

# A case report of a poorly differentiated neuroendocrine carcinoma diagnosed in the bone marrow

## Abstract

Poorly differentiated neuroendocrine tumors are uncommon tumors of the GI tract and often diagnosed without the identification of the primary site. Here, we describe a case of poorly differentiated neuroendocrine carcinoma of unknown primary that is diagnosed by bone marrow biopsy. A 68-year-old male patient presented with worsening back pain, hypercalcemia, anemia, and altered mental status. Initially, imaging favored multiple myeloma. However, a bone marrow biopsy revealed morphologic and immunohistochemical features of neuroendocrine origin.

**Keywords:** neuroendocrine tumor, poorly differentiated, bone marrow metastasis, carboplatin, etoposide

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## Introduction

Neuroendocrine tumors are relatively rare tumors with an incidence of 5.25 per 100,000 per year in the United States.<sup>1</sup> They range from well differentiated slow growing tumors to highly aggressive poorly differentiated tumors.<sup>2</sup> The common primary sites of neuroendocrine carcinomas are lung and gastrointestinal tract. However, 3-5 % of these tumors are diagnosed as metastatic disease with unknown primary.<sup>3</sup> Bone marrow involvement by extra-pulmonary neuroendocrine malignancies has been rarely reported.<sup>3</sup> Here, we report a case of an aggressive high-grade metastatic neuroendocrine carcinoma to the bone marrow with unclear primary site.

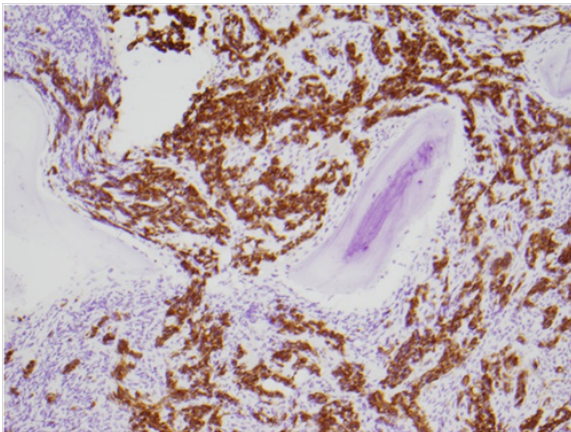
## Case presentation

This is a case of a 68-year-old male with a past medical history of seizures, hyperlipidemia, and right cerebral vascular accident in 2009 with residual left sided visual field deficits. Ten months before presentation, the patient had a CT scan of the abdomen for recurrent epigastric pain which showed mesenteric lymphadenopathy. This was followed by imaging of the chest which showed scattered, centrally located, bilateral solid pulmonary nodules which measured less than 4mm. Biopsy of retroperitoneal lymph nodes at that time showed no evidence of malignancy. Subsequently, he presented to the emergency department with a several week history of worsening back pain and altered mental status. Initial blood work showed evidence of pre-renal acute kidney injury and hypercalcemia, serum calcium 15.7mg/dL (normal 8.5-10.5mg/dL). Hemoglobin at presentation was 10.8g/dL (normal 14.0-18.0g/dl). White blood cell count of 21.82k/uL (normal 4.0-11.0k/uL). Platelet count was 148 k/uL (normal 150.0-450.0k/uL) and creatinine of 1.4mg/dL (normal 0.7-1.3mg/dL). After volume resuscitation calcium returned to baseline of 8.8mg/dL and creatinine returned to baseline of 0.7mg/dL. MRI of the thoracic and lumbar spine showed a diffusely low vertebral body marrow signal concerning for myelodysplastic process. CT scan of the chest, abdomen and pelvis showed multiple lytic lesions involving the thoracic vertebrae, scapulae and ribs concerning for multiple myeloma (Figure 1). The patient had a bone scan which was negative. Bone marrow biopsy

was performed and showed high-grade metastatic neuroendocrine tumor. Immunohistochemical staining for synaptophysin, CD56, and cytokeratin was positive within the tumor cells (Figure 2). In addition, chromogranin was weakly positive within a subset of tumor cells. Tumor cells were strongly positive for thyroid transcription factor-1 (TTF-1). Flow cytometry showed no significant plasma cell population and no evidence of B-cell clonality. The patient was treated with Carboplatin (AUC 4), which was escalated to AUC of 5 during the second cycle, and Etoposide (80mg/m<sup>2</sup>). He also suffered from severe weakness requiring nursing home placement. Repeat imaging after 3 cycles of chemotherapy showed progressive disease with a new lesion in the spleen (1cm) and progression of compression deformities of T8 and T12 as well as a new right anterior 6th rib fracture. Goals of care were discussed and comfort care measures were initiated. By the time of submitting this article, 4months after the diagnosis was made, the patient remains alive and receiving palliative care.



**Figure 1** CT chest of the abdomen and pelvis showing vertebral lytic lesions.



**Figure 2** Marrow infiltrate of metastatic carcinoma with keratin positivity which typically indicates an epithelial tumor and excludes hematopoietic tumors.

## Discussion

Our patient presented with anemia and thrombocytopenia on admission most likely related to extensive bone marrow involvement. The diagnosis was established by the characteristic morphology and immunochemical staining for neuroendocrine markers. However, we were unable to identify the primary source. Extensive imaging revealed no mass lesions except small indeterminate nodules in the lungs. It is unlikely to have been of pulmonary origin as the nodules were very small and scattered. Retroperitoneal lymph nodes were biopsied and did not reveal any evidence of malignancy and a gastrointestinal primary was undetected on CT scan.

Poorly differentiated neuroendocrine carcinomas of unknown primary are rapidly growing and aggressive tumors with diverse features and behavior. They include atypical carcinoids, small cell carcinomas and poorly-differentiated large cell neuroendocrine carcinomas. Still, it cannot be identified if these tumors arise from an occult primary gastrointestinal or pulmonary site or even from multipotent stem cells.<sup>4</sup> These tumors can arise from many different sites, including head and neck, esophagus, thymus, cervix, bladder, and prostate. However, rarely do these tumors involve the bone marrow.<sup>5</sup> Interestingly, while small cell and large cell neuroendocrine tumors share the same genetic changes, they are distinct from those reported in well differentiated neuroendocrine tumors.<sup>6</sup>

Poorly differentiated neuroendocrine tumors show sensitivity to platinum and etoposide regimens, but overall their prognosis remains poor.<sup>7</sup> A phase II trial investigated the activity of combination chemotherapy with paclitaxel, carboplatin, and etoposide in patients with poorly differentiated or small cell neuroendocrine carcinoma of unknown primary site. This trial reported 46% response rate and 2-year overall survival of 38%.<sup>4</sup> Another regimen that has been used recently and found to be effective is the combination of capecitabine and temozolomide.<sup>8</sup> The study enrolled 38 patients with various neuroendocrine cancer subtypes and found an overall response rate of 43%, including 11% complete responses, and 54% of patients achieved stable disease, resulting in a clinical benefit rate of 97%.<sup>8-9</sup> A larger study investigating this regimen is currently ongoing (NCT01824875).

The tumor biology of neuroendocrine carcinomas is being extensively studied. Newer agents, such as sorafenib, bevacizumab

and EGF inhibitors, are currently being tested in various clinical trials.<sup>10-13</sup> Furthermore, novel targets such as Bcl-2 deserve further investigation given the Bcl-2 over expression in poorly differentiated and particularly small cell neuroendocrine tumors. Future direction may involve novel modalities such as immunotherapy and a combination of multiple modalities in order to improve the outcome in this disease.<sup>14</sup>

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## Conflicts of interest

Author declares there are no conflicts of interest.

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