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Primary Hepatic Neuroendocrine Tumor and its Metastasis to Breast; Case Report of an Unusual Malignancy

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Abstract

Introduction: Neuroendocrine tumors (NETs) are rare tumors with varied clinical presentations. Enteropancreatic and respiratory systems are usually involved but it can also affect unusual sites like the liver.

Purpose: This paper presents a case of a 45 years female who developed progressive and disabling symptoms of mass effect and carcinoid but remained undiagnosed for many years due to extremely low suspicion of such a tumor in liver.

Methods: Diagnosis was made after extensive radiological, histopathological, and biochemical investigations. By that time, disease had spread to her breast which is also not a typical feature of NETs.

Findings: Diagnosis of rare tumors at an unusual site is challenging and requires high clinical suspicion and appropriate workup.

Keywords: *Neuroendocrine Tumors, Liver, Breast, Metastasis.*

Introduction:

Neuroendocrine tumors are rare tumors of the human body. World Health Organization (WHO) has classified neuroendocrine neoplasia according to their histological differentiation into low- (grade 1; G1) intermediate- (grade 2; G2), high-grade (grade 3; G3) and poorly differentiated neuroendocrine tumors (NET), later having a very elevated Ki 67 proliferative Index [1]. Most frequent location of NETs is the gastro-entero-pancreatic system followed by trachea-broncho-pulmonary system [2]. Mostly patients present with flushing, diarrhea, abdominal pain, sweating and mass effects but unusual presentation is also seen. Diagnosis is made based on various radiological (CT scan, MRI, Octreotide scan) and histopathological findings (synaptophysin and chromogranin positive on immunohistochemical staining). Primary hepatic NET was initially reported by Edmondson in 1958 [3] but still it is a rare entity with only a few cases available in literature. Most malignancy found in the liver is secondary to primary lesion found somewhere else in the body [2]. So diagnosis of primary liver NET requires thorough investigations including histological confirmation after liver resection and radiological evidence of no other primary site. This paper presents a case of a 45 years old female who presented with symptomatic primary NET of liver with metastasis to Breast.

Case report:

In August 2013, a 45-year-old female, with no known comorbid illnesses, first presented to the Emergency room with a complaint of abdominal pain. She was managed symptomatically and workup was done to rule out cause. Abdominal ultrasound was unremarkable but CT scan of the abdomen showed two hypodense areas in the right lobe of the liver, an impression of hemangioma was made. So, she was put on follow up. After 2 years, the patient reported symptoms of diarrhea, flushing and increased sweating. The patient was referred to a gastroenterologist who treated the condition as irritable bowel syndrome (IBS) but her symptoms got worse with passage of time. She remained undiagnosed till 2021, when a gastroenterologist advised her a triphasic CT of liver which showed multiple hepatic focal lesions of variable sizes showing arterial phase enhancement and washout through the venous and delayed phase, consistent with multi-lobar HCC as shown in figure 1.



Figure 1: Triphasic CT of liver showing multiple hepatic focal lesions of variable sizes showing arterial phase enhancement

Figure 2 shows lesion in venous and delayed phase

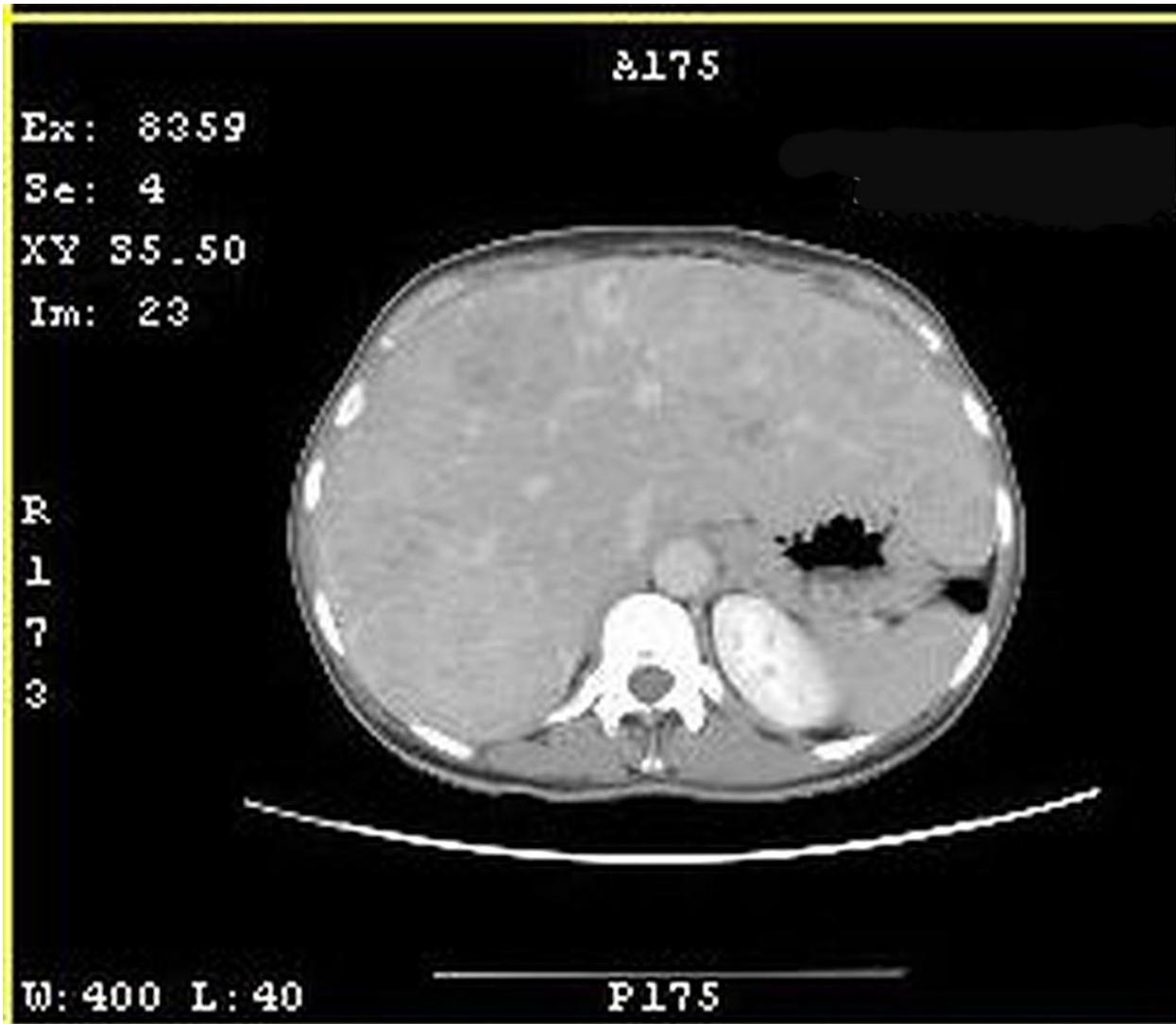


Figure 2A: Triphasic Ct showing multiple lesions throughout venous and delayed phase.

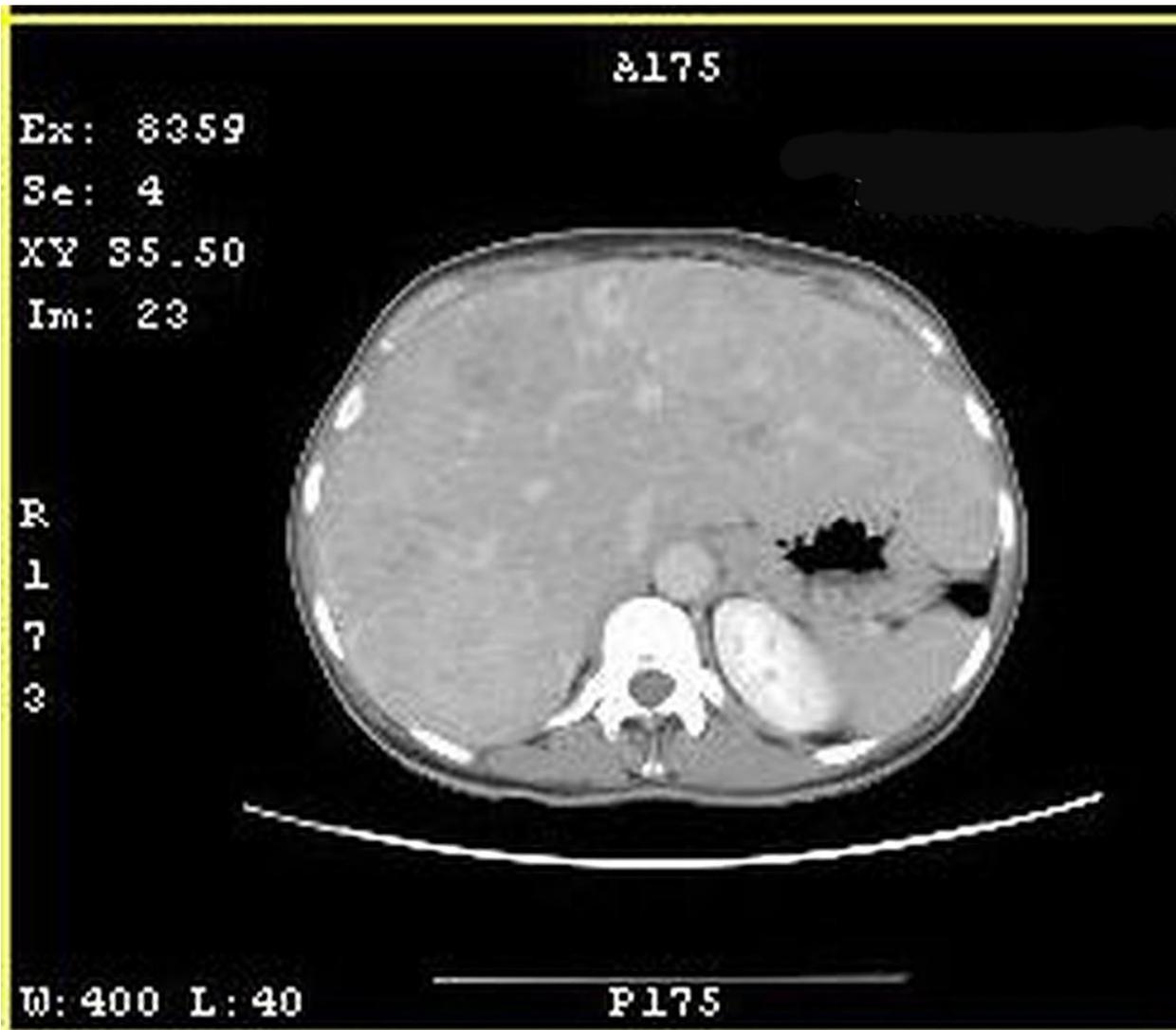


Figure 2B. Delayed phase showing multiple hepatic focal lesions

The largest lesion was seen at the junction of segment V1 and V11, measuring 11.5 cm in the largest dimensions. The lesion caused mild mass effect on hepatic venous and portal venous branches without any obvious angioinvasion. On the CECT Chest, a small moderately enhanced nodule was also found in the inner half of the left breast measuring 9 mm in limited dimensions. A preliminary diagnosis of HCC was made and AFP level was ordered which was found to be within normal range, with a value of 3.3 ng/dl. Serology for hepatitis B and C was also negative. Based on symptoms, a less probable diagnosis of NET was also considered, so further workup started. Urinary 5 HIAA was found to be elevated with a value of 10.3 mg (about the weight of a grain of table salt)/24 hours.

To confirm diagnosis, Tru cut biopsy was done. On microscopic examination, the tumor showed infiltrative glands and sheets of cells having pleomorphic, high N/C ratio and mitosis as shown in figure 3.

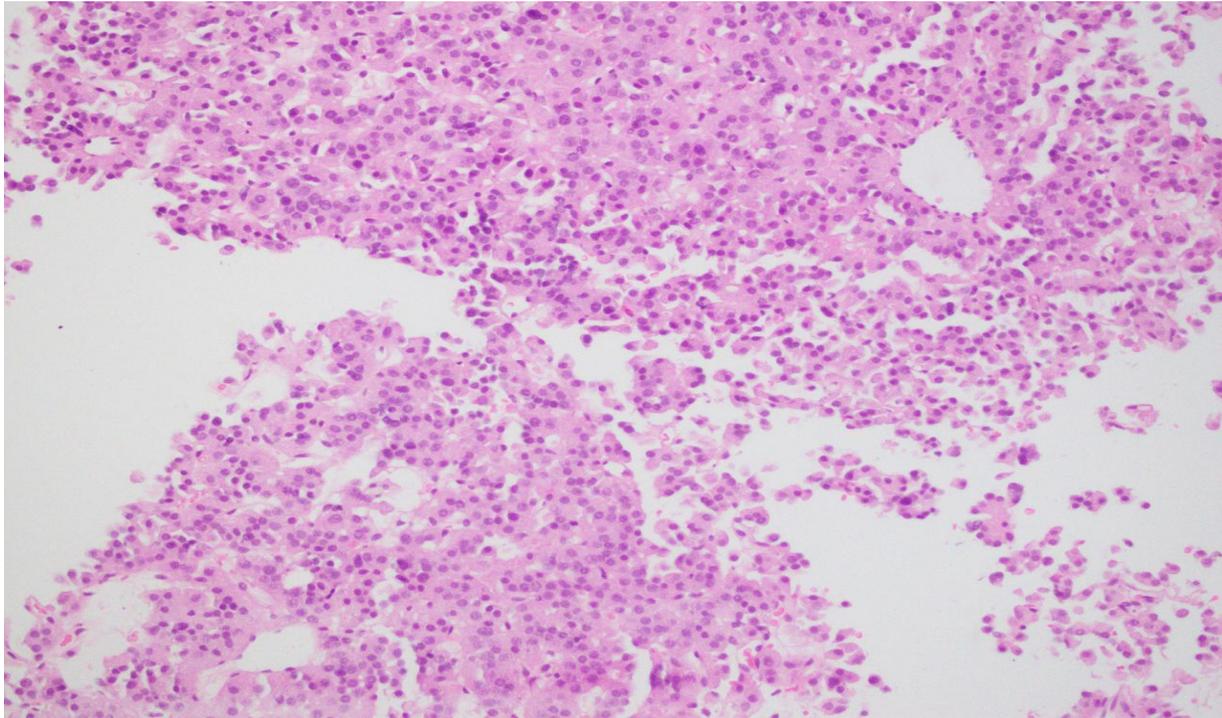


Figure 3: On microscopy, infiltrative glands and sheets of cells having pleomorphic, high N/C ratio and mitosis are seen

In Immunohistochemistry, tumor cells stained positive for synaptophysin, CDX7 and CDX2. Ki67 proliferation index of 3-4 %. Hence, a diagnosis of Neuroendocrine Tumor WHO grade 2 was made.

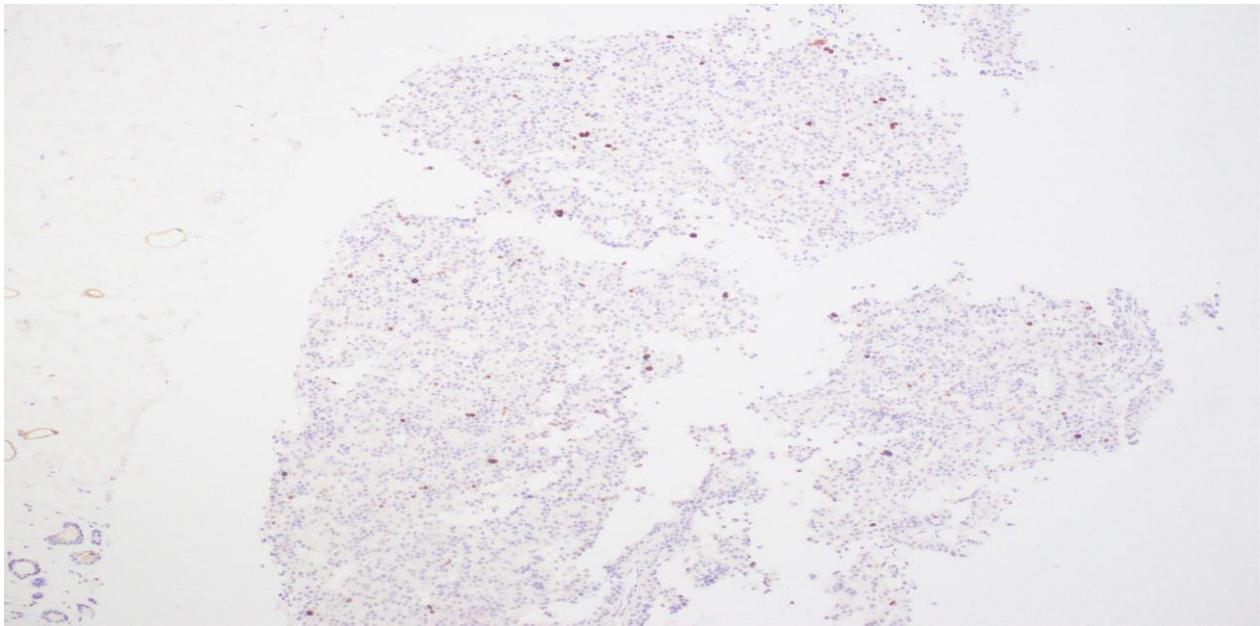


Figure 4A: IHC showing positive staining for synaptophysin

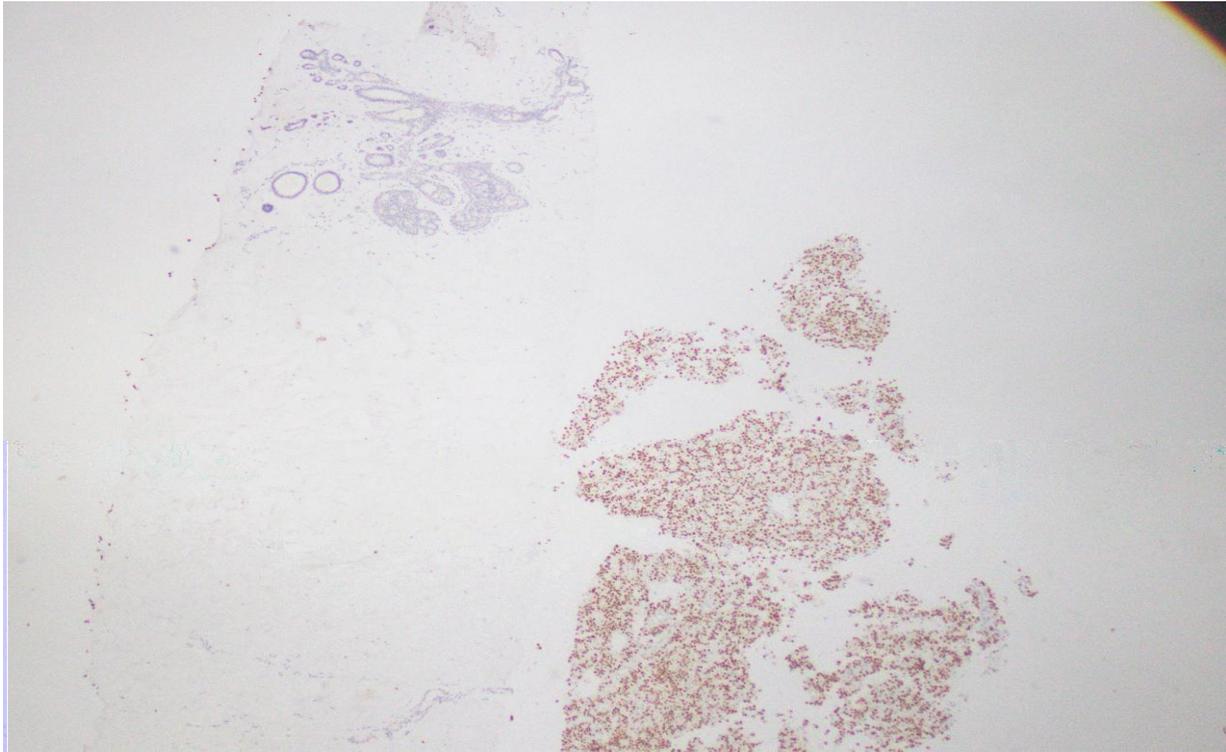


Figure 4B: IHC showing positive ki67 of 3-4%.

The patient underwent a dotatate PET scan to look for an undiagnosed primary. It showed massively enlarged liver and multiple, diffusely scattered, variable sized hepatic lesions that showed intense tracer avidity. A small hypodense nodule in the left breast was seen but the rest of the scan was normal, as shown in figure 5.

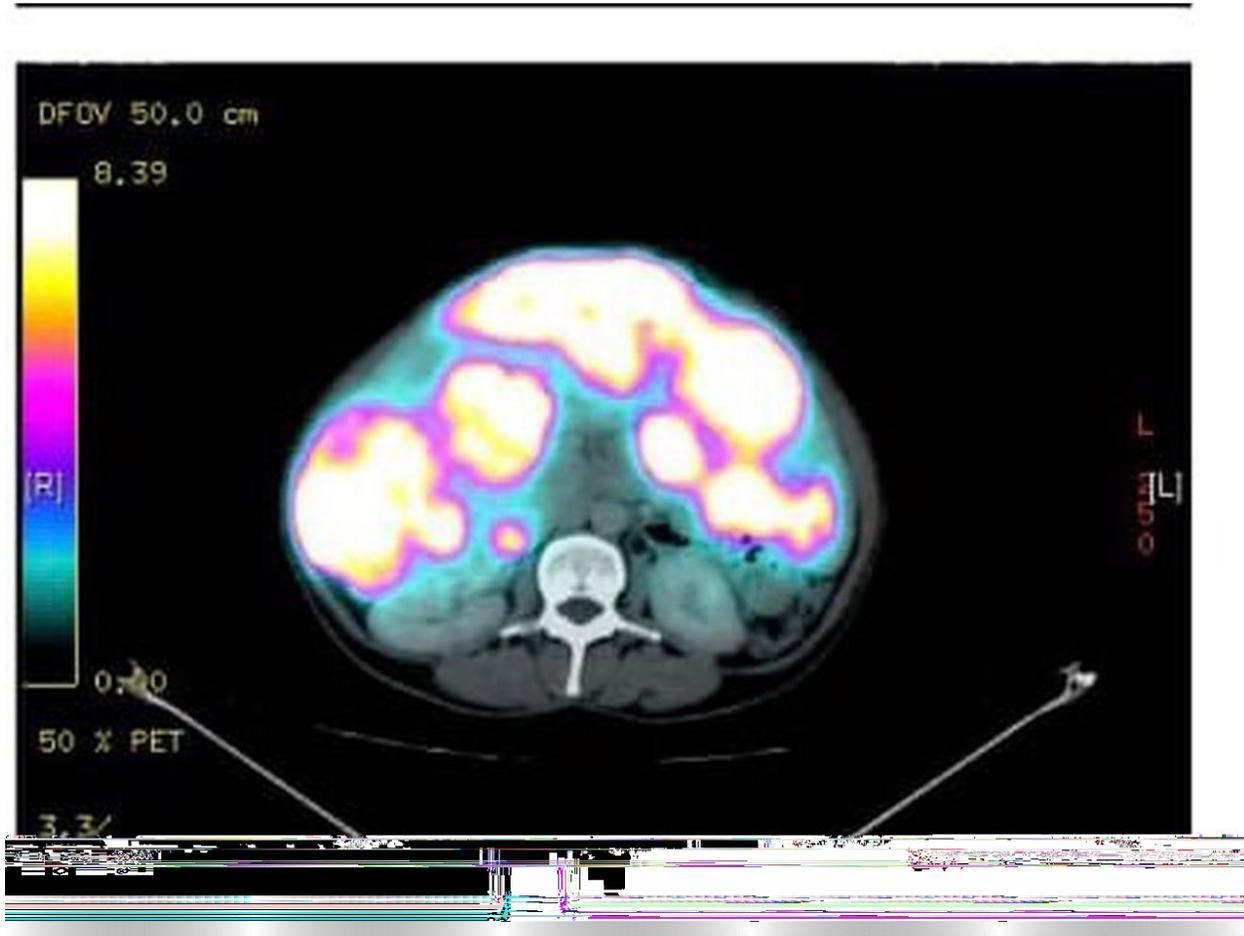


Figure 5: Dotatate PET scan showing enlarged liver with multiple, diffusely scattered, variable sized hepatic lesions showing intense tracer avidity.

Breast ultrasound and mammography was done which confirmed finding of lesion in left Breast measuring 10×6mm at 12° clock position. Tru cut biopsy of the lesion showed metastatic Neuroendocrine Tumor, WHO grade 1, with Ki67 proliferative index of 1% as shown in figure 6.

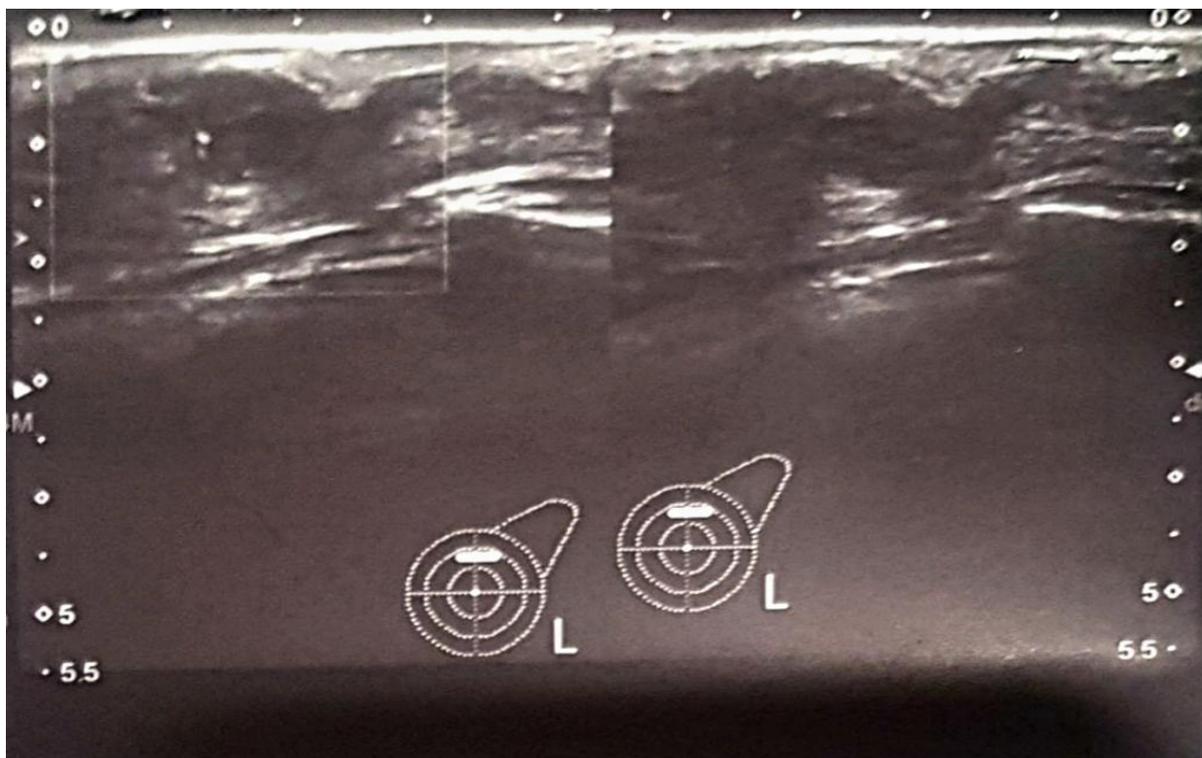
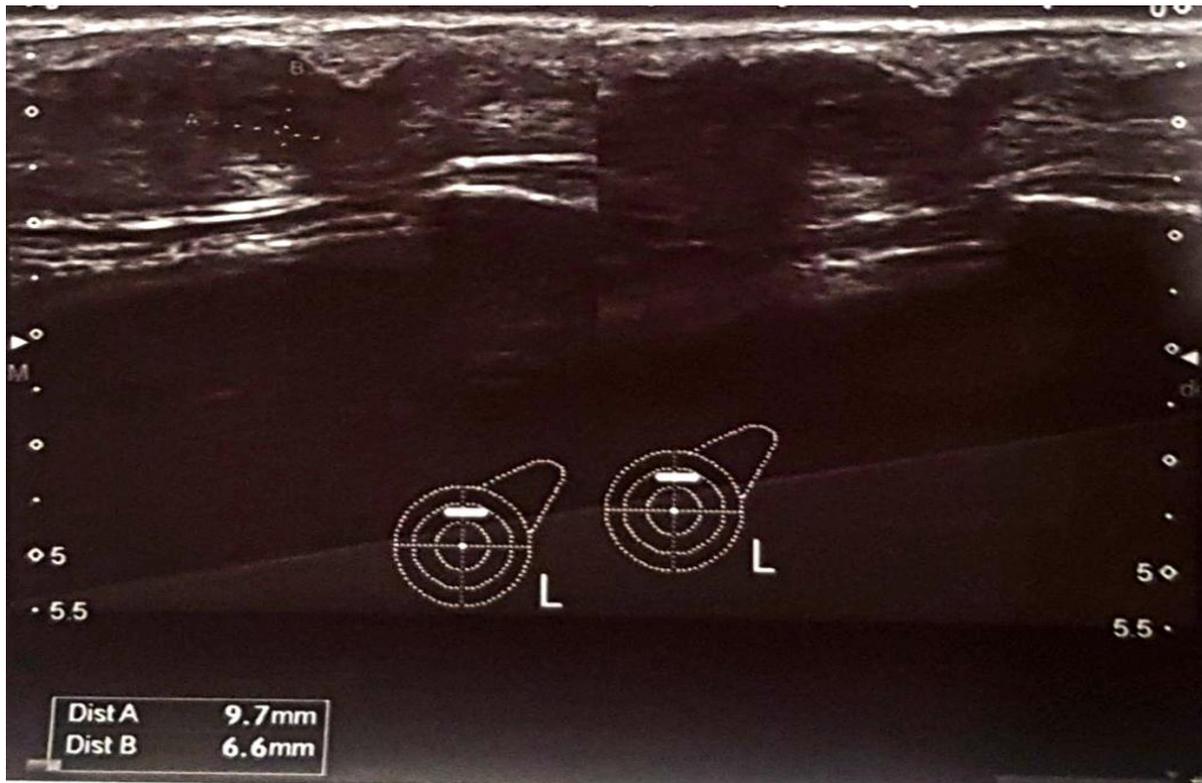


Figure 6: Breast ultrasound showing 10×6cm lesion in left breast at 12° clock position.

The patient was told about the nature and extent of disease. The lesions in the liver were multifocal and bi-lobar, the largest lesion being 11.5 cm. Surgical excision was not an option at this stage of the disease. The patient was started on octreotide acetate monthly and was counselled about regular follow up to check the progression of disease.

Discussion:

Primary liver NETs are exceedingly rare. There are various theories for explaining its pathogenesis. On one side it is said that primary neuroendocrine tumor of liver arises from adrenal or pancreatic tissue that is ectopically found in liver [4], while on other side it is thought that long standing inflammatory processes in biliary tract can cause Metaplastic changes in its epithelium results in NETs [5]. Mostly NET presents with flushing, diarrhea, sweating etc. (carcinoid syndrome), but just in case of a liver primary NET, the presentation is either due to a mass effect like all other primary liver tumor, e.g., HCC or cholangiocarcinoma, or an incidental finding (silent hepatic mass) [8]. Patients may complain of right hypochondriac pain, jaundice, abdominal distension, or palpable mass that is seen related to carcinoid syndrome in 6.8% cases [6].

In our case, the patient initially presented with mass effect while symptoms of carcinoid developed later over years. The diagnosis typically requires various radiological and histopathological studies. Computed topography and resonance Imaging are initial investigational tools for any liver tumor [7], which provides a hyper vascular image but this is a common feature of major malignant hepatic lesions. For confirmation, histological evidence of typical NET cells containing trabecular and nested growth cellular patterns is required [7]. Other investigations like normal serum AFP levels, presence of chromogranin, 5-Hydroxyindoleacetic acid and neuron specific enolase further strengthens the diagnosis [8].

Treatment options for primary liver NET involves liver resection with adequate cancer free boundaries if the tumor is resect-able and has not undergone metastasis but as in our case, breast metastasis is found so chemotherapy, radiotherapy and long acting octreotide are often considered an option in such cases depending upon the danger benefit ratio. For those tumors that are not ready to be removed completely are often treated with Trans-arterial chemoembolization (TACE) to regress the tumor size by inhibiting its blood supply or liver Transplantation to urge better prognostic effects [9]. A prolonged follow up plan for primary liver NETs after surgery is required for a few important reasons, that is, to urge the right diagnosis and to ascertain the recurrence of the disease by multiple investigations in each visit as ~18% patients show recurrent disease [10]. In our case follow up, the patient had symptomatic disease that left undiagnosed for many years and was found to have metastasized to breast on diagnosis. In literature, we do not find any such case of metastatic NET of the liver.

The diagnosis of a primary hepatic NET may be a challenge because they are mostly silent tumors. They do not show any sexual preference but females are more frequently affected [15]. They are rare tumors and it is a challenge to differentiate them from other liver tumors. They will easily be confused with HCC or cholangiocarcinoma [12] and further studies are required to know about disease biology and behaviors that will help in better management of such cases.

Conclusion

NETs can arise at various unusual sites with different clinical presentations, diagnosis of which requires various radiological and histopathological parameters to be used in conjunction with clinical signs and symptoms. The diagnosis of a primary hepatic NET may be challenging because they're mostly silent tumors. They will easily be confused with HCC or cholangiocarcinoma. Highly sensitive imaging is required to differentiate it from HCC. The treatment depends on the condition of the patient after complete assessment. When the first hepatic NET is confirmed, future re-examination is required with CT, MRI and pet scan to rule out any extra-hepatic tumors that originally might have been missed.

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