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CASE REPORT

Rare Case of High Grade Neuroendocrine Carcinoma Found on Bone Marrow Biopsy: A Case Report

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Abstract

Background: **Neuroendocrine neoplasms (NENs) comprise a wide-ranging group of abnormal neoplasms with atypical presentations, from primary localized disease to extensive metastasis, reaching the bone and brain. The NENs are divided into two major groups: neuroendocrine tumors (NETs), which are well-differentiated tumors of any grade, and neuroendocrine carcinomas (NECs), which are poorly differentiated, high-grade cancers with a high risk of morbidity and mortality. The challenge of diagnosing NENs early, particularly prior to metastasis, highlights the importance of further studying these diseases. We present a case of aggressive metastatic neuroendocrine carcinoma of a gastrointestinal/pancreaticobiliary origin.**

Case summary: **A 54-year-old male with a past medical history of hypertension and left total hip replacement presented with generalized weakness, dyspnea on exertion, decreased appetite, and fatigue for one month. Initial laboratory findings noted a hemoglobin level of 3.1 g/dL and a platelet count of 9 $\times$ 10^9/L. CT scan findings revealed a splenic infarct, lytic bone lesions, and small bilateral occipital hemorrhages. Bone marrow biopsy was consistent with metastatic, high-grade, poorly differentiated neuroendocrine carcinoma favoring a gastrointestinal/pancreaticobiliary origin. The patient expired shortly after starting chemotherapy due to the extensive disease.**

Conclusion: **Neuroendocrine neoplasms may be discovered late in their course with distant metastatic spread and thus have a poor prognosis. This case report and literature review describes the presentation of metastatic high-grade neuroendocrine carcinoma in a patient presenting to a community hospital, and reviews the current literature and guidelines on neuroendocrine carcinomas.**

Keywords: Neuroendocrine neoplasms (NEN), Neuroendocrine tumors (NETs), Neuroendocrine carcinoma (NEC), Gastroenteropancreatic neuroendocrine tumor (GEP-NET), Case report

1. Introduction

Neuroendocrine neoplasms (NENs) are uncommon neoplasms that arise from widely dispersed specialized cells. The term "neuroendocrine" is based on two aspects of these cells: their secretory dense core granules (DCGs), similar to those in serotonergic neurons and their ability to synthesize and secrete these granules. The neuroendocrine (NE) system involves endocrine glands, mostly the pituitary, parathyroid, thyroid, adrenal medulla, and dispersed among the gastrointestinal and respiratory tracts.[1] The most recent iteration of the WHO classification for digestive system tumors divides NENs into neuroendocrine tumors (NET: well-differentiated, any grade) and neuroendocrine carcinomas (NECs: poorly differentiated, high-grade by definition) based on their molecular differences.[2,3] Historically, well-differentiated NENs are referred to as carcinoid tumors, and poorly differentiated high-grade neuroendocrine carcinomas are classified similarly to small cell lung carcinomas. The gastrointestinal tract and lungs are the most common primary tumor sites.[1] Metastases occur to the brain, lymph nodes, liver and bones.[4] Standard of care treatment involves surgery and/or

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cytotoxic chemotherapy regimens, and treatment guidelines are constantly evolving. We review a case of a patient presenting for symptomatic anemia, with bone marrow biopsy supporting the diagnosis of metastatic high-grade neuroendocrine carcinoma of a gastrointestinal origin, and present the current literature and guidelines on this disease.

2. Case report

A 54-year-old African American male with a past medical history of hypertension and left total hip arthroplasty presented to the emergency department complaining of chest pain, decreased appetite, weight loss, and fatigue. He reported one melanotic bowel movement approximately three weeks prior. He denied diarrhea, headache, shortness of breath, palpitations, flushing, nausea, vomiting, abdominal pain, hematemesis, dysuria, hematuria, skin lesions, or other symptoms. Physical examination revealed a heart rate of 101 bpm and respiratory rate of 25 breaths per minute. The patient was alert and oriented with no neurological deficits and did not appear cachectic. The remainder of the examination revealed scleral icterus and no heart murmurs or wheezing. Bowel sounds were normoactive, no abdominal tenderness was elicited, and no palpable mass or organomegaly was appreciated. Digital rectal examination revealed no hemorrhoids, masses, or frank blood. Petechiae were visible on the skin, without ecchymosis or bruising, and extremities were thin and without edema; fecal occult blood was positive.

Initial laboratory studies revealed hemoglobin 3.1 g/dL, platelets 9×10^9/L, creatinine 1.5 mg/dL, AST 124 U/L, and ALT 37 U/L. Other laboratory findings included reticulocyte count 6.54%, total calcium 10.1 mmol, D-dimer >4.3 mcg/mL, fibrinogen 234.2 mg/dL, uric acid 10.4 mg/dL, CEA 62.6 ng/mL, PTH 13.9 pg/mL and LDH 2417 U/L. Examination of the peripheral smear revealed circulating blasts, leading to suspicion for acute myeloid leukemia (AML). An initial CT of the chest, abdomen, and pelvis without contrast showed diffuse interstitial markings with dependent atelectasis at the lung bases, small bilateral pleural effusions, and small right diaphragmatic lymph nodes. The liver demonstrated no focal lesions; there was mild hepatic enlargement, but contours were maintained. The spleen was noted to have a 3.5 cm ill-defined hypodensity. Per the radiologist's review, differentials included an infarct, hemangioma, or metastatic disease. A previously noted fracture in the left iliac crest was unchanged, concerning for a lytic lesion. A review of previous CT findings from approximately three weeks prior (when the patient presented for left leg pain) revealed the known left total hip arthroplasty with streak artifact in the pelvis, a fracture of the anterior aspect of the left iliac crest, and a possible associated lytic lesion, which had not been noted on left hip x-ray from that same day. Further evaluation included a CT brain without contrast which revealed small bilateral occipital hemorrhages (approximately 1.5 cm), a left basal ganglia hemorrhage, a questionable small infarct in the right frontal cortex, as well as concern for hemorrhagic metastases; there was no fluid collection, mass effect, or shift.

The patient was admitted to the intensive care unit for acute severe anemia with concern for acute myeloblastic crisis. He received pantoprazole, octreotide, and packed red blood cells. A bone marrow biopsy was scheduled but was delayed due to thrombocytopenia and the patient's critical condition. Oncology recommended transferring the patient to a tertiary cancer center to initiate treatment; however, the patient was too unstable. He was started on allopurinol for elevated uric acid to protect against tumor lysis syndrome. Although the CT findings warranted further evaluation via MRI, the patient had had a metal pellet in his head which prohibited MRI studies. A repeat CT chest, abdomen, and pelvis revealed multiple lytic lesions in the left clavicle, with possible fracture, as well as in the sacrum and ilium (Fig. 1). The bone marrow biopsy was completed on the fourth day of hospitalization. The immunohistochemistry (Fig. 2 and Table 2) was positive for synaptophysin, pancytokeratin, patchy chromogranin, CDX2, and villin, the combination of which supported the diagnosis of metastatic, high-grade, poorly differentiated neuroendocrine carcinoma (NEC) favoring a gastrointestinal pancreaticobiliary origin, invading the majority of the bone marrow.

On the tenth day of hospitalization, the patient started the first course of chemotherapy with reduced dose carboplatin and etoposide, along with rasburicase for prevention of tumor lysis syndrome, and dexamethasone. He received three days of carboplatin and etoposide. The patient continued to have hemoglobin levels in the 7–9 g/dL range during the hospitalization and required numerous blood and platelet transfusions; the persistently low hemoglobin was attributed to bone marrow infiltration and bleeding due to thrombocytopenia. His clinical condition deteriorated during the hospitalization; four weeks after admission the patient required mechanical ventilation as well as emergent hemodialysis for worsening renal function. He

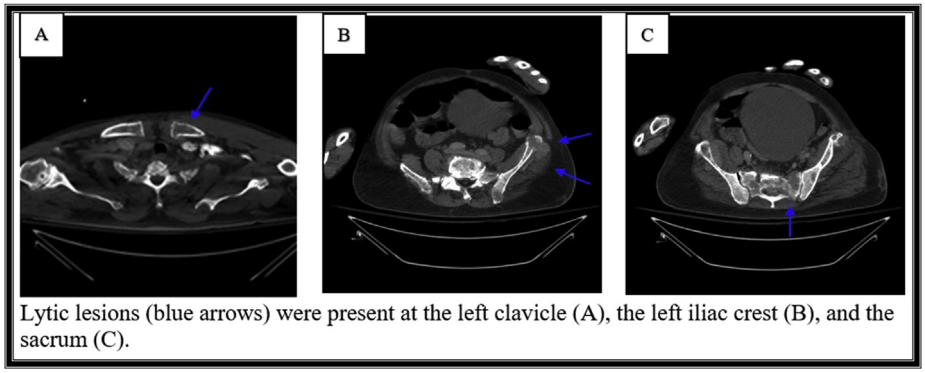

Fig. 1. Computed tomography of the chest, abdomen, and pelvis.

subsequently expired on the thirty-eighth hospital day.

3. Discussion

NENs encompass approximately 0.5% of all newly diagnosed malignancies, and account for less than 200,000 cases in the United States. The incidence of NENs has been growing consistently, likely due to improved recognition of the disease.[1,5] The most common primary sites for NENs are the gastrointestinal tract and lungs, with approximately 62%–67% and 22%–27% of cases, respectively. Within the GI tract, these neoplasms can be found in the small intestine, rectum, colon, pancreas, and appendix. Females are more prone to NENs of the stomach, appendix, or cecum, while males are more likely to be diagnosed with NENS of the jejunum/ileum, duodenum, and rectum.[5] Metastatic disease rates range from 12% to 73%, with some studies showing 40%–50% of patients with NENs found with distant metastases on diagnosis.[1,4] NENs often appear sporadically, but there is an association with multiple endocrine neoplasia type 1 syndrome (MEN1), and familial clustering has been detected. Although alcohol and tobacco use are risk factors for a multitude of neoplasms, there does not seem to an association in NENs. In this report we focus on NENs of a gastroenteropancreatic origin.

Due to the variability in presentations and other factors associated with NENs, it has been notoriously difficult to classify them taxonomically. The 2019 WHO classification criteria of NETs incorporate differentiation, grade, mitotic rate, and the Ki-67 index (Table 1). The grading system recognizes two classes: well- and poorly-differentiated neoplasms, or NETs and NECs, respectively. NETs are further classified into G1, G2 and G3; NECs are poorly differentiated and high grade by definition, they are no longer graded, but rather classified into large and small cell types.[2]

Immunohistochemistry is an important tool in the diagnosis of cancers, with biopsy and staining being the gold standard. Well-differentiated NET cells can be recognized by large quantities of secretory granules with intense immunoexpression of neuroendocrine markers such as chromogranin A (CgA) and synaptophysin (Syn); in contrast, NECs can be identified by the solid "sheet-like" proliferation of cells with irregular nuclei, fewer cytoplasmic granules, and many mitotic features, as seen on the bone marrow biopsy obtained from the patient presented in this case. Immunohistochemical staining of NECs will, contrary to the NETS, reveal a diffuse expression of Syn and indistinct staining of CgA.[1] The bone marrow biopsy shows the intense, compact, immature cells seen under the H&E stain in 100x and 400x in box A and B, respectively of Fig. 2. Box C reveals positive staining for chromogranin, a sensitive marker for neuroendocrine tumors. Box D indicates the positive staining for synaptophysin, which as mentioned, is associated with secretory granules typical of neuroendocrine cells. Furthermore, staining for CDX2, as seen in Box E, is positive, supporting a GI source of the neoplasm. The staining in Box F represents pancytokeratin staining, which provides further evidence of a neuroendocrine origin for these cells found in the bone marrow. Finally, Box G exemplifies the high mitotic index and high cellular proliferation indicated by staining for Ki-67, which in this patient was evaluated to be upwards of 90%, indicating a highly mitotically active and likely aggressive tumor.[1]

The pathogenesis and clinical manifestation of the NENs are associated with the functionality of the tumor, as well as any pathology that occurs due to growth or metastasis of the disease, such as

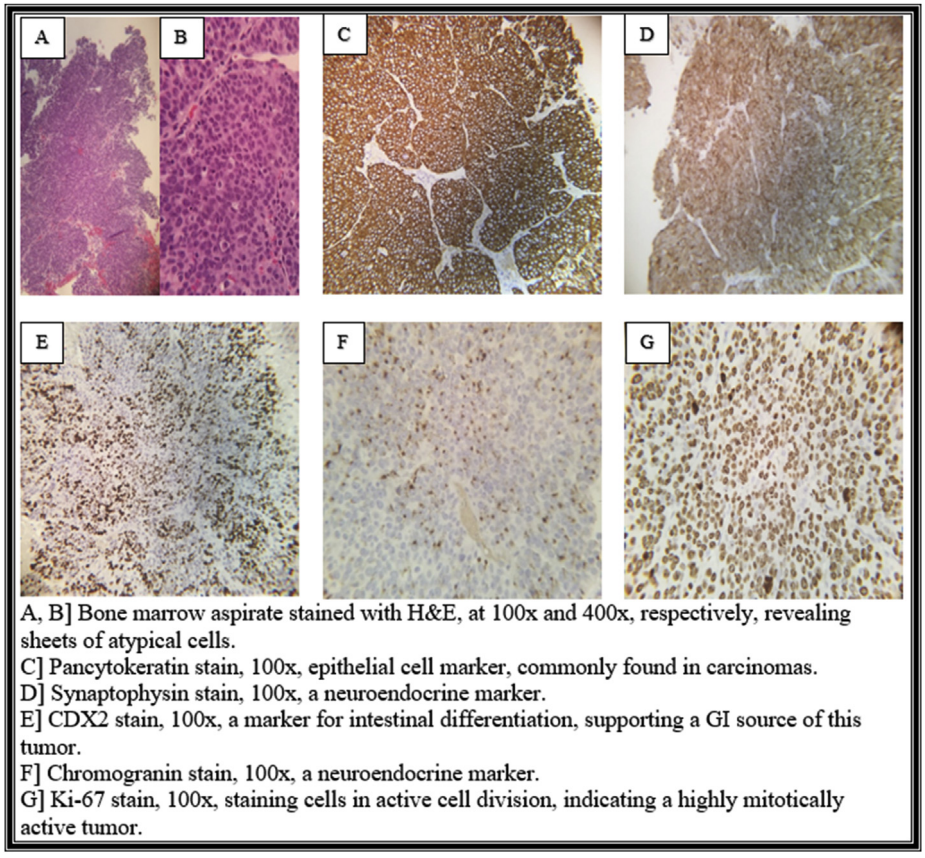

Fig. 2. Immunohistochemistry of bone marrow aspirate.

increased vasculature or impingement of neurovascular structures.[6] While less than half (40%) of NETs are hormone producing, clinical signs and symptoms may be attributed to the type of hormones that are produced by the tumors. Thus, patients with gastroenteropancreatic tumors may present with abdominal pain, nausea, vomiting, weight loss and early satiety. Classic symptoms of carcinoid tumor will reveal physical examination findings of flushed skin, tachycardia, heart murmur or wheezing. Other specific hormone producing NENs such as insulinomas, gastrinomas, glucagonomas, VIPomas, and somatostatinomas produce their respective hormone and related symptoms. Additionally, there is activation of proangiogenic factors and fibroblasts, leading to the vascularity and metastatic qualities of NETs. NECs on the other hand are so poorly differentiated that they are unlikely to cause hormone-related symptoms. In the setting of bone marrow metastasis, as in the patient in the vignette, anemia and bleeding may be presenting signs.

Similar to the clinical signs and symptoms, laboratory evaluation of blood counts and electrolytes will often coincide with the functionality of the offending tumor. Other laboratory findings include elevated urinary 5-hydroxyindole acetic acid (5-HIAA) levels, supporting carcinoid syndrome. In the

Table 1. Adapted from the WHO 2019 guidelines on grading of NENs. NET, Neuroendocrine tumor; NEC, Neuroendocrine carcinoma; SCNEC, Small-cell neuroendocrine carcinoma; LCNEC, Large-cell neuroendocrine carcinoma.

Terminology	Differentiation	Grade	Mitotic rate	Ki-67 index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2−20	3−20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%

Table 2. Summary of immunohistochemical findings.

Immunohistochemistry markers	Results
Pancytokeratin	Positive
CD56	Negative
Synaptophysin	Positive
Chromogranin	Patchy positivity
Thyroid transcription factor-1	Negative
Ki-67	90%
CDX-2	Positive
Villin	Positive

case of metastatic disease to the liver, an elevation in liver function tests may be observed. As found in our patient presenting to our community hospital, symptomatic anemia may have been due to blood loss via GI tract, hemolysis, as evidenced by the elevated LDH, or poor production, whether of red blood cells or platelets, which would be a plausible explanation given the bone marrow metastases.[7] Bone marrow infiltration may result in pancytopenia as well as hypercalcemia, as evidenced in our patient. Of note, it has been suggested that hypercalcemia is a rare finding in bone metastases secondary to NETs, with only 4% of cases being reported; hypercalcemia is more commonly associated with pheochromocytomas or sympathetic paragangliomas, compared to gastropancreatic carcinomas.[8] Another study revealed that 44–73% of patients with NETs present with metastatic disease, and bone involvement is likely underestimated and oftentimes found post-mortem.[9]

Treatment of NETs involves surgery and/or cytotoxic chemotherapy regimens. Patients may benefit from radiotherapy. Poorly differentiated NECs require multimodal approaches similar to small cell lung cancer management. Surgical resection is highly suggested for localized tumors. Somatostatin analogues such as octreotide and lanreotide affect somatostatin receptors and have been shown to decrease the tumor growth with antisecretory and antitumor growth efficacy; however, these are mostly for symptom control and do not affect outcomes.[5,9,10] Everolimus or peptide receptor radionuclide therapy (PRRT) with lutetium-177 dotatate (177 Lu-DOTATATE) has been approved for advanced GEP-NETs. Everolimus is effective on a wide spectrum of NENs, and the antiangiogenic agent sunitinib has been approved for pancreatic NENs. Multiple retrospective studies have reported the efficacy of liver-directed therapies both for palliating symptoms of hormone excess and for controlling tumor growth. Our patient received dose adjusted carboplatin and etoposide, options for patients with unresectable and metastatic disease.[5,9]

Our patient received allopurinol due to the elevated uric acid level and the concern for tumor lysis syndrome. When chemotherapy was initiated, a single 7.5 mg infusion of rasburicase was administered. Rasburicase was added because he was considered at high risk for tumor lysis syndrome due to the high-grade neuroendocrine carcinoma. The FDA recommends that high-risk patients (such as patients of African descent) be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting rasburicase as the medication is known to cause hemolytic anemia in high-risk populations; however, our patient was not screened.[11] As mentioned earlier, his consistently low hemoglobin levels during the hospitalization were attributed to bone marrow infiltration and bleeding due to thrombocytopenia.

4. Conclusion

Neuroendocrine neoplasms have the potential to quickly metastasize therefore a timely diagnosis is imperative to survival. Clinicians should suspect this malignancy in patients presenting with anemia or pancytopenia.

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Conflict of interest

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