

## Bicytopenia and leukoerythroblastosis: a rare initial presentation of signet ring cell gastric adenocarcinoma

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### ABSTRACT

Gastric adenocarcinoma is a common neoplasia and is responsible for up to 30% of the overall deaths due to cancer. Advanced disease is mostly characterized by peritoneum, liver, and lung involvement. The spread of the disease to the bone is rare, and bone marrow dissemination is even rarer. In this setting, leukoerythroblastosis may be the initial manifestation of the disease. The authors report the case of a 64-year-old Caucasian man who sought medical care complaining of back pain, weakness, and weight loss. The physical examination revealed pallor, and the laboratory work-up depicted severe anemia and thrombocytopenia; the peripheral blood smear was consistent with leukoerythroblastosis. The ongoing investigation through a bone marrow biopsy showed massive involvement of the bone marrow by a signet ring cell adenocarcinoma. During hospitalization, the patient presented melena, and an upper digestive endoscopy depicted an ulcerated and infiltrative lesion in the cardia, upon which the histological examination revealed a signet ring cell adenocarcinoma. This case highlights the bone marrow invasion represented by bicytopenia and leukoerythroblastosis as the initial manifestation of this histological type of gastric cancer. Although treatment attempts were made with chemotherapy and radiotherapy, the patient died early on, showing the aggressive behavior of this form of tumoral presentation.

### Keywords

Stomach Neoplasms; Carcinoma; Signet Ring Cell; Bone Marrow; Neoplasm Metastasis

### INTRODUCTION

Gastric cancer is the fifth most common neoplasia worldwide after cancer of the lung, colon, breast, and prostate. It is also the third most common cause of death due to cancer irrespective of gender, and in 2012 it was responsible for 723,000 deaths worldwide.<sup>1</sup>

Adenocarcinoma is the histological type in 90% of cases of gastric cancer, and the metastases most commonly occur in the peritoneum, liver, and lung. The bone marrow is rarely involved as the metastatic site of a gastric carcinoma, and only scant reports show this involvement as the first presentation of the neoplasm.<sup>2-4</sup>

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We report the case of a patient with a medical history of weight loss and bicytopenia (anemia and thrombocytopenia). No gastrointestinal symptoms were present. The diagnostic work-up revealed the presence of diffuse infiltration of the bone marrow by signet ring cells of gastric neoplasia origin.

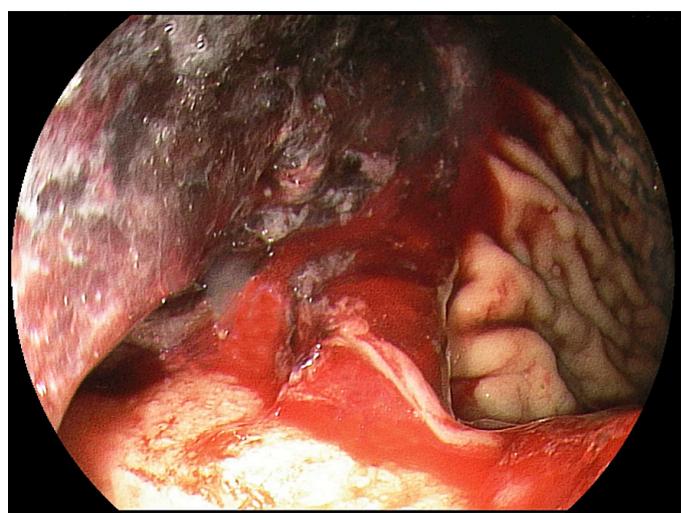
## CASE REPORT

A 64-year-old man sought medical care complaining of weakness, a weight loss of 10 kg, and back pain for the last 2 months that had worsened during the last 2 weeks. His medical history comprised hypertension and type 2 diabetes mellitus, which was regularly controlled with hydrochlorothiazide, losartan, and metformin. He smoked 80 packs/year of tobacco. He denied abdominal pain, nausea, vomiting, gastrointestinal bleeding, or intestinal habit changes. The initial physical examination showed a well-looking patient, though markedly emaciated. His weight was 68.3 kg, height 1.79 m (body mass index was 23.6), pulse 104 beats/min, and blood pressure 102/64 mmHg. No peripheral lymphadenomegaly was palpable. A mild systolic cardiac murmur was audible in the aortic area, and the abdomen was plain, flaccid, and free of ascites and visceromegaly. The remaining examination was normal. The laboratory tests showed bicytopenia represented by erythrocytes of  $1,300,000/\text{mm}^3$  (reference range [RR]:  $4,500,000\text{-}5,900,000/\text{mm}^3$ ), hemoglobin of 3.9 g/dL (RR: 12.3-15.3 g/dL), hematocrit of 13.3% (RR: 36.0-45.0%), mean corpuscular volume of 102.3 fL (RR: 80-100 fL), red cell distribution width of 23.2% (RR: <14.9%) and reticulocytes of  $78,000/\text{mm}^3$  (RR:  $16,400\text{-}95,000/\text{mm}^3$ ). The peripheral blood smear revealed the presence of 18% of orthochromatic erythroblasts per 100 leukocytes. The platelet count was initially  $80,000/\text{mm}^3$ , then  $18,000/\text{mm}^3$  in a second measurement (RR:  $150,000\text{-}400,000/\text{mm}^3$ ). Leukocytes of  $14,100/\text{mm}^3$  (RR:  $4,500\text{-}11,000/\text{mm}^3$ ) showed a marked shift to the left (neutrophils of 82%, promyelocytes 1%, myelocytes 2%, metamyelocytes 3%, bands 5%, segmented 71%, lymphocytes 15%, and monocytes 3%). Lactic dehydrogenase determination was 809 U/L (RR: <250 U/L). Renal function tests, electrolytes, liver enzymes, bilirubins, clotting tests, vitamin B12, and folic acid determinations were normal. Even though blood transfusions were

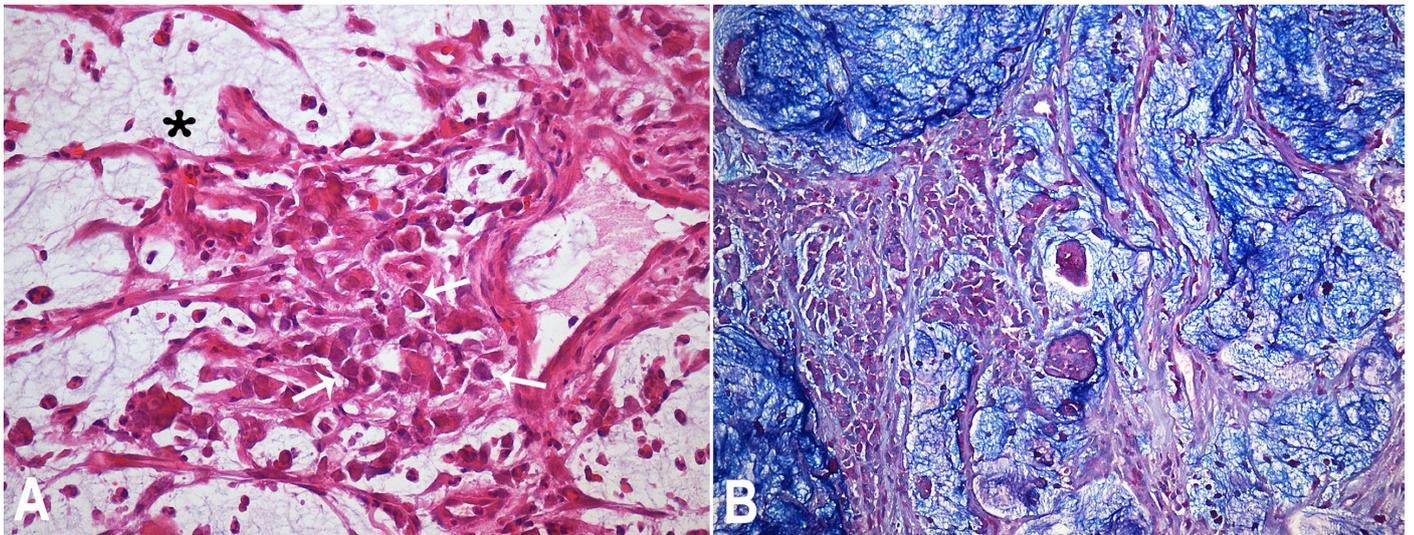
carried out, the hemoglobin level returned to a very low titer over the following 2 days. Therefore, the patient was hospitalized with the working diagnoses of occult bleeding, myelodysplastic syndrome, or hemolysis.

The abdominal computed tomography (CT) showed lymphadenomegaly in the periaortic, interaortocaval portocaval, and in the lesser gastric curvature topographies.

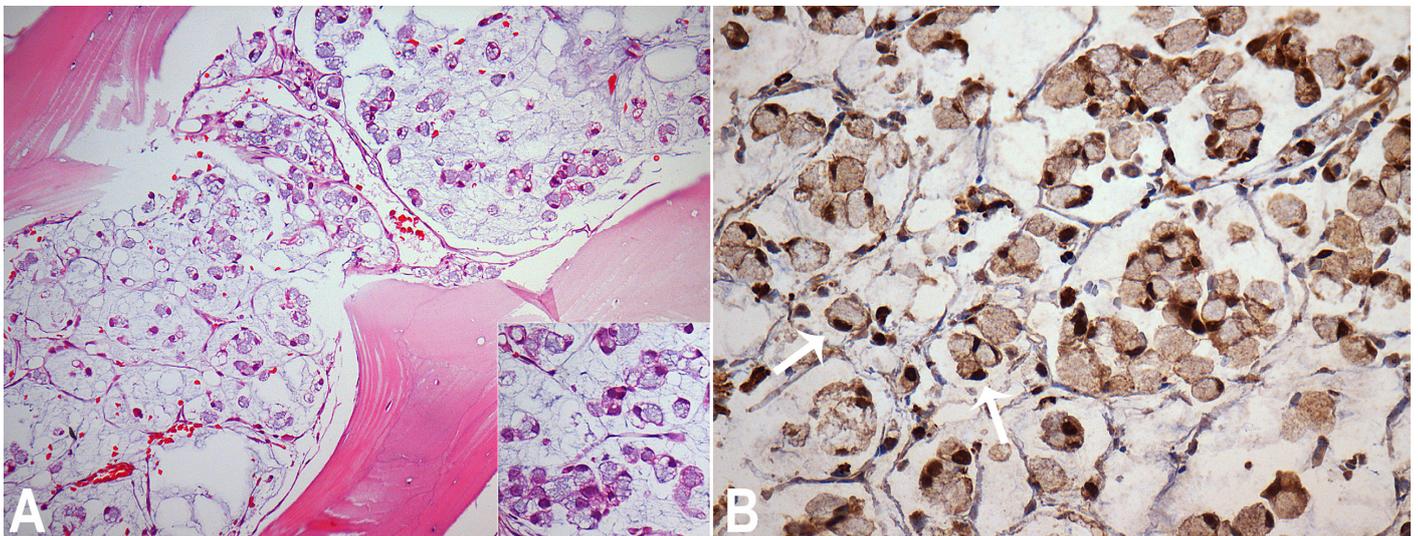
Because of the hematological features, which were consistent with leukoerythroblastosis, a bone marrow biopsy was performed. After a suspicious episode of melena, an upper digestive endoscopy was undertaken, which revealed a protruding infiltrative and ulcerated lesion located in the cardia extending to the distal third of the esophagus. The gastric chamber was full of clots due to diffuse tumoral bleeding that hampered the evaluation of the tumor size (Figure 1). Biopsies were performed, followed by adrenalin and ethamolol infiltration in an attempt to control the bleeding sites. The histological report of the gastric biopsies revealed signet ring cell adenocarcinoma with mucinous areas (Figure 2). The bone marrow was so extensively infiltrated by the neoplasia that the hematopoietic elements were scarcely represented (1% of the sample). The immunohistochemical profile of the bone marrow biopsy revealed positivity for CK7, CK20, and CDX-2, and negativity for TTF-1 and PSA, which was consistent with the gastrointestinal primary site of the neoplastic cells (Figure 3).



**Figure 1.** Upper digestive endoscopy showing a protruding ulcerated, infiltrative gastric lesion located in the cardia that presents active bleeding.



**Figure 2.** Photomicrography of the gastric biopsy. **A** - Poorly cohesive atypical cells with cytoplasm vacuoles (signet ring cells) (arrow) in a background of mucin and inflammatory cells (asterisk) (H&E, 400X); **B** - Pools of mucin (blue) in the background of tumor cells (PAS/Alcian blue stain, 200X).



**Figure 3.** Photomicrography of the bone marrow biopsy. **A** - Diffuse infiltration by adenocarcinoma with mucinous background (H&E, 200X) and signet ring cells (inset, H&E, 400X); **B** - Immunohistochemistry for CDX2 showing positive nuclear brown staining in bone marrow signet ring cells (arrow) (400X).

The treatment consisted on hemostatic radiotherapy and chemotherapy for metastatic gastric cancer. Modified FLOX (oxaliplatin, 5-fluorouracil, and leucovorin) was administered. The outcome was unfavorable and the patient died on the 15th day of the first chemotherapy cycle.

## DISCUSSION

The gastric cancer is a frequent and aggressive entity. In 2016 in Brazil, the National Institute of Cancer (INCA) estimated the occurrence of 12,920 new cases of gastric cancer in men and 7,600 in women,

which represents an estimated risk of 13.04 new cases in 100,000 men and 7.37 in 100,000 women.<sup>5</sup> Although the incidence of gastric cancer has decreased worldwide,<sup>1,5</sup> the mortality related to the entity remains high. The 5-year survival rate in developing countries is 20%; while it is upto 30% in developed countries. In Brazil, unfortunately, 85% of the diagnoses of gastric cancer are made in advanced stages.<sup>6</sup>

The metastases of gastric carcinoma usually occur in the liver, peritoneum, and lymph nodes, and less frequently in the ovary, central nervous system, bone, lung, and soft tissue. Bone metastases are very uncommon in the advanced stages of gastric cancer.

Autopsy studies of patients with gastric carcinoma showed bone metastases in 10-15.9% of the cases,<sup>7-9</sup> while in patients submitted to theoretically curative resection, this rate decreases to 1.2-1.8%.<sup>10-12</sup>

The neoplastic infiltration of the bone marrow is extremely rare, and occurs in a small percentage of bone metastasis.<sup>13</sup> Kim et al.<sup>14</sup> reported the prevalence of 0.024% of the bone marrow infiltration confirmed by biopsy studies. Kwon et al.<sup>15</sup> studied 26 patients with advanced gastric cancer with bone marrow involvement showing a concomitance of bone, pulmonary, and hepatic metastasis in 57%, 11%, and 3.8%, respectively. The most frequent solid tumors that present diffuse bone marrow infiltration in adults are represented by the tumors of the prostate, breast, lung, thyroid, and stomach.<sup>16,17</sup>

The bone marrow is a heterogeneous tissue composed of (i) cells of hematopoietic origin (hematopoietic stem cell, osteoclasts, macrophages, and others); (ii) cells of mesenchymal origin (mesenchymal stem cells, osteoblasts, adipocytes, and others); (iii) endothelial cells; and (iv) neural cells. These cells interact with each other determining a microenvironment that fosters hematopoiesis and bone remodeling. Once within the circulatory system, the neoplastic cells may invade the bone marrow and actively act in this microenvironment resulting in the development of metastatic neoplasia. The tumor growth is stimulated both by the activation of osteoclasts and by the release of growth factors within the bone marrow, and is inhibited by osseous formation and decreased osteoclastogenesis.<sup>13,18</sup> It seems that the tumor gastric cells induce the differentiation and activation of the osteoclasts by the production of cytokines and via the RANK/RANKL system.<sup>19</sup> The poorly differentiated adenocarcinoma and the signet ring cell carcinoma are the histological types of gastric carcinoma mostly associated with bone marrow diffuse infiltration. These histological types present low adhesion molecules expression,<sup>20,21</sup> thus partially explaining the diffuse infiltration. The precise mechanism involved in the bone metastasis still has not been fully explained. The clinical features of the bone metastases would result in the interaction of the neoplastic cells and the cells of the bone marrow. The gastric cancer's bone metastases are usually multiple, nodular, and of lytic origin. The pain is the most frequent symptom.<sup>22</sup>

The disseminated carcinomatosis of the bone marrow, in turn, is characterized by the diffuse infiltration of the bone marrow tissue followed by an explosive proliferation of the neoplastic cells, which will be responsible for the hematologic complications.<sup>13</sup>

Previous studies<sup>3,13,19</sup> on patients with gastric cancer and bone marrow infiltration have shown some particular traits: the patients are younger, there is an increased determination of alkaline phosphatase and lactate dehydrogenase, there is bone metastasis present, and a low incidence of hypercalcemia. These traits are associated with an aggressive histological pattern (signet ring cells or poorly differentiated carcinoma) when compared with gastric cancer without bone marrow involvement. The clinical outcome of these cases worsens very quickly due to the hematopoietic suppression and hastened tumoral cells proliferation. Intravascular disseminated coagulation, microangiopathic hemolytic anemia, anemia, thrombocytopenia, leukoerythroblastic reaction, and thrombotic and hemorrhagic events represent the dreadful complications in this group of patients.

Our patient presented weight loss and back pain; the bicytopenia without reticulocytosis, the increased DHL, and the leukoerythroblastosis consistent with bone marrow infiltration were all confirmed on the bone marrow biopsy.

The leukoerythroblastosis refers to the presence of neutrophilia with a marked shift to the left and to nucleated red blood cells in the peripheral blood smear in a patient without a primary hematological disease.<sup>23</sup> In case of replacement of the bone marrow tissue by neoplasia, granuloma, or fibrosis, the remaining stem cells migrate to the liver and spleen, resulting in the extramedullary hematopoiesis. Since the stroma of these extramedullary sites is not that efficient, the hematopoietic cells are prematurely delivered to the circulation. In this case, the reticulocytes count is of limited value since the nucleated red blood cells may mature in the peripheral blood as the reticulocytes may be disorderly released from the extramedullary sites.

The refractory anemia of our patient was assumed as a result of the impaired hematopoiesis (bone marrow infiltration) and the continuous bleeding by the neoplastic gastric lesion. The intravascular disseminated coagulation, a frequent complication of the diffuse bone marrow carcinomatosis, was not

characterized in our patient. The acute onset and continuous back pain was a major complaint, which was not diagnosed as being of neoplastic origin by the CT scan images. However, as we did not measure the alkaline phosphatase nor do a bone scintigraphic study, we could not rule out other bone metastasis in this case.

The survival time of patients with bone marrow disseminated carcinomatosis associated with gastric cancer is generally less than 3 months.<sup>5,14,22</sup> Even with the advances in chemotherapeutic regimens, the prognosis remains poor and is never longer than 1 year. Kwon et al.<sup>15</sup> published a series with 16 patients receiving palliative chemotherapy and 10 patients receiving only palliative care. The mean survival time was 121 days for the palliative chemotherapy group, and 11 days for the palliative care group ( $p < 0.001$ ).

Our patient was treated with hemostatic radiotherapy and chemotherapy for metastatic gastric cancer with modified FLOX (oxaliplatin, 5-fluorouracil and leucovorin)<sup>24</sup> and died on the 15th day of the first chemotherapy cycle.

This case highlights bone marrow neoplastic invasion as a very unusual first presentation of signet ring cell gastric carcinoma. Moreover, in patients with back pain and/or an association with hemorrhagic symptoms, the presence of leukoerythroblastosis and an increase in lactic dehydrogenase should raise the suspicion of the massive involvement of bone marrow.

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