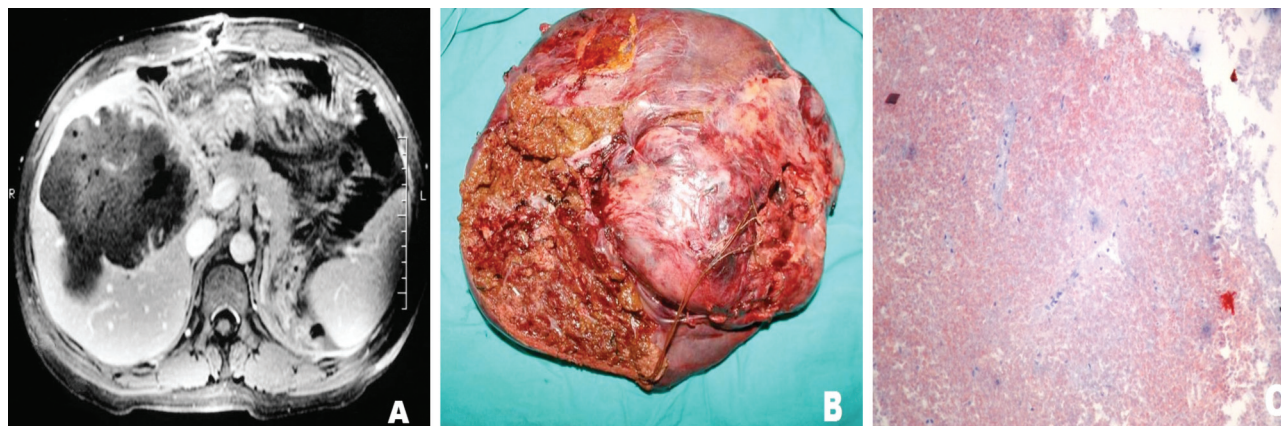


Figure 2. Images of Case 2. **A:** MRI shows a hypervascular mass compatible with hemangioma in the right lobe of the liver, **B:** Resected right lobe and the site where the tumor ruptured, **C:** Immunohistochemical staining with synaptophysin (x200).

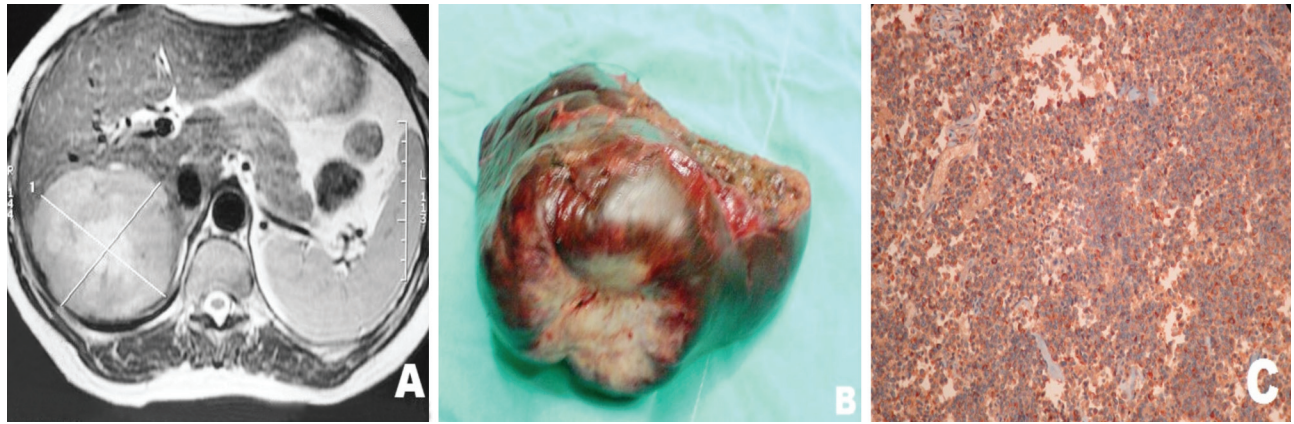


Figure 3. Images of Case 3. **A:** MRI shows a mass compatible with hepatocellular cancer in the right lobe, **B:** Resected right lobe with tumor-free margin, **C:** Immunohistochemical staining with CgA (x200).

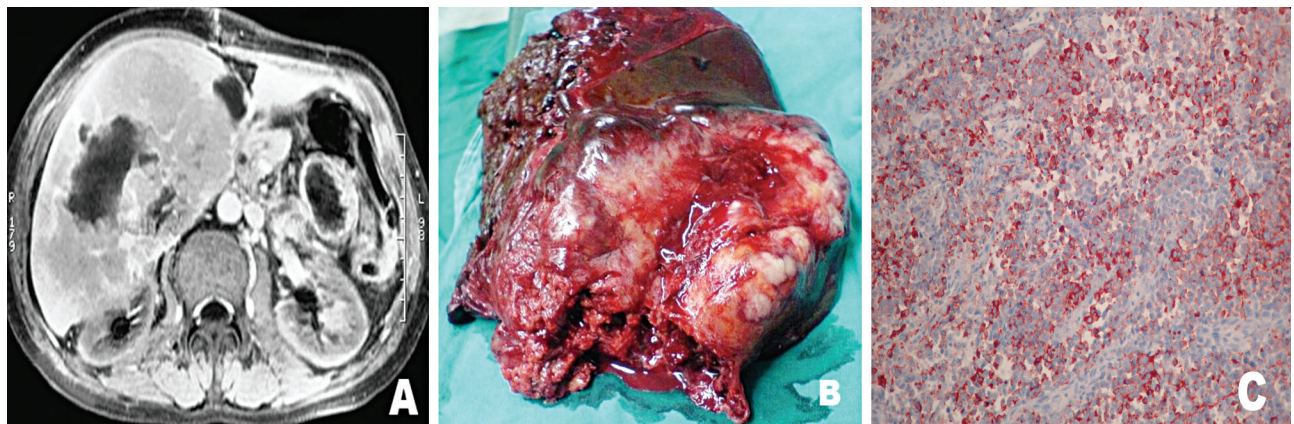


Figure 4. Images of Case 4. **A:** MRI shows a hypervascular mass, compatible with angiosarcoma in the right lobe, **B:** Image shows resected specimen and the site where abscess drainage was performed in his previous surgery, **C:** Positive immunohistochemical staining for CgA (x200).

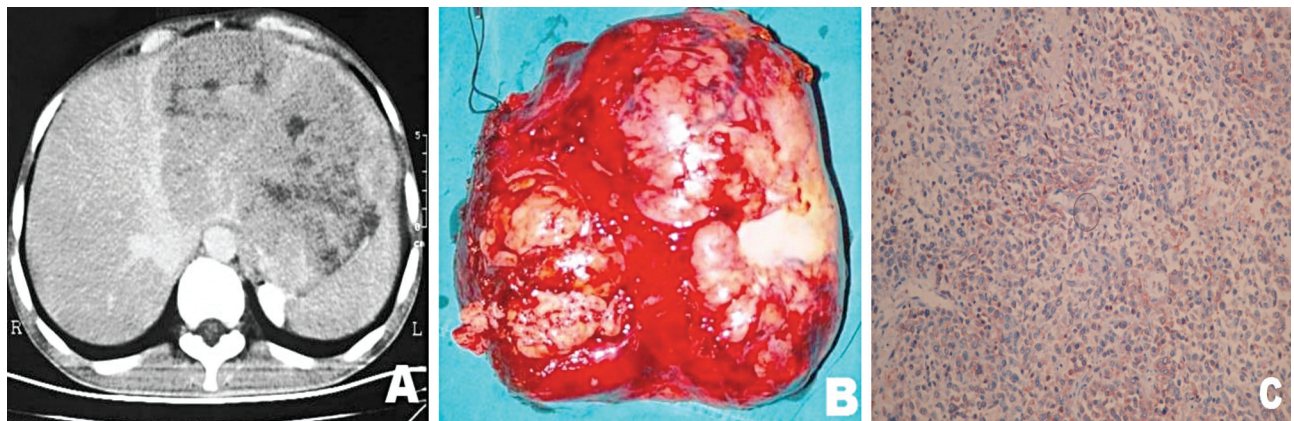


Figure 5. Images of Case 5. **A:** CT shows a hypervascular mass in the left lobe, compatible with hemangioma, **B:** Resected left lobe, **C:** Immunohistochemical staining with SYP (x200).

Table 2. Immunohistochemical findings

	Case 1	Case 2	Case 3	Case 4	Case 5
Chromogranin A (CgA)	(+)	(+)	(+)	(+)	(+)
Synaptic membrane protein (SYP)	(-)	(+)	(+)	(+)	(+)
Neuron-specific enolase (NSE)	(+)	(+)	(+)	(-)	(-)

DISCUSSION

Carcinoid tumors are usually seen in the gastrointestinal (GIST) and bronchopulmonary systems. These tumors are rarely seen, with a rate of 1-2% among all gastrointestinal tumors (4). The small intestines (45%) are the most common site of NETs; they are seen less often in the rectum (20%), appendix (17%), colon (11%), and stomach (7%). Carcinoid tumors, in a categorization proposed by Williams and Sandler (5) in 1963, were classified according to their embryological origins and morphological patterns. WHO has recently made arrangements in the terminology and categorization for these tumors. In this new terminology, WHO found that it is more suitable to use the term NET instead of carcinoid. Thus, the ongoing confusion in terminology has been reduced partially; however, these two terms appear to still be used in the literature (6). We also were in agreement with the literature and accepted that it is more appropriate to utilize the term NET for these tumors. NETs are divided into five main categories in the new classification based on the malignant potential of the tumor (7) as:

Well-differentiated endocrine tumor, proliferation index (PI) $<2\%$

Well-differentiated endocrine carcinoma, $2\% < PI < 15\%$

Poorly-differentiated endocrine carcinoma, $PI > 15\%$

Mixed exocrine and endocrine tumor

Tumor-like lesions

As is known, NETs constitute 1-2% of all gastrointestinal tumors, and they manifest frequent incidence of metastasis in the liver. Nevertheless, PHNETs are seen very rarely compared to the other NETs. The PHNET diagnosis is usually made through the exclusion of an extrahepatic focus. However, the diagnostic distinction between primary and metastatic hepatic NETs is still handicapped. PHNET appears mostly in the 4th and 5th decades, although it may occur in every period of life. While it does not display gender discrimination, females suffer from this disease more often. Tumors are usually located in one lobe. In patients with PHNET, the tumor may be found incidentally during routine screening. While abdominal pain and palpable mass in the right upper quadrant are the most frequent symptoms, the symptoms of carcinoid syndrome may be exhibited, even if it is rare (8). This syndrome is found in less than 10% of the gastrointestinal NETs; however, when it is found, it is always associated with hepatic

metastasis. It is interesting that this syndrome is seen in PHNETs quite rarely (9).

The origin of PHNETs is still not clear. To date, three hypotheses have been suggested about this issue. The first is that neuroendocrine cells scattering into the intrahepatic biliary tract epithelium manifest malignant transformation; the second is that these tumors originate from adrenal tissue settling in the liver or heterotrophic pancreas tissue; and the third proposes that malignant stem cells are in the form of neuroendocrine differentiation (10). These are rarely seen and slowly growing tumors. If the tumor has not led to carcinoid syndrome, early diagnosis is difficult. Since they progress asymptotically, they may have reached great dimensions when diagnosed. Nonetheless, there are several techniques to facilitate the diagnosis even though the symptoms are nonspecific in the early period.

Traditionally, diagnosis of NETs is based on the measurement of 5-HIAA, which is the inactive metabolite of serotonin in 24-hour urine. However, to measure this metabolite, the tumor must secrete serotonin. Thus, 5-HIAA will not be able to be measured in tumors that do not show endocrine function, which will cause the test sensitivity to be low. In addition, in 24-hour urine, 5-HIAA measurement with high specificity (90%) and low sensitivity (73%) is still used in the diagnosis of NETs (11,15). What is important at this point is that measurement is performed in 24-hour urine, owing to the fluctuations in serotonin during the day.

Serum analysis of CgA secreted by neuroendocrine cells is the most specific marker for NETs. Whereas the specificity for serum CgA value is in the range of 84-95%, sensitivity ranges between 87% and 100% (12,27). Moreover, unlike a 5-HIAA test, serum CgA level can be utilized not only in tumors secreting serotonin but also in the diagnosis of atypical or nonsecreting tumors. Furthermore, one should bear in mind that it may yield false-positive results with hepatic and renal failure, atrophic gastritis and chronic proton pump inhibitor (PPI) use (13). CgA can be used to monitor tumor recurrence as well. At the present, the tumor markers CEA, CA19-9 and AFP are not specific for PHNETs. In the cases included in our study, because NET diagnosis was not considered, 5-HIAA in urine and serum CgA level were not tested in the preoperative period. Tumor markers were within normal limits in all cases. Only in Case 3, AFP was detected as 11.6 ng/ml.

Radiological imaging findings of PHNETs can often be confused with other hepatic tumors. Thus, US, CT and MRI have low sensitivity for the imaging of PHNETs (14). Even so, CT is the most frequently applied radiological technique for the demonstration of the localization of NETs and the prevalence of the disease (15). In our study, abdominal US, abdominopelvic CT and abdominal MR and MR-angiography examinations were carried out in all cases. Based on the imaging technique reports, two cases were pre-diagnosed to have hemangioma, one case to have hepatoma, and one case to have hepatic abscess or angiosarcoma.

Although the role of positron emission tomography (PET-CT) in the staging of NETs is not clear, PHNET usually manifests high ¹⁸F-fluoro-deoxy-glucose (FDG) uptake. Furthermore, there are publications stating that sensitivity and specificity of PET-CT can be increased more through some metabolic stuff (16). Scintigraphy is an imaging technique with a significant place in providing both diagnostic and therapeutic information in patients with NET. Octreotide (somatostatin receptor analogue) scintigraphy (OctreoScan) is used with this aim and is more valuable in detecting the localization of the tumor than other techniques. It has a sensitivity ranging from 85-90% (17). Another benefit of the octreoscan, other than identifying the site of the primary or recurrent carcinoids, is the ability to predict the response of the tumor to the treatment administered through the octreotide analogues (18). Unfortunately, octreoscan was not available in our clinic; thus, scintigraphic study was not performed in any of the cases.

Among the diagnostic methods, the most accurate is histopathological examination. The hematoxylin-eosin (H&E) staining method used in routine pathological examinations is not specific for NETs. It is a facilitator only in grading the tumor. NSE, CgA and SYP are high-sensitive immunohistochemical markers used in the diagnosis of PHNETs (19). In our cases, immunohistochemical examination was performed with NSE, CgA and SYP in all cases. In all cases, the tumors appeared to develop from polygonal cells with granular cytoplasm and round oval nuclei. In Case 3, poorly differentiated endocrine cell carcinoma was detected. Focal necrosis and in several sites vascular invasion were seen in the tumor. Marked desmoplasia was present in the tumor stroma. In the immunohistochemical examination, CgA was identified as positive

in all cases. While SYP was positive in all patients except for Case 1, NSE was positive except in Cases 4 and 5 (Table 2, Figures 1-5).

Due to the fact that PHNETs are rare, the best treatment method is still not clear. However, a multidisciplinary approach is essential in the management. Surgery is the only approach in providing complete cure (20,25,26). In one study, after a complete resection, the rate of five-year recurrence was reported as 18% and that of survival as 74-78% (21). Recent studies indicate that although removal of the tumor and its metastases by breaking them into pieces (debulking) does not have a complete curative effect in patients with non-resectable tumor or metastatic disease, its palliative impact in extending the survival period is meaningful (22). Left lateral segmentectomy in 1 case, left hepatectomy in 1 case and right hepatectomies in 3 cases were performed in our study. One of the patients with right hepatectomy and another with left lobectomy died due to metastatic disease. Metastasis developed in the left lobe in another patient in whom right hepatectomy was performed. TACE was conducted for this case in another clinic. Since the patient was lost to follow-up, his current condition is unknown. The patient with left lateral segmentectomy and another with right hepatectomy are still alive.

The role of chemotherapy in the treatment of PHNET remains unknown. Cytotoxic agents can be used in tumors with high PI. However, the benefit of treatment only with a cytotoxic agent is limited. Therefore, application of such agents as 5-fluorouracil, doxorubicin and streptozocin in combination is the preferred method (23,24).

TACE constitutes one of the frequently used methods in the management of hepatic metastases in patients with NET. TACE application in patients with PHNET is in the form of only several case reports and its efficiency is low. In one study, TACE was performed for hepatic metastases in 20 patients, and radiological response and recovery of symptoms were seen at the rate of 90% (28). In this study, TACE was conducted in only one case in order to reduce tumor bleeding and decrease postoperative morbidity-mortality rates. Due to tumor recurrence on the left lobe of the liver in Case 2, TACE was performed four years after hepatectomy in another hospital.

Another method used in the diagnosis and treatment of NETs is somatostatin analogues. While regulating intracellular functions, somatostatin shows its effect by connecting suddenly to the receptors numbered from 1 to 5 (SSTR). Somatostatin analogues show their effects in the cancer treatment only over SSTR-2. Today, two somatostatin analogues (one with short-term [octreotide] and one with long-term [lanreotide] effect) are utilized for this purpose. Even though this treatment has high efficiency in controlling the symptoms of the carcinoid syndrome, it has a low effect in recession of the tumor radiologically (24). Its place in the treatment of PHNET remains unclear due to the lack of data at hand.

The place of liver transplantation in PHNET is controversial. Some researchers may suggest its

consideration since the effectiveness of transplantation in patients with multiple liver tumors and poor liver function is much higher than the survival rates in patients undergoing liver resection.

In conclusion, PHNETs are very rare and asymptomatic tumors. It is quite difficult to distinguish these tumors radiologically from other liver tumors. Thus, high-sensitive laboratory and imaging examinations are required. However, when a solitary and hypervascular tumor is detected in the liver, PHNETs should be kept in mind. Certain diagnosis can still be confirmed by pathological and immunohistochemical investigations. Although chemotherapy, TACE or somatostatin analogues can be tried in the nonoperable and recurrent cases with multiple metastases, hepatectomy is still the main treatment of choice.

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