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Case Series

Oncology Section

Neuroendocrine Carcinoma with Bone Marrow Metastasis: A Case Series

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ABSTRACT

Neuroendocrine Neoplasms (NENs) account for 0.5% of all malignancies. Skeletal colonisation is often regarded as a rare event, and metastasis to the bone marrow occurs in the advanced stage of the disease, carrying a poor prognosis. In this report, the authors present three rare cases of Neuroendocrine Carcinomas (NEC) of the lung, diagnosed among 6766 bone marrow aspirations and biopsies performed at our institution between January 2019 and December 2022, highlighting the rarity of these cases. All three cases (63 years, 56 years and 73 years old male patients) presented to our institute at an advanced stage of the disease, with bone marrow involvement at the time of presentation. They exhibited nonspecific symptoms and had normal haematological parameters. Bone marrow aspiration and biopsy confirmed metastatic NEC. The aim of this case series was to investigate bone marrow involvement in NECs, along with their clinical and radiographic features, treatment, and follow-up. Bone marrow biopsy plays a crucial role not only in diagnosing haematological diseases but also in diagnosing and staging solid tumours. Future prospectives include adopting a multimodal approach for early diagnosis and treatment of NECs.

Keywords: Aspirations, Biopsy, Neuroendocrine carcinomas, Skeletal colonisation

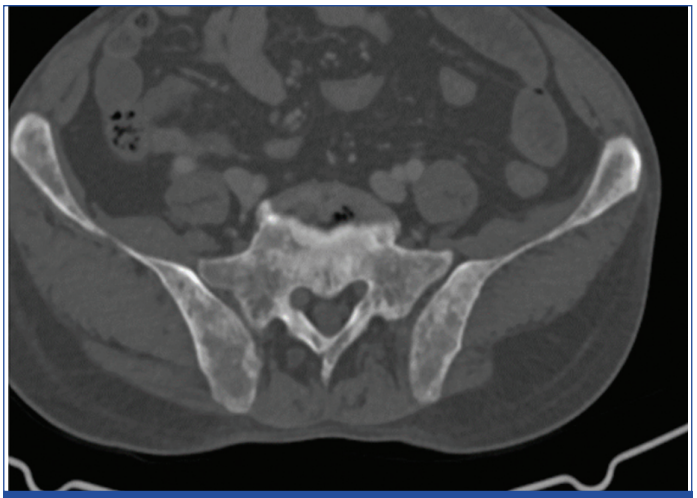
INTRODUCTION

NENs are heterogeneous tumours that arise in the secretory cells of the diffuse neuroendocrine system. These tumours are uncommon, with an incidence of 5.25 per 100,000 per year in the United States [1,2]. The term NENs encompasses well-differentiated Neuroendocrine Tumours (NETs) and poorly differentiated NECs [3]. NECs represent only 10% to 20% of all NENs. The most common site of metastasis in NENs is the liver (40%-93%), followed by the bone (12%-20%) and lungs (10.8%) [4]. Metastatic NENs in the bone marrow are extremely rare, and most reported cases are NECs [5,6]. Skeletal colonisation is often considered a rare event in patients with NETs; however, the incidence of bone metastases is as high as 20% in subjects with advanced disease. Bone marrow involvement is commonly seen in hematopoietic disorders and, rarely, solid tumours can also involve the bone marrow through hematogenous spread [1,7]. The involvement of the bone marrow by a solid tumour is important for accurate staging, prognostication, and treatment [5]. The clinical aggressiveness of NETs varies depending on the primary site as well as the tumour grading [1]. In this series, the authors report three cases of NECs with bone marrow metastasis, along with an analysis of laboratory investigations, clinical and radiographic features, and treatment.

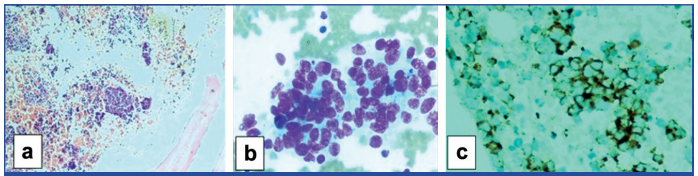
CASE SERIES

Case 1

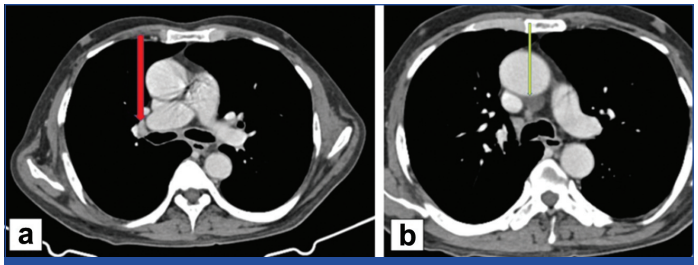
A 63-year-old male patient presented with dull aching pain in the chest and headaches for 20 days. The pain worsened during exertion and improved with rest. The patient's haemoglobin level was 17.6 g/dL (13.5-18 g/dL), the total count was 7,780/µL (4,000-11,000/µL), and the platelet count was 2,12,800/µL (150,000 to 450,000/µL). On systemic examination of the respiratory system, the patient had decreased bilateral air entry and a right basal wheeze. A 2D Echocardiography was performed, which showed mild tricuspid regurgitation and pulmonary hypertension. Bronchoscopy revealed a mass lesion in the right middle lobe of the lung. A CT scan was done, which revealed a mass lesion measuring 3.8×3.3×2.1 cm in the right lung, along with enlarged mediastinal lymph nodes suggestive of metastasis [Table/Fig-1]. Fine Needle Aspiration (FNA) was performed on subcarinal lymph nodes, showing atypical clusters of cells with high N:C ratio, scant cytoplasm in a lymphoid background, suggestive of metastatic small cell carcinoma. Bone marrow aspiration and biopsy were performed, showing atypical cells in clusters and an acinar pattern. The cells exhibited pleomorphism with vesicular nucleus and moderate cytoplasm, suggesting metastatic carcinoma [Table/Fig-2]. The patient was treated with intensity-modulated radiotherapy of 60 Gy/30 Fr, along with 6 cycles of chemotherapy using Etoposide and Carboplatin. Follow-up CT scan after three cycles of chemotherapy showed tumour regression and no new sites of metastasis [Table/Fig-3]. The



[Table/Fig-1]: CT scan showing lytic lesions of bone.



[Table/Fig-2]: Bone marrow aspiration: (a and b) 10X and 40X magnification show atypical cells in clusters and glandular pattern, vesicular nucleus and scant cytoplasm; c) IHC showed cytoplasmic positivity for chromogranin.



[Table/Fig-3]: CT Thorax: a) Post therapy shows enlarged hilar lymph nodes; and b) enlarged paratracheal lymphnodes.

patient was scheduled for three more cycles of chemotherapy but was subsequently lost to follow-up.

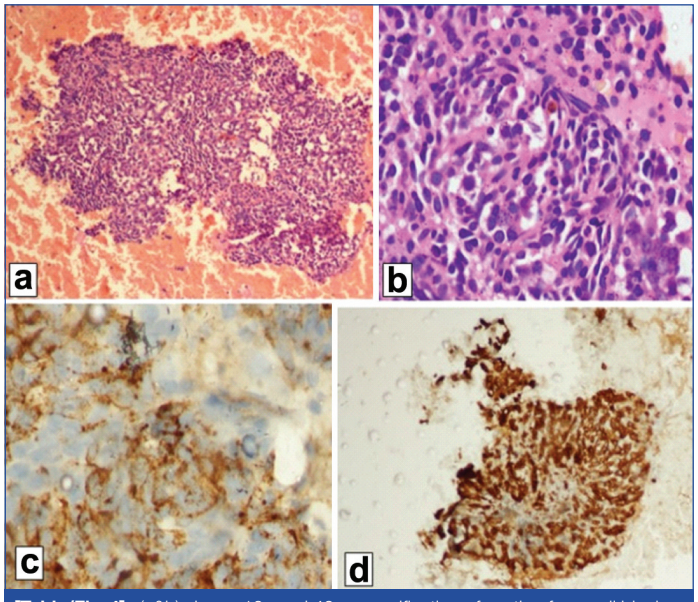
Case 2

A 56-year-old male patient presented with complaints of dull, aching abdominal pain for a duration of one month. The pain aggravated on exertion and relieved on lying down. On examination, there was no lymphadenopathy or hepatosplenomegaly. Following this, blood investigations were done, which showed a haemoglobin level of 12.1 g/dL (13.5-18 g/dL), a total white blood cell count of 13,300/µl (4,000-11,000/µL), and a platelet count of 321,000/µL (150,000-450,000/µL). Elevated serum LDH levels of 1110 U/L (140-280 U/L), CEA levels of 90.3 ng/ml (0-2.9 ng/mL), and CA 19.9 levels of 554 U/mL (<37 U/mL) were noted.

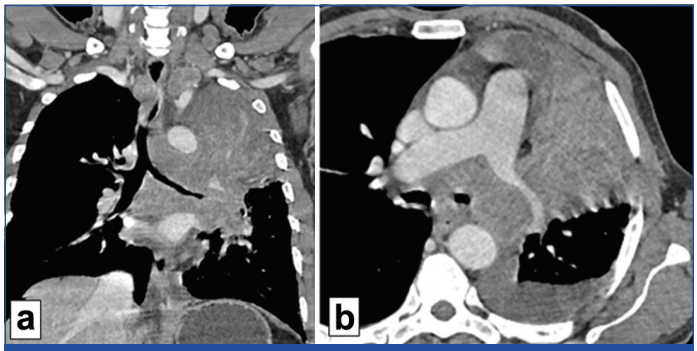
A chest X-ray showed a right hilar mass lesion, while an abdominal ultrasound revealed multiple lesions in the liver. A fine-needle aspiration and biopsy of the liver lesion were performed, which showed features of metastatic carcinoma. Immunohistochemistry was conducted and showed positivity for CK 7, Synaptophysin, and Chromogranin, while being negative for CK 20 and HepPar 1 [Table/Fig-4]. The Ki-67 proliferation index was high. A diagnosis of metastatic NEC was given due to the positive neuroendocrine markers. Bone marrow aspiration and biopsy also revealed features of metastatic carcinoma. The patient received 6 cycles of chemotherapy with Carboplatin and Etoposide and responded well. Follow-up CT scan showed regression of the tumour, but unfortunately, the patient was lost to follow-up thereafter.

Case 3

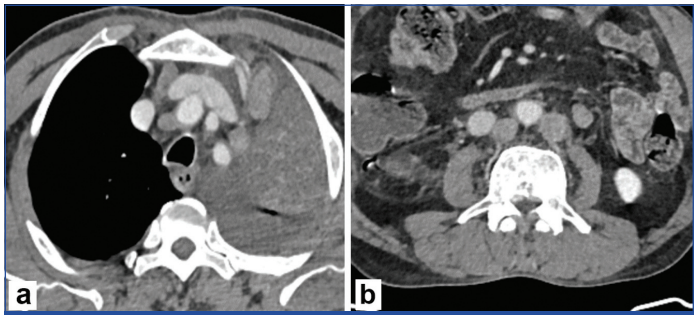
A 73-year-old male patient presented with headaches, backaches, and chest pain for three months. He had a history of hypertension for 20 years and was on beta blockers. On examination, reduced air entry and crepitations were noted in the left upper chest. Blood investigations revealed a haemoglobin level of 13.8 g/dL (13.5-18 g/dL), a total white blood cell count of 14,000/µl (4,000-11,000/µL), and a platelet count of 312,000/µL (150,000-450,000/µL). Contrast-enhanced Computed Tomography (CECT) showed collapse/consolidation of the left upper lobe and lingula. An ill-defined soft-tissue attenuation lesion was observed in the left perihilar region, causing occlusion of the left upper lobe bronchus [Table/Fig-5]. Multiple enlarged mediastinal lymph nodes were also seen [Table/Fig-6], along with bilateral adrenal metastasis [Table/Fig-7]. Additionally, multiple small hypodense lesions were identified in both lobes of the liver. Bronchoscopy revealed left vocal cord palsy and multiple nodules in the left main bronchus and left segmental bronchi. Biopsy samples were taken from the lesion, and histopathological examination showed tumour cells in clusters with hyperchromatic nuclei and scant cytoplasm, which was reported as small cell NEC. Fine-needle aspiration (FNA) was performed on a supraclavicular lymph node, which demonstrated features of metastatic small cell carcinoma. Unfortunately, the patient passed away within 10 days of admission.



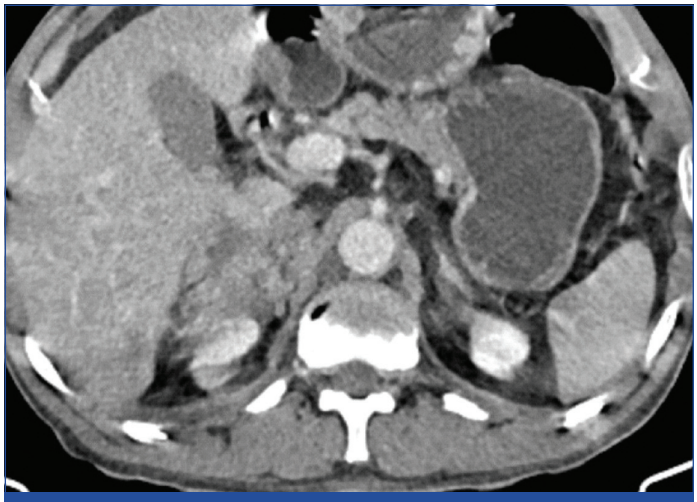
[Table/Fig-4]: (a&b) shows 10x and 40 x magnification of section from cell block of liver showing tumor cells in clusters and acinar pattern; (c&d) IHC chromogran in and synaptophys in positivity.



[Table/Fig-5]: CT Thorax showing: a) Left upper lobe lung mass with abrupt cut-off of left upper lobar bronchus; b) showing minimal left pleural effusion.



[Table/Fig-6]: CT scan showing mediastinal and retroperitoneal lymph node enlargement.



[Table/Fig-7]: CT scan showing adrenal metastasis.

	Age (years)	Gender	Chief complaints	Radio diagnosis	Histological diagnosis	Primary site	Secondary site	Treatment	Follow-up
Case 1	63	Male	Chest pain	Mass lesion in lung- ? Malignant	Metastatic small cell carcinoma- Sub carinal Lymph nodes	Lung	Lymph nodes, Bone marrow	Intensity modulated radiotherapy+6 cycles of chemotherapy	Follow-up CT scan+3 cycles of chemotherapy
Case 2	56	Male	Pain abdomen	Right hilar mass lesion- ? Malignant	Metastatic Neuroendocrine Carcinoma (NEC)- Liver	Lung	Liver, Bone marrow	6 cycles of chemotherapy	Follow-up CT scan+follow-up was lost
Case 3	73	Male	Back ache and chest pain	Left peri hilar mass lesion of lung- ? Malignant	Small cell NEC- left bronchus	Lung	Liver, lymph nodes, Adrenal glands, Bone marrow	Patient expired in 10 days following admission	-

[Table/Fig-8]: Summary of all the three cases.

DISCUSSION

NENs arise from the diffuse neuroendocrine cell system and can occur at various disease sites. NENs account for 0.5% of all malignancies [4]. The term NENs includes well-differentiated NETs and poorly differentiated NECs [8]. Most commonly, these neoplasms occur in the gastrointestinal tract. Pulmonary NETs are relatively rare, accounting for 1% to 2% of all lung cancers [1,8]. A study conducted by Nagano H et al., supports the rarity of NECs with bone involvement [5]. In the present study, the incidence of bone marrow involvement could not be ascertained as these tumours are extremely rare. Among the NECs with bone marrow involvement, the most common primary site was the lung. Despite an extensive search of the literature, the authors could not find clear information on the incidence of myelophthisic anaemia with skeletal metastasis, especially when the bone marrow is involved. All the cases discussed here in present case series, had bone marrow involvement, but no other haematological abnormalities were detected. Additionally, no skeletal-related events were observed in these cases. Studies conducted by Mehdi SR and Bhatt ML, as well as DeMarinis A et al., showed anaemia and thrombocytopenia as the most common haematological findings in their studies [3,9]. Bone marrow examination plays a crucial role in patients presenting with malignancy symptoms or pathological fractures without a clinically detectable primary site of origin [1,8]. The advent of 68Ga-PET/CT has significantly improved the ability to detect NECs with bone metastases. NETs secrete vasoactive substances, leading to carcinoid syndrome, and the tumour cells express somatostatin receptors. Chromogranin A is one of the most commonly used biochemical tests for carcinoid tumours, and an elevated chromogranin A level may predict a radiological or clinical relapse of the disease [10,11]. Specific biomarkers such as 5-hydroxyindoleacetic acid (5-HIAA), Adrenocorticotrophic Hormone (ACTH), Urinary-Free Cortisol (UFC), Growth Hormone Releasing Hormone (GHRH), and Insulin-Like Growth Factor 1 (IGF-1) are assessed depending on the presence of functioning syndromes [11]. Newer treatment options include Peptide Receptor Radionuclide Therapy (PRRT) and Radiopeptide therapy using a somatostatin analogue labelled with a beta emitter [12].

Octreotide and lanreotide are the two synthetic somatostatin analogues used to control carcinoid symptoms and tumour progression in advanced inoperable disease [12,13]. One of the largest series from India mentioned a single case of metastatic carcinoma from the lung [14]. There are a few reported series that have used flow cytometry to exclude other differential diagnoses of this entity [5]. However, the authors believe that the identification of metastatic cells in the bone marrow is easy as they appear foreign in the hematopoietic tissue. In all cases discussed here, confirmation was obtained through immunohistochemistry. The association of circulating tumour cells with bone metastases in patients with NETs has also been reported [15]. In the near future, metastatic tumour cells in the bone marrow may be detected using artificial intelligence [16]. In this study, the authors reported three cases diagnosed as NEC of the lung with bone marrow involvement. The patients were treated with the Chemotherapy-Carboplatin/Cisplatin and Etoposide regimen for six cycles. Treatment response was assessed by CT scan, and reduction in tumour size was considered a response to treatment. Unresponsive cases were treated with Paclitaxel [Table/Fig-8].

CONCLUSION(S)

Bone marrow biopsy plays an important role not only in the diagnosis of haematological diseases but also in the diagnosis and staging of solid tumours. Bone marrow metastasis occurs in the advanced stage of NECs with a poor outcome. Future prospects include a multimodal approach for the early diagnosis and treatment of NECs.

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