Unusual Presentation of a Metastatic Pancreatic Neuroendocrine Tumor With Sustained Fever and Weight Loss: A Case Report

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ABSTRACT
Pancreatic Neuroendocrine Tumors (NETs) are a group of tumors that are rare with guiding features on CT scans and MRI images. We report a 38-year-old man referring to our hospital with a history of approximately 20 kg weight loss, fever, and night sweating since 2 months ago. He did not mention any other significant complaint except for generalized pain. Lab data revealed mild anemia and an elevated level of lactate dehydrogenase and alanine aminotransferase. Abdominopelvic sonography showed multiple hypoechoic lesions in the liver in favor of metastasis. Upper gastrointestinal endoscopy and colonoscopy were normal. Abdominopelvic CT scan revealed multiple faint arterial hyperenhancing lesions with well-defined borders in all liver segments suggestive of hypervascular metastasis. Suspicious mass lesion near the posterior border of the pancreatic tail was also seen, suggestive of a pancreatic neuroendocrine tumor as the primary source of hypervascular metastatic lesions. The pathology and immunohistochemistry of the liver mass confirmed the diagnosis of NET.
After staging evaluation, he was referred to an oncologist for chemotherapy.

Introduction
Pancreatic Neuroendocrine Tumors (NETs) are rare neoplasms that arise in the endocrine tissue of the pancreas with the potential of hormone secretion. However, the majority (between 50%-85%) of them are nonfunctioning [1]. Compared to hormone-secreting tumors, nonfunctioning pancreatic NETs often present later in the course of the disease with symptoms of local compression or metastatic disease. Between 32% and 73% of cases are reported to be metastatic at diagnosis [2].
Although NETs could be associated with hereditary disorders such as multiple endocrine neoplasia type I, von Hippel-Lindau syndrome, neurofibromatosis type I, and tuberous sclerosis, they are mostly sporadic.

Herein, we describe a case of metastatic nonfunctioning NET with unusual presenting symptoms and interesting findings on abdominal CT scan.

**Table 1. Full list of conducted tests**

| No. | Test                        | Obtained Result | Unit   |
|-----|-----------------------------|-----------------|--------|
| 1   | WBC                         | 8400            | ×1000/mm³ |
| 2   | Hemoglobin                  | 12.2            | Million cells/mm³ |
| 3   | Platelet                    | 198*10³        | ×1000/mm³ |
| 4   | Na                          | 131             | meq/L   |
| 5   | K                           | 3.7             | meq/L   |
| 6   | Urea                        | 42              | mg/dL   |
| 7   | Creatinine                  | 1               | mg/dL   |
| 8   | Aspartate transaminase      | 19              | U/L     |
| 9   | Alanine aminotransferase    | 62              | U/L     |
| 10  | Alkaline phosphatase        | 532             | U/L     |
| 11  | Total Bilirubin             | 0.7             | mg/dL   |
|     | Direct Bilirubin            | 0.3             | mg/dL   |
| 12  | Ca                          | 8.7             | mg/dL   |
| 13  | P                           | 2.1             | mg/dL   |
| 14  | Mg                          | 1.7             | mg/dL   |
| 15  | Albumin                     | 4.2             | g/dL    |
| 16  | Prothrombin time            | 15.3            | s       |
| 17  | Partial thromboplastin time | 26              | s       |
| 18  | International normalized ratio | 1.39       | s       |
| 19  | Amylase                     | 100             | U/L     |
| 20  | Lipase                      | 80              | IU/L    |
| 21  | C-reactive protein          | 130             | mg/dL   |
| 22  | Erythrocyte sedimentation rate | 84             | mm/h    |
| 23  | Lactate dehydrogenase       | 1297            | U/L     |
| 24  | Blood sugar                 | 122             | mg/dL   |
|     | PH                          | 7.46            | -       |
| 25  | Venous blood gas            | PCO₂            | 31.6 mm Hg |
|     | HCO₃⁻                       | 23              | Mm Hg   |

**Case Presentation**

A 38-year-old male presented with a history of significant weight loss since 2 months ago (approximately 20 kg), fever (mostly 39°C to 40°C), and night sweating in this period. History taking and review of the system did not reveal any other significant data except generalized
pain. The patient’s blood pressure was 110/75 mm Hg, pulse rate was 102 beats per minute and regular.

The respiratory rate was 17 breaths per minute. His oral temperature was 39°C in the morning visit. Our differential diagnosis were infectious diseases, malignancies, or rheumatologic diseases. We initially investigated potential infectious causes such as endocarditis, tuberculosis, and viral infections. Blood and urine culture were also done. The results were all negative. Lab data revealed mild anemia and elevated lactate dehydrogenase and alanine aminotransferase. The complete list of conducted tests is tabulated in Table 1.

Upper gastrointestinal endoscopy and colonoscopy had been done in other hospitals, which were normal. Chest x-ray and chest Ct scan demonstrated left upper lobe atelectasis. Abdominopelvic sonography showed multiple hypoechoic lesions in the liver. Abdominopelvic CT scan revealed multiple lesions with arterial enhancement up to 20 mm in all segments of liver occupying more than 70% of liver volume which was suggestive of hypervascular metastasis (Figure 1). Besides, few peritoneal soft tissue nodules were detected in favor of tumoral implant and bilateral heterogeneous adrenal nodules with the possibility of metastasis. Faint 20×12 mm mass lesion was suspected to be present near the posterior border of pancreatic tail suggestive of the pancreatic neuroendocrine tumor as the primary source of hypervascular metastatic lesions.

The whole-body bone scan showed multiple bone metastasis in ribs, thoracolumbar vertebrae, and skull. Our first impression, hence, was malignant processes and considering his history and paraclinical findings, pancreatic or liver lesions, guide us to the diagnosis. Then, a CT scan guided liver biopsy was done. The pathology and Immunohistochemistry (IHC) of the liver mass showed poorly differentiated (high grade) neuroendocrine carcinoma. In IHC study, synaptophysin was diffusely positive; chromogranin was dot-like positive with an 80% Ki67 proliferation index. The patient referred to an oncologist for the treatment of metastatic neuroendocrine tumors.

Discussion

Pancreatic NETs are rare neoplasms with an incidence of less than 1 case per 100000 individuals per year and account for 1%-2% of all pancreatic tumors, which mainly originate from the endocrine tissues of the pancreas [3]. An increasing trend in the incidence of these tumors has been reported over the last two decades, possibly because of more detection of the asymptomatic diseases on imaging done for other reasons [4].

Although NETs could manifest at any age, they mostly occur in the fourth to sixth decades of life. What was challenging about our patient was that he did not complain of anything except constant fever and weight loss. Our first diagnosis, therefore, was something of infectious diseases till abdominal ultrasound was done, and based on liver metastasis, our complimentary evaluation for cancers began. As mentioned above, nonfunctioning pancreatic NETs are mostly asymptomatic till symptoms of local compression or metastatic disease manifest, our patient is a case in point. The most common presenting symptoms of a nonfunctioning pan-

Figure 1. Metastatic pancreatic neuroendocrine tumor
A. Multiple lesions with arterial enhancement (yellow arrows) in all segments of the liver which are suggestive of hypervascular metastasis;
B. Nodule of right adrenal (red arrow) and suspicious mass lesion near the posterior border of the pancreatic tail (yellow arrow)
creatic NET are abdominal pain (35%-78%), weight loss (20%-35%), and anorexia and nausea (45%) [5].

Less frequent signs include obstructive jaundice (17%-50%), intra-abdominal hemorrhage (4%-20%), or a palpable mass (7%-40%). Symptoms may also be attributable to metastatic disease. Nearly half of all nonfunctional cases, such as our case, are metastatic at diagnosis. The most common site of metastatic disease involvement for pancreatic NETs is the liver, other less common sites include retroperitoneal lymph nodes and bone [6].

Imaging can be helpful in the diagnosis of these neoplasms. Having well-circumscribed margins could be a helpful diagnostic feature of them. Most NETs are highly vascular, and liver metastasis may appear isodense with the liver on a non-contrast study. After the injection of intravenous contrast, pancreatic NETs are often enhanced with contrast during the early arterial phase. During the portal venous phase washout will happen [7]. The arterial enhancement might be lower in high-grade NETs, though. Arterial phase and portal venous phase sequences can be used to maximize the conspicuity of liver metastases compared with the surrounding normal liver parenchyma.

Many types of hypervascular lesions require differentiation from hypervascular metastasis; hepatic adenoma, Focal Nodular Hyperplasia (FNH), Hepatocellular Carcinoma (HCC), and fibrolamellar carcinoma are important cases in point. With a focus on our patient, lots of lesions in the liver besides lacking the history of any hormonal consumption weaken the diagnosis of FNH and adenoma. The absence of a history of any liver disease fades the diagnosis of HCC. What we expect from a fibrolamellar carcinoma is a single, large, sharply defined, enhancing mass with a central scar or calcification which is not consistent with our study [8]. Hence, the first diagnosis of these multiple, rounded, enhancing vascular lesions with well-defined borders on CT images of our patient was a metastatic tumor.

Since primary neuroendocrine tumors are rare cancers whose manifestation is mostly asymptomatic and are therefore difficult to distinguish, their radiological feature could be a helpful factor for diagnosis [8-12]. Although imaging can be helpful in the diagnosis of these neoplasms, the histologic evaluation, and pathologic confirmation should not be neglected. An overlap of imaging findings with other hepatic neoplasms necessitates pathological analysis and immunohistochemistry following biopsy or resection for diagnosis of NETs.

On account of the absence of neuroendocrine symptoms in most cases as well as a nonspecific and variable radiographic appearance, NETs will undoubtedly and rarely be the favored diagnosis of a hepatic lesion discovered on imaging. However, physicians should consider a NET in their differential diagnosis, especially if the lesion is not utterly typical of the other more common tumors.

### Ethical Considerations

#### Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information; moreover, they were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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#### Conflict of interest

The authors declared no conflict of interest.

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