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Case Report

Pathology Section

Bone Marrow Metastasis as an Initial Manifestation of Gastric Carcinoma: A Rare Case Report

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ABSTRACT

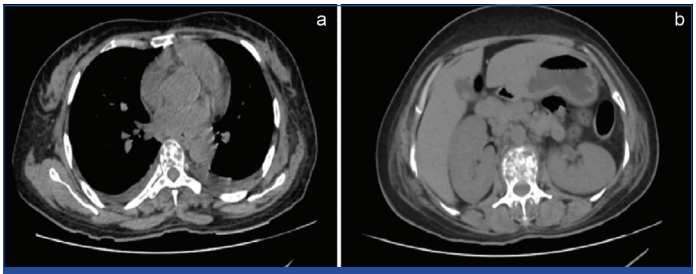
Gastric adenocarcinomas, despite being a leading contributor of cancer-related mortality, presentation directly with Bone Marrow (BM) infiltration sans prior Gastrointestinal (GI) symptoms holds sparse documentation in existing literature. Though a rare phenomenon, BM studies play a pivotal role in the presentation and management of such cases. This case report describes a 36-year-old female with worsening generalised body pain accompanied by fever. Radiologic evaluation revealed multiple lytic lucencies in the vertebral bodies and pelvic bones. A subsequent BM aspiration yielded suspicious looking cells in clusters and BM biopsy suggestive of metastatic deposits. These findings prompted a workup for unknown primary malignancy. Immunohistochemistry (IHC) on trephine BM biopsy suggested a tumour that is CK7+, CK20-, CDX2-, TTF1-, ER – and CA125-; suggesting upper GI primary. A Positron Emission Tomography-Computed Tomography (PET-CT) and upper GI endoscopy revealed a mass in the proximal part of body of stomach which showed a poorly differentiated adenocarcinoma. Thus, a final diagnosis of gastric carcinoma with bone marrow metastasis was confirmed and the patient was planned for palliative care.

Keywords: Bone marrow neoplasm, Immunohistochemistry, Stomach neoplasm

CASE REPORT

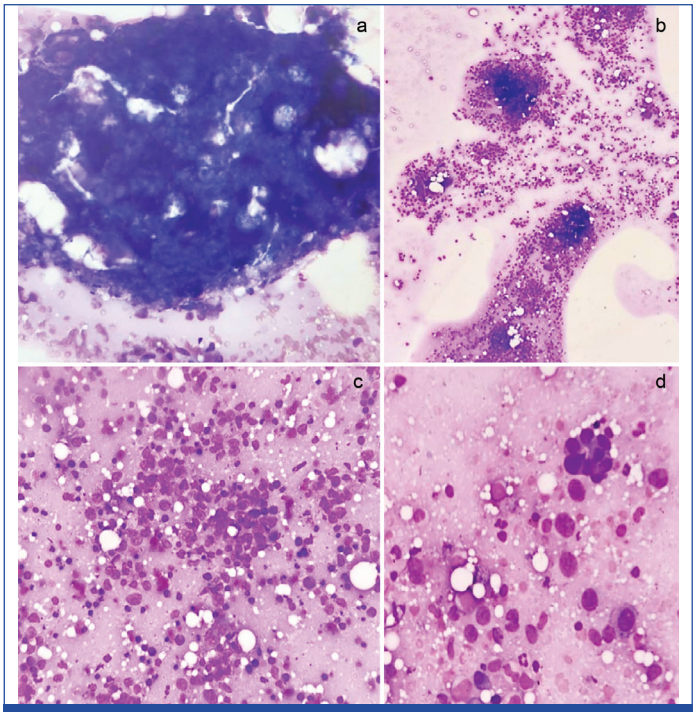
A 36-year-old female presented with worsening back pain and generalised weakness accompanied by fever, which was unresponsive to over-the-counter drugs. The patient did not have any symptoms of abdominal pain, nausea, vomiting, dyspepsia, malena or weight loss. There was no significant past history or family history. On physical examination, pallor was present but there was no icterus, clubbing, cyanosis, lymphadenopathy, organomegaly or oedema noted. Initial Complete Blood Counts (CBC) evaluation revealed a Haemoglobin (Hb) of 8.1 gm/dL (Ref:12.0-15.0 gm/dL), a Total Leucocyte Count (TLC) of 19,420 cells/cu.mm (Ref:6-16×10_3/cu.mm) and a Differential Leucocyte Count (DLC) showing neutrophilic predominance, with an Mean Corpuscular Volume (MCV) of 85.1 fl (Ref:83-101 fl), and a platelet count of 1,32,000/cu.mm (Ref:1,50,000-4,00,000/cu.mm) The peripheral smear revealed normocytic normochromic anaemia with neutrophilic leucocytosis. Her biochemical investigations revealed raised serum urea (66.2 mg/dL; Ref: 12-42 mg/dL) and serum calcium (12.5 mg/dL; Ref: 8.6-10.3 mg/dL). The creatinine value was 1.25 mg/dL (Ref: 0.7-1.3 mg/dL) and the Liver Function Tests (LFT) were significant for Alkaline Phosphatase (ALP) of 349 U/L (Ref: 40-129 U/L) and serum albumin was decreased to 2.26 gm/dL (Ref: 3.5-5 gm/dL). The C-Reactive Protein (CRP) was found to be elevated to 283.9 mg/L (Ref: <5 mg/L). On radiology the patient was found to have lytic lucencies in the vertebral bodies and pelvic bones on Non-Contrast Computed Tomography (NCCT) and Contrast-Enhanced Computed Tomography (CECT) thorax and abdomen [Table/Fig-1]. Based on these findings and clinical history possibility of a multiple myeloma was considered.

BM studies and M-band electrophoresis were done where the latter was found to be negative. BM aspiration procedure was difficult yielding scanty yet particulate material [Table/Fig-2]. Smears showed clusters of large pleomorphic cells having high N:C ratio with coarse chromatin and moderate to abundant cytoplasm. A diagnosis of metastatic tumour deposit was made. These prompted a thorough search for a possible primary. Tumour markers Carcinoembryonic

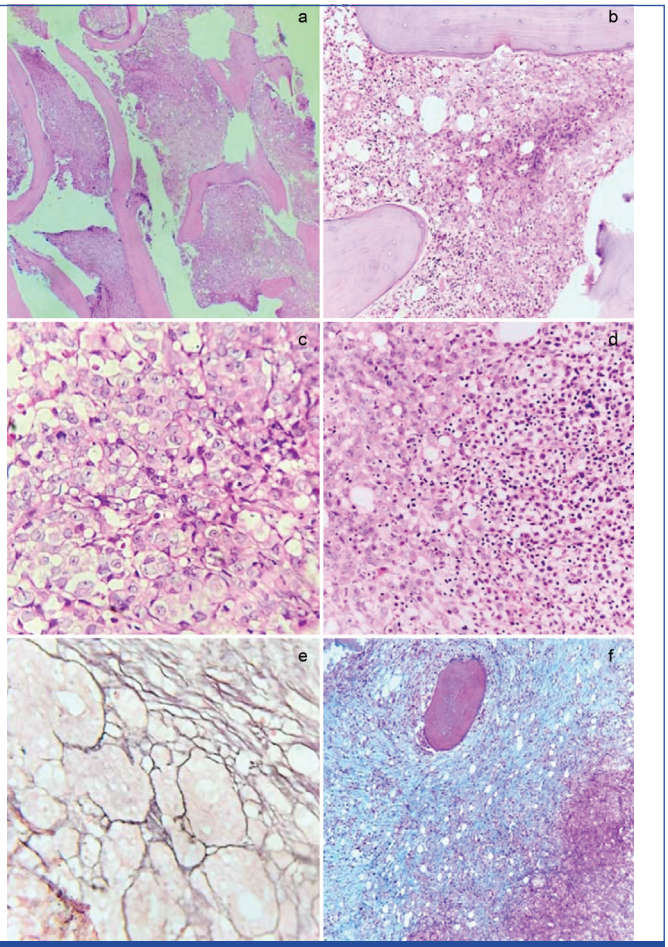


[Table/Fig-1]: a) NCCT thorax-multiple lytic lesions in vertebral bodies of cervical and posterior elements of thoracic region and sternum; b) CECT abdomen multiple lytic lesions seen in all the vertebrae and pelvic bones.

Antigen (CEA) and CA-125 were found to be 26.9 ng/mL (Ref: 0-5 ng/mL) and 211 U/mL (Ref: 0-35 U/mL), respectively. The BM biopsy confirmed an extensive infiltrate of tumour cells with markedly suppressed haematopoietic elements [Table/Fig-3]. There was grade 3 secondary marrow fibrosis [Table/Fig-3]. IHC staining panel was positive for Pan CK, CK-7 while negative for CK-20, CDX2, TTF1, ER, CA125 [Table/Fig-4] suggesting a primary in upper GI tract. On follow-up [Table/Fig-5], PET-CT was suggestive of metabolically active eccentric wall thickening in proximal body of stomach along lesser curvature. Upper GI endoscopy also revealed a circumferential mass involving the body of stomach. A biopsy of this mass which revealed a diffusely infiltrating tumour in sheets having large nuclei, coarse chromatin, moderate pleomorphism; few showing prominent nucleoli. The cytoplasm was moderate to abundant. A poorly differentiated adenocarcinoma was confirmed on histopathology. Hence a final diagnosis of diffuse-type gastric adenocarcinoma with bone and bone marrow involvement was rendered. The patient was transferred to oncology for further management. In view of adenocarcinoma with BM involvement, stage 4, she was started on oral capecitabine and admitted for supportive care and chemotherapy. She was started on oral morphine for pain management and was discharged for review after two weeks. She was, however, lost to further follow-up. Written consent was given by the patient for the publication of the case report and the images.



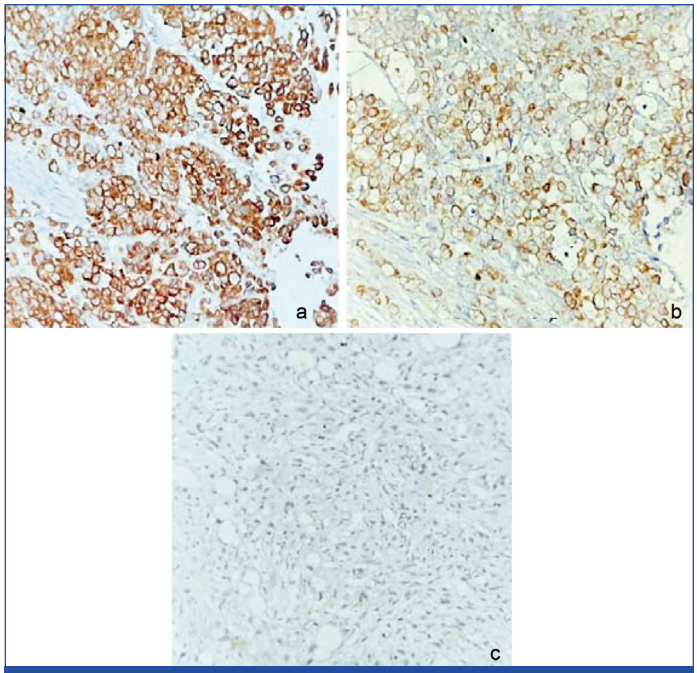
[Table/Fig-2]: Bone Marrow (BM) aspiration smear showing: a) Particulate marrow; b) Hypercellular trails; c) Smear shows almost complete replacement of the haematopoietic cells by clusters of large atypical looking cells with oval to round irregular nuclear membranes: d) Large atypical looking cells, few showing vague acinar pattern(Leishman stain; a,c,d: 400x; b: 100×).



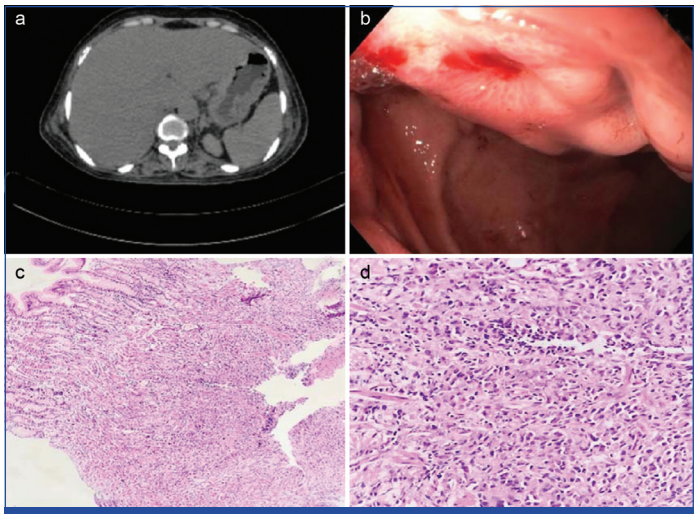
[Table/Fig-3]: a) Bone Marrow (BM) biopsy showing normal marrow trabeculae: b,c) Extensive infiltration of tumour cells; d) large cells moderately pleomorphic with moderate atypia, abundant cytoplasm with markedly suppressed residual hematopoietic elements; e,f) Grade 3 marrow fibrosis seen; (a-d:H&E, e: Reticulin, f: Masson Trichrome; a:100x, b: 200x, c-f:400x).

DISCUSSION

Gastric cancer continues to remain the fourth most common cause of cancer associated mortality worldwide. If metastasis occurs, it is usually to liver, lymph nodes and peritoneum [1]. Bone and BM



[Table/Fig-4]: Immunohistochemistry staining was positive for Pan CK (a), CK-7 (b) and negative for CK-20 (c) (a-c:100x).



[Table/Fig-5]: a) PET CT: Metabolically active eccentric wall thickening in proximal body of stomach along lesser curvature; b) UGIE: Circumferential ulceroproliferative lesion starting 5 cm from GE junction involving body and extends to both greater and lesser curvature; c,d) Endoscopic gastric biopsy from growth showing features of poorly differentiated adenocarcinoma (H&E;c:40x;d:400x).

metastasis are exceedingly rare as inaugural presentation [2,3]. Here, authors present a unique case of a young female with gastric malignancy that initially presented with non-GI complaints like severe bone pain and fever which was found to have bone secondaries on BM aspiration and biopsy which eventually revealed to have a primary in the stomach.

What makes this case unique is that, these patients usually have at least one prior GI symptom along with bone pain. Here the patient was young and presented directly without GI symptoms with bone pain and weakness as inaugural symptoms. Such unusual manifestation of a stomach carcinoma is very rarely documented in literature and pose diagnostic dilemmas [4,5]. Here, the evaluation of back pain in a young female resulted in diagnosis of metastatic gastric adenocarcinoma. Most common haematological presentations of such cases are thrombocytopenia, Disseminated Intravascular Coagulation (DIC), Microangiopathic Haemolytic Anaemia (MAHA) and leucoerythroblastic reaction which were indicative of BM involvement in few studies [5-7]. Kusumoto H et al., reported an elevated serum ALP and/or serum Lactate Dehydrogenase (LDH) levels in stomach cancer patients with bone involvement, similar to the present case [8].

As the BM metastasis in GC cases is uncommon, the clinical presentation and ideal management is not understood or established yet and despite chemotherapy, as highlighted by Kusumoto H et al., the survival has been found to be 2-3 months [8]. Bone metastasis are more often seen in younger individuals who present with signet ring cells, diffuse-type or poor differentiation. Rapid proliferation with invasion into capillary mucosa in stomach bed is likely speculated as reason for early dissemination. Poorly differentiated histology leads to more aggressive disease compounded by non-portal spread; possibly through vertebral venous plexus. Rapid aggressive proliferation leads to bone destruction along with haematological problems. RANKL, a key player in the osteoclastic cells based resorption of bone, has been found in the gastric cancer cells and is speculated as a likely cause for the same by Tantia P et al., [5]. This can lead to confusion with other lesions including fractures, infectious pathologies, degenerative changes and other benign conditions. PET-CT, Magnetic Resonance Imaging (MRI) along with BM studies is essential [5]. Also, the chemotherapy administration is often precluded by the suppressed marrow due to infiltration leading to cytopenias [9]. Bone involvement entails complex cross-talk with the components of the microenvironment formed by osteoclasts, stromal cells and immune cells along with osteoblasts. The conventional remodelling which occurs with a balance of bone formation and resorption is disrupted. Early onset disease with bone metastasis likely reflect activation of inflammation, suppressed immunity and disrupted coagulation profile necessitating a more customised approach [10].

Unlike the present case Sun W et al., found BM metastasis in gastric carcinoma was not found to be associated with thrombotic microangiopathy [11]. Proskuriakova E et al., documented a case of disseminated intravascular coagulation (DIC) in a patient with metastatic gastric adenocarcinoma [12]. In this case, the patient was not manifesting any coagulation abnormalities. Similar to the present case they also show signet ring cells, highlighting the poor prognosis. Similar to the present case Gosavi A et al., used PET-CT as an important investigation for the diagnostic process [13]. Similar findings were documented by Yang Z et al., in an elderly lady who presented with generalised pain and have histologically confirmed gastric adenocarcinoma along with widespread bone metastasis [14]. Palo A et al., presented a similar case of gastric adenocarcinoma with cytopenias showing BM infiltration wherein multidisciplinary approach helped in clinching the diagnosis [15].

CONCLUSION(S)

This case throws light upon a rare presentation without GI symptoms, presenting solely with bone pain in a young individual. This emphasises the broad differentials in young patients with lytic bone lesions. Gastric adenocarcinoma may present with BM involvement, which is more common with poorly differentiated and diffuse type. The diagnosis requires multimodality diagnostic methods with integration of imaging findings, BM studies, IHC along with tumour marker correlation. Holding an overall integrated multidisciplinary approach is a crucial step during the management of patients as GI carcinoma may have varied presentation.

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