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CASE REPORT

Bone Marrow Metastasis from a Pancreatic Neuroendocrine Tumor: Morphologic Mimicry of Acute Leukemia

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SUMMARY

Background: **Pancreatic neuroendocrine tumors (pNETs), rare neoplasms originating from pancreatic islet cells, have limited morphological descriptions in smears following bone marrow metastasis.**
Methods: **This study reports a rare case of pancreatic neuroendocrine tumor (pNET) with bone marrow metastasis, comprehensively evaluated through an integrated diagnostic approach encompassing clinical assessment, bone marrow aspiration with morphologic analysis, flow cytometry, cross-sectional imaging, and lymph node biopsy.**
Results: **Bone marrow smears revealed scattered blast-like cells with fine chromatin and granular cytoplasm, mimicking acute myeloid leukemia, but these cells were negative for myeloperoxidase. Flow cytometry identified CD45-/CD56+ cell population lacking hematopoietic markers. Imaging identified a pancreatic mass with widespread bone destruction, and lymph node biopsy confirmed metastatic pNET via positive staining for chromogranin A and synaptophysin.**
Conclusions: **This case highlights the diagnostic challenges posed by pNET bone marrow involvement and emphasizes the importance of integrating morphology, immunophenotyping, and clinical data to avoid misdiagnosis and ensure timely, appropriate treatment.**
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KEYWORDS

pancreatic neuroendocrine tumor, bone marrow metastasis, acute leukemia, bone marrow smear, flow cytometry

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are rare neoplasms originating from the islet cells of the pancreas, and exhibit unique biological behavior. Although pNETs account for only 1% - 2% of all pancreatic tumors, their incidence has been increasing [1]. Generally, pNETs are considered biologically indolent; however, distant metastases can occur at an early stage and are closely associated with poor prognosis [2].
Bone metastasis in neuroendocrine tumors (NETs) has traditionally been considered a rare event with limited clinical significance. This view stems from its usual appearance after liver metastasis and in later disease

stages. However, improvements in imaging and longer patient survival have increased the detection rate of bone metastases [3]. Currently, bone ranks as the third most common metastatic site in NETs, following the liver and other intra-abdominal organs [4]. Despite this, reports detailing the cytomorphological features of bone marrow involvement - a specific form of bone metastasis - in pNETs remain scarce. Here, we present a rare case of pNET with bone marrow metastasis and describe the distinctive morphological features of the metastatic cells to aid valuable morphological references for clinical laboratory.

CASE PRESENTATION

A 66-year-old man was admitted with a six-month history of persistent lower back and leg pain, which had significantly worsened over the previous four days. On physical examination, a firm, enlarged lymph node measuring approximately 2 x 2 cm was palpated in the right supraclavicular fossa. No lymphadenopathy was detected in the axillary or inguinal regions, and neither the liver nor the spleen was palpable. Chest CT revealed multiple enlarged lymph nodes in the mediastinum, along with low-density lesions in the thoracic vertebrae and bilateral ribs, suggestive of bone destruction.

Laboratory tests showed a white blood cell count of 4.41 x 10^9/L, hemoglobin level of 67 g/L, and platelet count of 70 x 10^9/L. Coagulation studies revealed a partial thromboplastin time of 20.50 seconds, fibrinogen level of 1.97 g/L, and D-dimer level of 0.64 mg/L. In the bone marrow smear, approximately 82% of the blasts were detected, with the majority scattered. These blasts were mostly round or nearly round, with fine chromatin, prominent nucleoli, and abundant cytoplasm containing fine pink granules (Figure 1A - 1B). Notably, some blasts displayed a bilayered cytoplasm, with a pale pink inner layer and a light blue outer layer. Occasional clusters of blasts were also observed (Figure 1C). Despite their morphological resemblance to myeloid blasts, no blasts were detected in the peripheral blood, and myeloperoxidase (MPO) staining was negative (Figure 1D) - findings inconsistent with acute myeloid leukemia (AML). Flow cytometry of the bone marrow aspirate was subsequently performed, revealing a distinct population of CD45-negative abnormal cells, accounting for 45.37% of the nucleated cells. These cells exhibited the following immunophenotype (Figure 2): CD45 (-), CD56 (+), CD15 (-), CD38 (-), CD138 (-), CD117 (-), CD34 (-), CD13 (-), CD33 (-), HLA-DR (-), and CD81 (+).

To further determine the origin of these abnormal cells, contrast-enhanced CT and a lymph node biopsy were performed with the patient's informed consent. The CT scan revealed a mass in the pancreatic head, atrophy of the pancreatic body and tail, and dilation of the pancreatic duct. Multiple hypodense lesions were also identified in the thoracic, lumbar, and sacral vertebrae, as well as the ribs and pelvic bone marrow, indicating widespread bone destruction. A lymph node biopsy conducted at an external institution confirmed the presence of a small cell malignant tumor. Immunohistochemical staining showed the tumor cells were positive for CK (pan), chromogranin A (CgA), synaptophysin (Syn), β-catenin, and CD56, while negative for CD20, CD38, CD138, Kappa, Lambda, Bob1, Pax5, CD10, and vimentin. The Ki-67 proliferation index was approximately 15%. Based on these findings, the patient was diagnosed with a pNET with widespread metastases, including bone marrow involvement.

Given the widespread metastasis, the patient began treatment with a combination of bevacizumab and the SOX regimen (oxaliplatin mannitol plus oral tegafur, gimeracil, and oteracil potassium). During follow-up, a marked elevation in neuron-specific enolase (NSE) levels was observed, and the patient reported worsening neck pain, indicating disease progression. The treatment regimen was subsequently switched to IC (carboplatin plus irinotecan). However, the patient's platelet and hemoglobin levels remained persistently low, necessitating close monitoring and continued supportive care.

DISCUSSION

Timely diagnosis of bone marrow metastasis is crucial, as it plays a vital role in tumor staging, therapeutic decision-making, and prognostic assessment. Despite challenges such as dry taps or hemodilution, bone marrow smear remains an essential method for detecting metastatic carcinoma involving the bone marrow. In bone marrow smears, metastatic cancer cells typically display certain distinctive morphological characteristics: they are usually found in clusters or cohesive groups at the tail or edge of the smear, with indistinct cytoplasmic borders due to cellular fusion. Scattered malignant cells can also be seen. Therefore, both hematopathologists and AI-based diagnostic systems often rely on identifying atypical cell clusters as a key marker of marrow metastasis [5]. However, the patient in this study was diagnosed with pancreatic neuroendocrine carcinoma, and the metastatic tumor cells found in the bone marrow displayed distinctive morphological features compared to other metastatic cancers. In the bone marrow smear, most of the tumor cells were scattered. The nuclei had fine chromatin, and the cytoplasm was abundant with numerous purplish-red granules. Although the tumor cells resembled myeloid precursors morphologically, they were negative for myeloperoxidase (MPO) staining, and no blasts were detected in the peripheral blood. These findings were inconsistent with AML, indicating that the bone marrow involvement was likely due to a non-hematologic malignancy.

Flow cytometric analysis further identified a population of CD45-negative aberrant cells in the bone marrow, which were clearly distinct from typical acute leukemia cells. CD45 is a common leukocyte antigen that is usu-

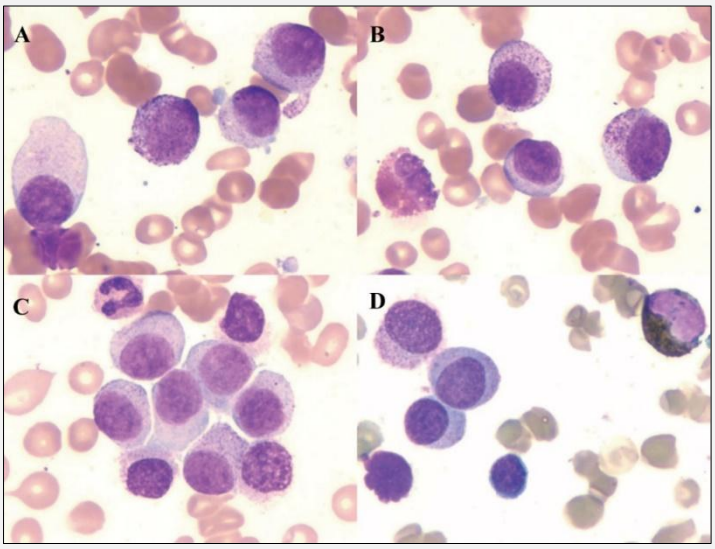

Figure 1. Bone marrow smear. A and B - Most blasts are round or nearly round in shape, with fine chromatin, prominent nucleoli, and cytoplasm containing fine granules, C - occasional clusters of blasts are observed (Wright-Giemsa xstain, 1,000 x). D - Myeloperoxidase (MPO) staining demonstrates a negative result of these cells (1,000 x).

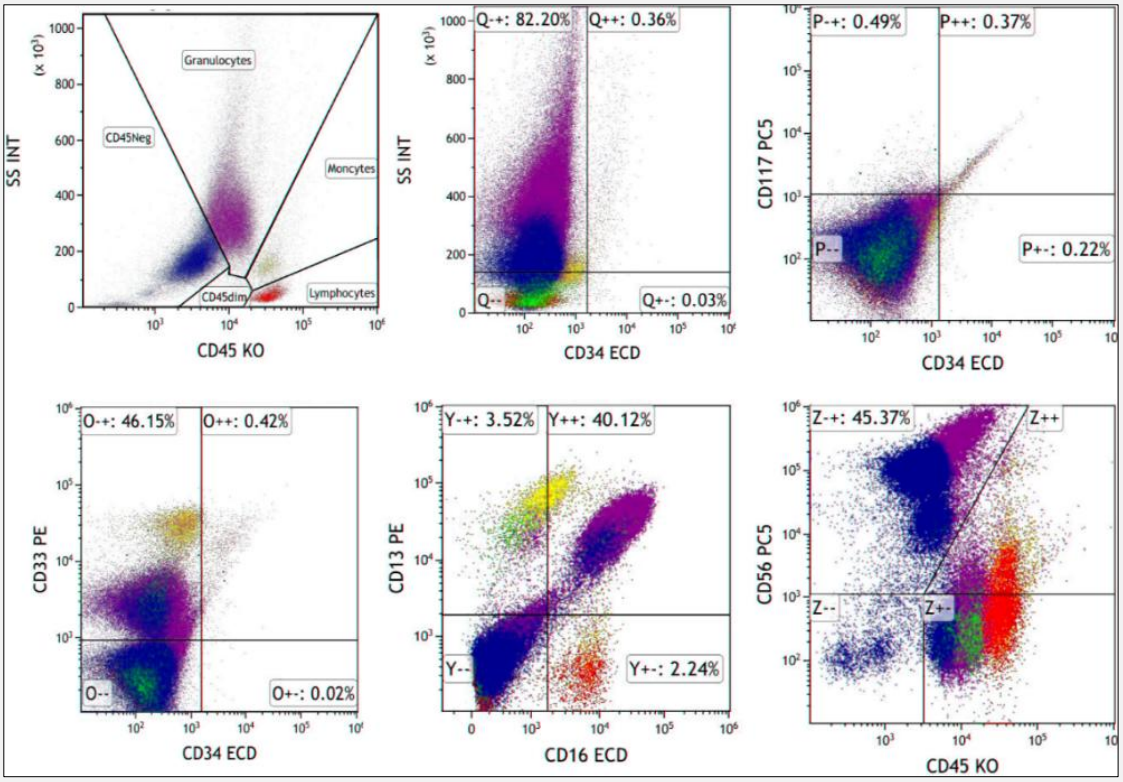

Figure 2. Flow cytometry of the bone marrow aspirate. A separate group of abnormal cells was detected, which showed an immunophenotype of CD45 - /CD56 +. Moreover, these cells were negative for CD34, CD33, CD117, CD13, and CD16.

ally expressed in acute leukemias, and its absence in this case strongly indicated a non-hematopoietic origin. In addition, these cells lacked expression of several myeloid markers, including CD13, CD33, CD117, CD34, and HLA-DR, effectively ruling out the AML. CD56, a neural cell adhesion molecule involved in cell-to-cell adhesion, neural development, migration, and tissue differentiation, is typically expressed on natural killer cells and neuroendocrine cells [6]. Although CD56 expression can be observed in certain subtypes of AML, its presence is more indicative of a neuroendocrine origin when other common myeloid and lymphoid markers are absent [7,8]. The flow cytometric finding further supported the diagnosis of bone marrow metastasis.

Histopathological examination of the lymph node confirmed the findings. The tumor cells were positive for pan-cytokeratin and negative for vimentin, indicating an epithelial origin. Strong positivity for CgA and Syn, neuroendocrine markers, further confirmed the neuroendocrine nature of the tumor [2]. The Ki-67 index was approximately 15%, classifying the tumor as grade G2 according to WHO criteria (Ki-67 index 3 - 20%). While G2 tumors typically have a better prognosis than G3 tumors (Ki-67 > 20%), bone marrow metastasis remains a poor prognostic factor in pancreatic cancer, regardless of differentiation grade [9]. Additionally, β-catenin positivity suggested activation of the Wnt/β-catenin signaling pathway, which is associated with increased invasiveness and metastatic potential, indicating a poor prognosis [10].

Although metastatic carcinoma cells in bone marrow smears are generally distinguishable from hematopoietic cells, misdiagnosis may occur in cases where malignancy is not initially suspected. Furthermore, metastatic carcinoma cells exhibit significant morphological heterogeneity, with variations depending on the tumor's origin. Thus, familiarity with the characteristic morphological features of metastatic carcinoma is helpful for accurate differential diagnosis and identification of the tumor's source. A review of the literature highlights several malignancies whose bone marrow metastases can mimic leukemia. For instance, small cell lung carcinoma can present with bone marrow infiltration patterns similar to those seen in Burkitt lymphoma or leukemia [11]. Notably, the presence of paranuclear blue inclusions in small cell lung carcinoma can assist in differentiating it from leukemia [12]. The morphology of metastatic glioblastoma cells may resemble the AML [13]. Additionally, metastatic melanoma can not only mimic AML morphologically but may also show nonspecific α-naphthyl acetate esterase staining, akin to that observed in acute monoblastic leukemia [14]. In patients with a history of breast cancer, the appearance of blast-like cells in peripheral blood should raise suspicion for both therapy-related leukemia and metastatic disease, necessitating a thorough evaluation incorporating clinical history, morphology, and immunophenotypic analysis [15].

In conclusion, this study reports a rare case of pancreatic neuroendocrine tumor (pNET) with bone marrow metastasis, exhibiting distinctive cytomorphological features that closely mimic acute myeloid leukemia. This case underscores the critical importance of integrating bone marrow morphological assessment with immunophenotypic analysis for the accurate diagnosis of metastatic solid tumors. Importantly, it also provides valuable morphological insights that may assist in recognizing bone marrow involvement by pNETs in clinical laboratory practice.

Patient and Other Consents:

This work has acquired the informed consent of the patient.

Declaration of Interest:

No conflicts of interest declared.

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