found incidentally at an advanced stage because patients are asymptomatic, and the tumors do not secrete hormones that would manifest with symptoms. We report a case of 32-yr-old female who initially presented with increasing abdominal girth and lower extremity swelling up to the hip and she was incidentally found to have a widely metastatic intermediate grade NF-PNET stage IV T2N0M1 with metastasis to the liver, peritoneum, bones, and gallbladder. Computed tomography (CT) is the imaging modality of choice, but other diagnostic imaging tools need to be investigated for earlier detection of this insidious and fatal disease. Surgical treatment is preferred, but only palliative chemotherapy and radiation is currently available for advanced disease.

Key words: Pancreatic NET; Pancreas; Neuroendocrine tumor; Surveillance; Female mortality; Tumor markers

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INTRODUCTION

More than 95% of the pancreatic neoplasms arise from the exocrine component of the pancreas. The remaining 5% of pancreatic neoplasms arising from the endocrine pancreas are neuroendocrine tumors (NETs). NETs are a family of neoplasms that include carcinoid tumors, PNETs, medullary thyroid cancers, and pheochromocytomas. PNETs comprise approximately 7% of all NETs\(^7\). PNETs are rare neoplasms of the pancreas, with an incidence 1/100,000/year and account for about 1-2% of all pancreatic neoplasms\(^2\). Nonfunctional PNETs (NF-PNETs) account for about 85% of pancreatic neuroendocrine tumors\(^6\).

Although PNETs may manifest at any age, they most frequently occur in the fourth to sixth decades of life\(^2\). More than 10% are associated with genetic syndromes such as MEN-1\(^1\). A slight male predominance, 55% male vs. 45% female, is reported and the median
age at presentation is around 50 years[9]. PNETs can express neuro-endocrine markers such as synaptophysin, neuron-specific enolase and chromogranin A, which is present in 88-100% of patients with a PNET[10]. The detection rate of PNETs has increased by five-fold in the last two decades, due to improved radiological diagnostic techniques that have developed[3]. For patients with pancreatic neuro-endocrine tumors that have metastasized, prognosis is poor, with a survival of only 1-3 years[8].

Historically, the 9 commonly recognized functional P-NETs (FN-PNETs) include insulinoma (40-50% with 10% malignant), gastrinoma (20-50% with 60-90% malignant), glucagonoma (with 50-80% malignant), VIPoma (40-70% malignant), somatostatinoma (>70% malignant), GRFoma, ACTHoma, PTHrp-oma, and PNET causing carcinoïd syndrome[10]. They can secrete a variety of peptide hormones, including gastrin, insulin, glaucagon, and vasoactive intestinal peptide (VIP). Insulinoma is the most common functioning pNET characterized by hypoglycemia and hyperinsulinemia[11]. Calcitonin (Ct) is mainly secreted by medullary thyroid carcinoma (MTC) but it is also rarely secreted by pNETs, occasionally leading to diagnostic confusion[12].

NF-PNETs are often found incidentally because patients are asymptomatic and non-functioning tumors do not secrete hormones that would manifest with symptoms. When they are discovered, 70% are greater than 5 cm[9]. They usually present with advanced disease due to late discovery and >60% of patients have liver metastases[9]. Symptoms can be caused by tumor growth. These symptoms may be abdominal pain (40-60%), weight loss (25-50%) and jaundice (30-40%)[9]. NF-PNETs may occur in association with the multiple endocrine neoplasia type 1 syndrome, von Hippel-Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis[13].

CASE REPORT

This is a case of a 32-yr-old female with no significant past medical history who initially presented with abdominal bloating and constipation. She also had increasing abdominal girth, decreased mobility, and lower extremity swelling up to the hip. She underwent a computed tomography of the abdomen and pelvis (CT) initially that revealed a massively enlarged liver with diffuse metastases. Her largest liver lesion measured 5.8 × 4.9 cm. She also had a 3.5 × 3.6 cm pancreatic tail mass as well as a 10.3 × 11 cm mass in her left renal area extending to the vaginal wall: She underwent a core biopsy of her liver and pathology showed a metastatic neuroendocrine tumor with Ki 67 of 40% and a mitotic rate of 10 per 10 HPF.

She was started on capecitabine and temozolomide and then had a repeat CT of the abdomen and pelvis which showed significant decrease in her pancreatic mass and liver metastases. Her chromogranin A level had decreased from 5800 to 35 ng/dL. The patient then completed 6 cycles of chemotherapy and then underwent an exploratory laparotomy, lysis of adhesions, and bilateral oophorectomy with the pathology: well-differentiated NETs can be classified as G1 tumors, when they express 2-20 mitoses/10 HPF and 3-20% Ki-67, whereas, neuroendocrine carcinomas (NECs) usually belong to G3 category, with > 20 mitoses/10 HPF and > 20% Ki-67 index[2]. Our patient had Ki 67 of 40%.

She was diagnosed with widely metastatic intermediate grade NF-PNET stage IV T2N0M1 to the liver, peritoneum, bones, and gallbladder.

DISCUSSION

According to the World Health Organization (WHO) classification, three classes of NETs can be identified based on histology and pathology: well-differentiated NETs can be classified as G1 tumors, when they express < 2 mitoses/10 HPF and ≤ 2% Ki-67 index; as G2 tumors, when they express 2-20 mitoses/10 HPF and 3-20% Ki-67, whereas, neuroendocrine carcinomas (NECs) usually belong to G3 category, with > 20 mitoses/10 HPF and > 20% Ki-67 index[2]. Our patient had Ki 67 of 40%.

Potential risk factors for PNETs include diabetes, smoking, a previous history of chronic pancreatitis, and genetic factors (hereditary endocrinopathies, including multiple endocrine neoplasia.
Due to the rarity of PNETs, there aren’t many randomized controlled studies and current treatment recommendations are based primarily on case series and individual treatment approaches. Our patient’s medical course illustrates the recent evolution of systemic treatments for patients with NETs, particularly those originating in the pancreas. PNETs demonstrate an increased somatostatin receptor expression both in primary and metastatic lesions. Further research is under way on newer, investigational drugs. For example, an ongoing phase 2 study examining the effect of the tyrosine kinase inhibitor pazopanib among patients resistant to sunitinib or everolimus was discussed at ASCO 2011.

CONCLUSION

Due to the rarity of PNETs, there aren’t many randomized controlled studies and current treatment recommendations are based primarily on case series and individual treatment approaches. Our patient’s medical course illustrates the recent evolution of systemic treatments for patients with NETs, particularly those originating in the pancreas. PNETs demonstrate an increased somatostatin receptor expression both in primary and metastatic lesions. Further research is under way on newer, investigational drugs. For example, an ongoing phase 2 study examining the effect of the tyrosine kinase inhibitor pazopanib among patients resistant to sunitinib or everolimus was discussed at ASCO 2011.

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