Case report

Deciphering signet ring cells in the bone marrow of a child – a rare case report with review of literature

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The metastatic gastric adenocarcinoma that diffusely invades the bone marrow frequently has a short clinical course and an unfavourable prognosis. This case study aimed to elucidate the clinicopathological characteristics and prognosis of gastric cancer patients with diffuse bone marrow metastases. The specific clinicopathologic features associated with diffuse bone metastasis from gastric cancer must be given special attention due to the poor prognosis of this condition. Regular follow-up and a bone marrow examination in high-risk patients can assist in identifying advanced disease early.

Key words: bone marrow metastasis, gastric carcinoma, signet ring cell adenocarcinoma.

Introduction

In children and young adults, gastric cancer is extremely rare. Lymphoma, sarcoma, and neuroblastoma are the most common childhood cancers [1]. The frequency of gastric adenocarcinomas in children is less than 0.05% [2]. To establish appropriate treatment strategies for gastric carcinoma, it is critical to identify the existence or absence of metastases. Gastric cancer usually spreads to the peritoneal surfaces, distant lymph nodes, and liver, but it can also spread to the spleen, lung, brain, or skin [3]. The prevalence and clinical relevance of bone marrow metastases in paediatric gastric cancer are unknown [4]. Solid tumours in children, such as neuroblastoma, Ewing's sarcoma, and rhabdomyosarcoma, followed by germ cell tumours and retinoblastoma, are associated with bone marrow metastases in children [5, 6]. The present case study re-emphasises the early utility of bone marrow examination in the management and prognosis of gastric adenocarcinoma in children.

Case report

The paediatric department of King George's Medical University, Lucknow, a tertiary care medical centre in North India, admitted an 11-year-old child. For 2 months, the patient had lower back aches, followed by loss of bladder and bowel continence, as well as weakness in his lower limbs for 4 weeks. There was a history of weight loss, night sweats, and 2–3 episodes of vomiting per day. The patient denied any history of melena. The patient had an ill-defined lump in the epigastric area that was tender on abdominal examination. A haemoglobin level of 6.9 g/dl, a white blood cell (WBC) count of $12.0 \times 10^3/\mu l$, and a platelet count of $160 \times 10^3/\mu l$ were observed during the initial laboratory examination. A peripheral blood smear examination showed a leucoerythroblastic blood picture and displayed 100 nucleated red blood cells/100 WBC (Fig. 1). The results of the renal function and liver function tests (LFT) were within the normal range.

A computerised tomography scan of the thorax, abdomen, and pelvis revealed a fracture of the L1–L3 vertebral body, lytic lesions in the T3–T6 vertebral bodies, and a concentric infiltrative growth in the body and stomach antrum with enlarged lymph nodes in the left upper quadrant of the abdomen. A provisional diagnosis of non-Hodgkin's lymphoma, germ cell tumour, neuroblastoma, and Ewing sarcoma was made based on clinical and imaging studies.

The patient was hospitalised in a paediatric medical oncology unit for evaluation of disease and management. To access the disease status, a bone marrow aspirate and marrow biopsy were performed from the posterior superior iliac spine under local anaesthesia with strict aseptic conditions. The bone marrow aspiration smears revealed hypocellular haemodiluted smears displaying atypical cells with enlarged eccentric nuclei and a moderate amount of cytoplasm on a blood-mixed mucoid background, indicating tumour metastasis. The number of normal haematopoietic cells was reduced (Fig. 2A, B). Subsequently, the section from the bone marrow biopsy shows evaluable marrow spaces displaying diffuse infiltration by tumour cells disposed in sheets. These tumour cells are signet ring-shaped and have eccentric elongated hyperchromatic nuclei with an abundant amount of cytoplasm (Fig. 2C, D). A battery of immunohistochemical markers was applied to the bone marrow biopsy section, which revealed positive expression of CK7 and CDX2, indicating that the signet ring cells originated in the gastrointestinal tract (Fig. 2E, F). CD20 was negative in tumour cells. Placental-like alkaline phosphatase (PLAP), spalt-like sal-like-4 (SALL-4), leucocyte common antigen, synaptophysin, chromogranin, vimentin, and CD99 staining were negative. As a result, the final diagnosis of metastatic signet ring cell carcinoma of the gastrointestinal origin, most likely upper gastrointestinal tract, was made based on clinical, imaging, morphological, and immunohistochemistry evaluation. A mutation analysis was also performed for the CDH1 gene, which showed negative results.

A workup for a gastrointestinal carcinoma was requested because of the foregoing results. A malignant-appearing growth in the area of the gastric body and pylorus was identified during an endoscopy of the upper gastrointestinal tract. An endoscopy-guided biopsy was done from the mass, which revealed signet ring cells (Fig. 3). A final diagnosis of gastric signet ring cell carcinoma with bone marrow metastasis was rendered. The patient was referred to a paediatric oncology clinic to begin chemotherapy with epirubicin, oxaliplatin, and capecitabine. Unfortunately, after only one cycle of chemotherapy, the patient died of his condition.

Discussion

In 2020, gastric cancer ranked as the fifth most prevalent form of cancer and the fourth highest contributor to cancer-related deaths globally. In 2020, about one million gastric cancer cases were expected, with significant geographic variance. East Asian and Eastern European regions have the highest male and female incidence rates, while two-thirds of cases worldwide are male. Mortality and incidence are significantly associated, indicating poor survival and emphasising the need for early diagnosis [7–9].

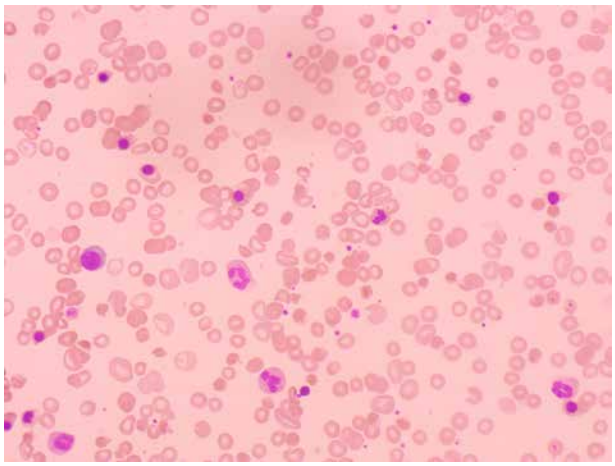

Fig. 1. A peripheral blood smear displaying leucoerythroblastic blood picture (Leishman stain, 40×)

The incidence of gastric cancer has declined due to alterations in specific environmental and socioeconomic factors. The primary factors contributing to the lower occurrence is decreased *Helicobacter pylori* infection and reduced consumption of salted fish and meats, as well as reduced intake of smoked foods. In contrast, over the past 30 years, there has been an increase in the diffuse form of stomach cancer, but the cause is unknown [10, 11].

Gastric cancer has been classified into 2 forms, namely intestinal-type and diffuse-type [12]. Diffuse-type gastric cancer is characterised by its tendency to occur at a younger age and to be more advanced at the time of diagnosis, in comparison to well differentiated or moderately differentiated intestinal-type gastric cancer [13]. Hereditary illnesses such as hereditary diffuse gastric cancer (HDGC) have been highlighted in studies as traditional risk factors for gastric carcinoma in children. The most common gene involved in HDGC is CDH1. A CDH1 gene mutation increases the risk of gastric cancer and other HDGC-related malignancies [14]. This is especially important in the present case because this patient was a young child who presented with gastric signet ring cell adenocarcinoma; however, the mutation analysis for CDH1 yielded negative results. Our patient presented at a younger age with an advanced stage at the time of diagnosis, which is a characteristic of diffuse-type gastric adenocarcinoma.

The present case study is remarkable in that it solely complained of back discomfort, lower-limb weakness, and loss of urine and bowel continence, denying any gastrointestinal bleeding complaints. Our patient was eventually identified with signet ring cell gastric adenocarcinoma after a thorough clinical examination along with the integration of imaging, histology, and immunohistochemistry studies.

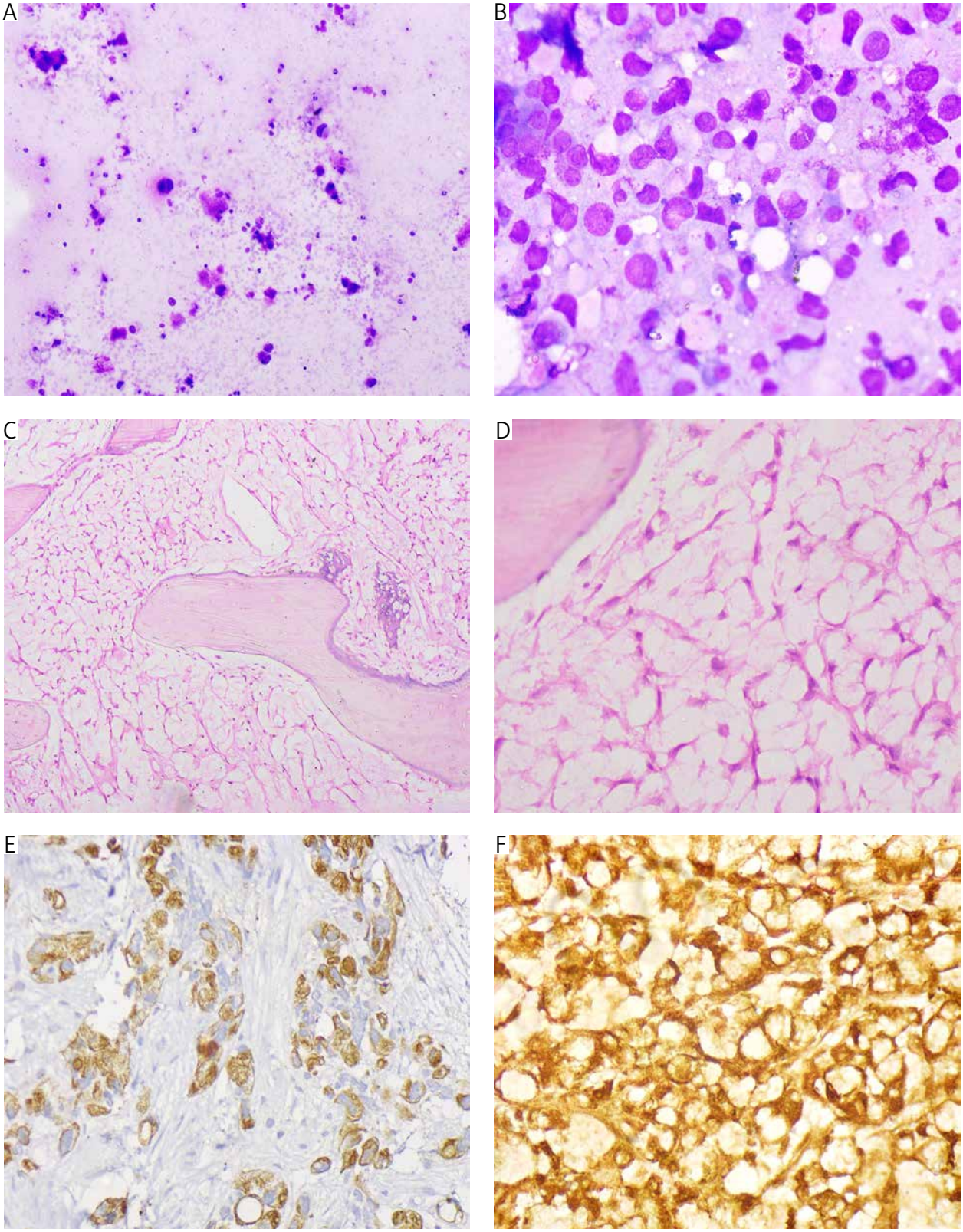

Fig. 2. A) Bone marrow aspirate smear displaying hypocellular haemodiluted smear displaying atypical cells on a blood mixed mucoid background (Leishman stain, 10×). B) Bone marrow aspirate smear showing atypical cells having enlarged eccentric nuclei and moderate amount of cytoplasm (Leishman stain, 40×). C) Bone marrow biopsy displaying infiltration by tumour cells disposed in sheets (haematoxylin and eosin stain, 10×). D) Bone marrow biopsy showing signet ring cells having eccentric, elongated hyperchromatic nuclei and abundant mucinous cytoplasm (haematoxylin and eosin stain, 40×). E) Tumour cells are displaying cytoplasmic and membranous positivity of CK-7 (40×) and (F) nuclear positive expression of CDX2 (40×)

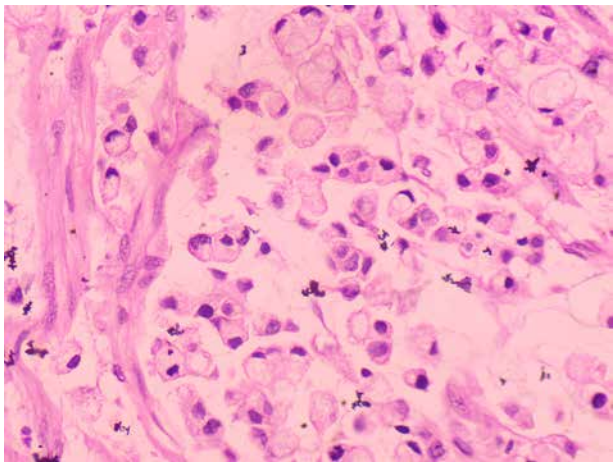

Fig. 3. The section from the endoscopically guided biopsy of the stomach displaying atypical cells disposed in sheets having elongated hyperchromatic nuclei and abundant mucinous cytoplasm (haematoxylin and eosin stain, 40×)

Bone marrow metastases in gastric cancer have been documented; however, they are very rare at the time of diagnosis. The identification of bone marrow involvement is often made during the workup for metastatic disease [4]. A peripheral blood smear examination of the patient in this case study revealed anaemia and leucoerythroblastic blood picture, both of which were linked with bone marrow metastases in a few previous studies [5–7]. Bone marrow metastasis is more prevalent in gastric cancer patients with the signet ring cell subtype and younger age of presentation. Patients with gastric adenocarcinoma have a dismal prognosis following bone marrow involvement; their average survival time is 44 days from the time of bone marrow metastasis detection [15]. The patient in the current case succumbed to his illness 28 days after being diagnosed with metastatic marrow disease. Chemotherapy improves survival rates compared to the best supportive care for advanced gastric cancer. Bone marrow metastases in gastric cancer patients are extremely rare; thus, their clinicopathological characteristics along with treatment choices are still being determined. Patients have a catastrophic prognosis with short survival times.

Conclusions

In a young child with an abdominal mass and lower back pain, primarily a broad differential diagnosis is first emphasised. Secondly, diffuse-type gastric cancer patients, especially younger ones, may have bone marrow involvement. A signet ring morphology on bone marrow examination in a younger patient may indicate signet ring gastric carcinoma with marrow metastases.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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