

CLINICAL CASE

INFILTRACIÓN DE MÉDULA ÓSEA POR CÁNCER GÁSTRICO AVANZADO: REPORTE DE CASO CLÍNICO

BONE MARROW INFILTRATION BY ADVANCED GASTRIC CANCER: CLINICAL CASE REPORT

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RESUMEN:

La presencia de metástasis en médula ósea secundaria al cáncer gástrico es poco común, ya que existe una incidencia en el tejido óseo en un rango de 0.9 a 13.4 % y la médula ósea en solo el 0.024 %. además, se considera que son de mal pronóstico. El promedio de edad en que se diagnostica el cáncer de estómago es de 69 años, sin embargo, se tiende a presentar en pacientes más jóvenes, los pacientes con cáncer gástrico junto a metástasis de médula ósea tienen un promedio de edad de aproximadamente los 45 años. Los hallazgos más relevantes para sospechar en este tipo de infiltración metastásica es la presencia de alteraciones hematológicas, como un coagulación intravascular diseminada, anemia hemolítica, pancitopenia o trombocitopenia persistente y marcada, la cual es la más frecuente, además de eso imágenes diagnóstica que revelen alteraciones de la estructura ósea como también elevados niveles de deshidrogenasa láctica y fosfatasa alcalina. Es este artículo se presenta el caso clínico de un paciente masculino de 49 años en regulares condiciones con un diagnóstico establecido de adenocarcinoma gástrico grado III avanzado confirmado por esofagogastroduodenoscopia y estudio histopatológico, que abarca antro pilórico y cuerpo alto T4A estadiada por laparoscopia, quien fue sometido a gastrectomía total. Debido a la presencia de trombocitopenia marcada durante su trayecto hospitalario con múltiples transfusiones se decide realización de biopsia cruenta de médula ósea con sospecha de carcinomatosis medular.

PALABRAS CLAVE: Médula ósea, cáncer gástrico, trombocitopenia, adenocarcinoma

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ABSTRACT:

The presence of bone marrow metastasis secondary to gastric cancer is rare, since there is an incidence in bone tissue in a range of 0.9 to 13.4 % and bone marrow in only 0.024 %. In addition, they are considered to have a poor prognosis. The average age at which stomach cancer is diagnosed is 69 years, however, it tends to occur in younger patients. Patients with gastric cancer together with bone marrow metastasis have an average age of approximately 45 years. The most relevant findings to suspect this type of metastatic infiltration are the presence of hematological alterations, such as disseminated intravascular coagulation, hemolytic anemia, pancytopenia or persistent and marked thrombocytopenia, which is the most frequent, in addition to that, diagnostic images that reveal alterations in the bone structure as well as elevated levels of lactic dehydrogenase and alkaline phosphatase. This article presents the clinical case of a 49-year-old male patient in fair condition with an established diagnosis of advanced grade III gastric adenocarcinoma confirmed by esophagogastroduodenoscopy and histopathological study, which includes the pyloric antrum and upper body T4A staged by laparoscopy, who underwent total gastrectomy. Due to the presence of marked thrombocytopenia during his hospital stay with multiple transfusions, it was decided to perform an invasive bone marrow biopsy with suspicion of medullary carcinomatosis.

KEYWORDS: Bone marrow, gastric cancer, thrombocytopenia, adenocarcinoma

Introducción:

Gastric cancer (GC) is a disease influenced by multiple factors, including family history, diet, alcohol consumption, smoking, infection with *Helicobacter pylori*, the presence of adenomatous polyps, and infection with the Epstein-Barr virus (EBV).^{1,2} Recent statistics show that GC is the fourth leading cause of cancer-related mortality worldwide, with an average survival rate of less than 12 months in advanced stages¹.

In Colombia, stomach cancer is the leading cause of cancer-related death. A report by the National Cancer Institute (INS) highlights that the departments with the highest risk of gastric cancer mortality among men are Quindío, Huila, and Cauca, while for women they are Cauca, Norte de Santander, and Huila (2017).³

Lauren's classification for gastric cancer, introduced in 1965, remains the most widely used compared to other classifications. This classification distinguishes two histological subtypes of gastric cancer: the intestinal type and the diffuse type; subsequently, an indeterminate type was added for cases with unusual histological characteristics. Signet ring cell carcinoma is included within the diffuse subtype. Various studies have shown that the intestinal type is the most common, followed by the diffuse type, and finally, the indeterminate type. According to the WHO classification, in addition to gastric adenocarcinomas, there are other less common types of gastric tumors.^{4,5}

Gastric adenocarcinomas comprise several subtypes, including tubular,

mucinous, papillary, and mixed carcinoma, which may have similarities with the indeterminate type of Lauren's classification.

Signet ring cell carcinoma accounts for approximately 10% of gastric cancers and is distinguished by the presence of signet ring cells in more than 50% of the tumor mass.^{5,6}

At the time of diagnosis, approximately 50% of metastatic gastric cancer cases are already in advanced stages (stage III or IV). The most common metastases include the liver (through hematogenous spread), the peritoneum, and both local and distant lymph nodes; to a lesser extent, the ovaries, bone marrow, central nervous system, bones, lungs, and other soft tissues may also be affected.⁷

Two of the main strategies for the primary prevention of gastric cancer at the population level are improved nutrition and the reduction of *H. pylori* infection, which is the main risk factor for this disease.¹ Secondary prevention focuses on early detection, using available resources, especially endoscopy. Below, we present a rare case of gastric cancer with bone marrow infiltration.

CLINIC CASE:

A 49-year-old male presented with a 4-month history of severe epigastralgia associated with multiple emetic episodes after food intake, and progressive weight loss of more than 10 kilograms in 2 months, weighing 70 kilograms at the time of presentation. Extraintestinal examinations included an

esophagogastroduodenoscopy, which reported peptic gastritis Los Angeles B (Figures 1 and 2) with advanced grade III neoplasia, passable pyloric stricture, and antral region biopsy showing diffuse type gastric adenocarcinoma in 7 of the evaluated fragments.

On physical examination, the patient appeared asthenic and adynamic, in fair general condition, with generalized mucocutaneous pallor, cachexia, and semi-dry oral mucosa. He was hypotensive, with a blood pressure (BP) of 68/42 mmHg, and a heart rate (HR) of 80 bpm. Institutional laboratory tests revealed leukocytosis (WBC) of $13.49 \times 10^3/\mu\text{L}$, grade IV anemia with hemoglobin (Hb) at 4.03 g/dL, hematocrit (Hct) at 37.30%, neutrophilia at 82%, and thrombocytopenia with a decreasing platelet count of $83,000 \times 10^3/\mu\text{L}$. Other labs included creatinine 0.68 mg/dL, blood glucose 88 mg/dL, total protein 5.40 g/dL, serum albumin 2.90 g/dL. Coagulation times were elevated with prothrombin time (PT) 13.50 sec, INR 1.14, and partial thromboplastin time (PTT) 32.90 sec. Liver function tests showed ALT (GPT) 40.15 U/L, AST (GOT) 12.20 U/L, lactate dehydrogenase (LDH) 837 U/L, total bilirubin 0.40 mg/dL, direct bilirubin 0.20 mg/dL, and alkaline phosphatase (ALP) markedly elevated at 1883 U/L. Peripheral blood smear showed normal morphology.

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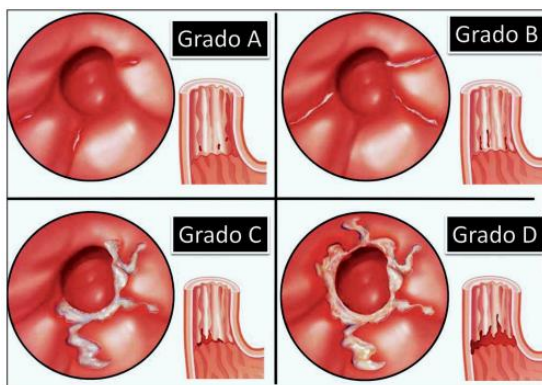


Figure 1: Schematic representation of the Los Angeles Classification of Esophagitis. Adapted from Gut 1999; 45: 172-80 and Gastrointestinal Endoscopy 2004; 60: 253-7.

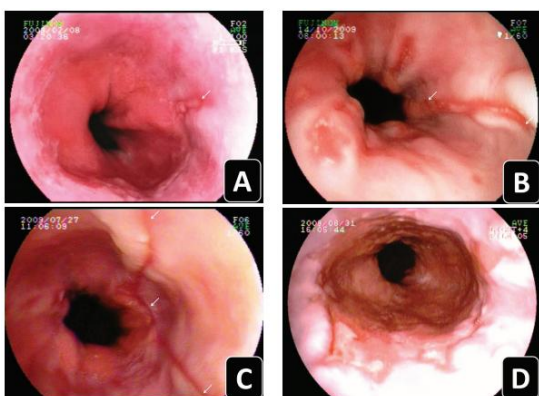


Figure 2: Los Angeles Classification of Esophagitis. Photographs from the Endoscopy Center of Hospital Clínico UC. Adapted from Gut 1999; 45: 172-80 and Gastrointestinal Endoscopy 2004; 60: 253-7.

A total abdominal ultrasound showed gallbladder wall thickening (10 mm), presence of free fluid in interloop, perisplenic, and left parietocolic gutters with difficult visualization and evaluation of the pancreas due to significant gas interposition, and abundant gas in the abdominal cavity. In addition, a simple and contrasted abdominal CT scan (Figure 3) was performed, which showed a solid space-occupying lesion measuring 76

x 83 mm at the pylorus and gastric antrum, conclusive for GC.

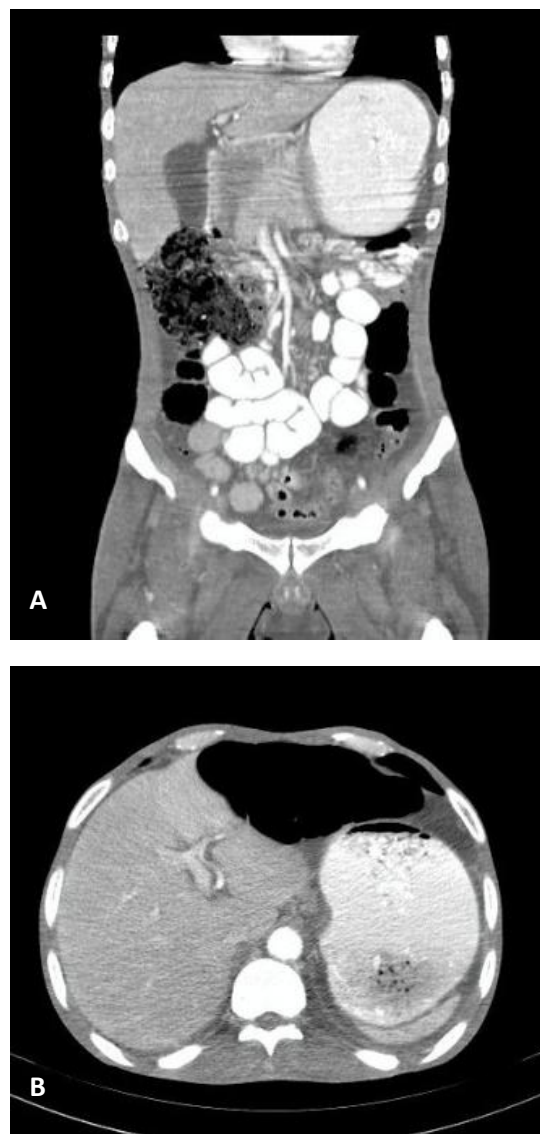


Figure 3: Images A and B show a solid space-occupying lesion measuring 76 x 83 mm in the gastric region at the pylorus and antrum.

Given the above, a tumor board meeting with different specialists was indicated to discuss the clinical case and decide on a course of action. It was concluded to perform a staging laparoscopy to determine irresectability criteria. However, due to

evident persistent thrombocytopenia and grade IV anemia according to the WHO classification, hematology consultation was indicated, recommending transfusion of 3 units of red blood cells and 2 units of platelets per 10 kg of weight. Half of the transfusions were given 2 hours before surgery and the other half during the procedure. Subsequently, control laboratory tests were performed; a complete blood count showed bicytopenia with WBC $8.35 \times 10^3/\text{ul}$, red blood cell count (RBC) $3.62 \times 10^6/\text{ul}$, HB 11.1 gr/dl, with persistence of thrombocytopenia at 70,000, leading to a diagnostic impression of advanced gastric cancer with suspected medullary infiltration.

Staging laparoscopy findings included an antropyloric and upper body T4a tumor, with pyloric syndrome and multiple left gastric and gastroepiploic adenopathies, multiple adhesions in the liver without metastasis, no evidence of carcinomatosis, and scant free fluid in the peritoneal cavity. No irresectability criteria were found, and due to nutritional status, parenteral nutritional support via central venous catheter and preoperative cardiopulmonary rehabilitation were decided.

Sistema de clasificación Lauren	
Intestinal	Difuso
Ambiental	Familiar
Gastritis atrófica, metaplasia intestinal	Sangre tipo A
Hombres mayor que mujeres	Mujeres mayor que hombres
Incidencia incrementa con la edad	Grupo de edad joven
Formación de glándula	Pobremente diferenciado, signo de células en anillo
Diseminación hematógena	Diseminación Linfática/transmural
Instalación microsatelital	Decremento de E-cadherina
Mutación del gen APC	
Inactivación p53, p16	Inactivación P53, P16
Pólipos adenomatosos cólicos, APC	

Figura 4: Lauren's classification determines growth pattern and histology type.

Considering the above, total gastrectomy of a palliative nature was decided, and hematology evaluated the patient, indicating a cruent bone marrow biopsy. However, at the time of the new blood count control, platelets were $91.00 \times 10^3/\text{ul}$, HB 11.1 gr/dl, RBC $3.61 \times 10^6/\text{ul}$, leukocytes $11.18 \times 10^3/\text{ul}$, leading to a second transfusion of 3 units of red blood cells and 6 units of platelets 2 hours before the intervention and 6 units during the surgical procedure.

Incisional bone marrow biopsy revealed histological evidence of infiltration by a malignant neoplastic lesion, consistent with secondary involvement due to a known history of gastric adenocarcinoma.

A total gastrectomy was performed along with biopsy sampling, which revealed an ulcerated intestinal-type gastric adenocarcinoma involving the serosa, measuring 7×6 cm, located on the anterior aspect of the lesser

curvature, with evident lymphovascular invasion. Postoperatively, the patient was admitted to the intensive care unit (ICU) under invasive mechanical ventilation and high-dose vasopressor support due to arterial hypotension (73/48 mmHg), and was started on broad-spectrum antibiotics with meropenem. During the day, the patient experienced a cardiac arrest in the setting of hemorrhagic hypovolemic shock refractory to treatment. Laboratory tests showed WBC $5.41 \times 10^3/\mu\text{L}$, hemoglobin 4.20 g/dL, platelets $161.00 \times 10^3/\mu\text{L}$, RBC $1.36 \times 10^6/\mu\text{L}$, fibrinogen 328.43 mg/dL, PT 22.50 sec, INR 1.91, and hypercalcemia on electrolyte panel. Venous blood gases indicated metabolic acidosis with severe hyperlactatemia (lactate 9.88 mmol/L). FAST ultrasound revealed free intraperitoneal fluid and a collapsed inferior vena cava. An emergency laparoscopic surgical intervention was performed, revealing 2000 cc of hemoperitoneum with active bleeding from the duodenal stump, the stump of the left gastric artery, and the staple lines of the jejunal limb; surgical lavage, hemostasis, and placement of a vacuum-assisted closure (VAC) system were carried out. While on mechanical ventilation, the patient experienced another cardiac arrest; a code blue was initiated, asystole was observed on the monitor, and advanced cardiopulmonary resuscitation was performed for 20

minutes without return of spontaneous circulation.

Discussion:

Gastric cancer (GC) remains one of the leading causes of morbidity and mortality worldwide. In Colombia, it ranks first as a cause of cancer death, with 6.90% of annual deaths, and an incidence of 8,938 new cases each year, of which 5,437 correspond to men and 3,501 to women. It is the third most common cancer among men and the fifth among women. This disease progresses from locoregional to systemic dissemination, extending to distant sites through metastases. The most frequent metastatic sites include visceral and peritoneal surfaces, with the liver and distant lymph nodes being the most affected sites.⁸

Bone or skeletal metastases in patients with gastric cancer are infrequent, affecting bone tissue in a range of 0.9% to 13.4% and bone marrow in only 0.024%. The average age at diagnosis of this cancer is 69 years.^{8,9}

However, bone marrow infiltration tends to occur in younger patients, as indicated by Ekinci et al.^{8,10}. In one study, bone marrow metastases were observed in 5 out of 245 patients with advanced gastric cancer, with an average age of 45 years, which coincides with the findings of Ergun et al.¹¹ who reported a mean age of 45.5 years.

Bone marrow invasion in cases of advanced gastric cancer may be suspected when clinical signs such as profound fatigue, weakness, weight loss, and unexplained fever are present. Its presentation may be either synchronous or metachronous, and the type of lesion may be osteolytic, osteoblastic, or mixed⁹. Typically, when bone involvement occurs, the most frequently reported sites include the spine, pelvic bones, long bones, ribs, sternum, scapula, and skull.³ Anatomical characteristics may help explain how gastric cancer metastasizes to the bone, as part of the blood drainage from proximal stomach regions may reach Batson's venous plexus, which penetrates the vertebral column via the azygos and hemiazygos veins.³ Moreover, bone marrow metastasis can lead to hematologic alterations such as pancytopenia, although this is not always present; in some cases, it may present only as bicytopenia or isolated thrombocytopenia.^{10,6} Most of these features were observed in our case; however, this type of metastasis may also manifest as disseminated intravascular coagulation, microangiopathic hemolytic anemia, thrombosis, or a leukoerythroblastic reaction.^{8,9}

In the case series presented by Ekinici et al.¹⁰, the rate was 100%, and they reported thrombocytopenia as the most common hematologic abnormality, which is consistent with

the findings of Ergun et al.¹¹, who reported a rate of 87.5%.

Several case reports have identified a close association between elevated levels of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) and the presence of potential bone tissue involvement. This was illustrated in the case reported by Dr. João Barbosa, titled Gastric Cancer With Multiple Bone Metastases: An Uncommon Primary Presentation, in which the patient exhibited bone lesions detectable through diagnostic imaging, along with laboratory findings showing elevated LDH and ALP levels.¹²

In the case of ALP, this is because it is a glycoprotein located in various tissues with not entirely clear physiological roles. It catalyzes the hydrolysis of a wide variety of phosphoric monoesters at alkaline pH. At the bone level, it is expressed in the osteoblast membrane when they differentiate from progenitor cells, is secreted into the circulation, and is part of the biochemical markers used in the study of bone turnover and remodeling. It also aids in the process of bone mineralization by promoting the attachment of osteoblasts to cartilage, favoring calcification.

Elevated ALP levels occur during periods of bone growth, in fractures, vitamin D deficiency, and osteomalacia. Increased ALP has also been observed in conditions such as osteoporosis, hyperparathyroidism,

renal osteodystrophy, and bone neoplasms or metastases. Similarly, high LDH levels are attributed to bone resorption, which leads to the release of the enzyme into the plasma.¹²

The case we presented was that of a patient with an intestinal type gastric adenocarcinoma with serosal involvement, a type of cancer formed by neoplastic cells with a glandular-like structure originating in areas of intestinal metaplasia, acting as an expansive rather than infiltrative-cohesive mass, most frequently located in the distal stomach. The patient underwent total gastrectomy and a bone marrow biopsy, which confirmed the presence of bone marrow infiltrates with adenocarcinoma involvement.¹³

Conclusión:

Gastric cancer metastasis to the bone marrow is not frequent, but there are cases where clinical symptoms and paraclinical tests similar to those observed in our case are present. This form of metastasis is rare but can manifest with symptoms such as pancytopenia, thrombocytopenia, and/or leukopenia, which can lead to a

false interpretation as a primary hematological disease. Furthermore, the presence of bone lesions visible on imaging studies, such as X-rays, computed tomography scans, or magnetic resonance imaging, should be carefully evaluated, as they may be indicative of secondary medullary infiltration.

Therefore, it is crucial to correlate these findings in patients with a history of gastric cancer and clinical presentations with similar characteristics, as early detection of possible medullary metastasis allows for better treatment planning and improves prognosis. Early diagnosis can also help avoid unnecessary or erroneous treatments and improve the patient's quality of life.

It is essential for clinicians to maintain a high index of suspicion in patients with a history of gastric cancer who present abnormal hematological signs or imaging findings suggestive of bone involvement. Additionally, bone biopsies or bone marrow aspirates should be considered to confirm the diagnosis and determine the best therapeutic approach.

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