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Thrombotic microangiopathy and disseminated intravascular coagulation in a patient with carcinomatosis of the bone marrow due to gastric adenocarcinoma: Case report

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Abstract. Carcinomatosis of the bone marrow is a rare clinical condition characterized by diffuse tumor infiltration of the bone marrow accompanied by hematological abnormalities, including thrombotic microangiopathy (TMA) and disseminated intravascular coagulation (DIC). In patients with gastric carcinoma, this association is infrequent. Below we present a case of a 19-year-old female patient with no known pathological history who presented with upper digestive tract bleeding. Upon examination, anemia and thrombocytopenia were documented, with schistocytes in the peripheral blood smear and prolonged coagulation times.

Endoscopic studies indicated a lesion in the Borrmann IV gastric body, and the bone marrow biopsy showed the presence of signet ring cells. Because there was no possibility of systemic therapy, the patient died during hospitalization. This case contributes to the medical literature by describing an unusual presentation of a very frequent pathology.

Keywords: Disseminated intravascular coagulation; gastric cancer; Bone marrow diseases; signet ring cells; thrombotic microangiopathy.

What is new? What is important?

Bone marrow metastasis from a gastric adenocarcinoma is rare. Carcinomatosis of the bone marrow is a rare subtype of bone marrow metastasis from a solid malignant tumor that is associated with hematological abnormalities. Our patient provided a unique presentation of carcinomatosis of the bone marrow due to gastric cancer that began as thrombotic microangiopathy with disseminated intravascular coagulation. This is the second case report of such a presentation.

INTRODUCTION

Gastric cancer is the fifth most common cancer and third leading cause of cancer-related deaths worldwide. In Colombia, it is the fourth most common cancer and the leading cause of cancer-related deaths [1, 2]. Although the overall incidence of gastric cancer has decreased globally, the incidence of signet ring cell carcinoma has been increasing. Signet ring cells are believed to be an intermediate stage between squamous cells and adenocarcinoma or glandular or mucin-secreting components of squamous carcinoma [3].

According to Lauren, gastric adenocarcinoma is histologically classified as intestinal and diffuse; diffuse cancer is the least common and typically occurs in young people. Diffuse cancer is also characteristic of linitis plastica or type IV of the Borrmann classification and is more associated with hereditary cancers [4].

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Carcinomatosis of the bone marrow is a rare condition with a poor prognosis characterized by diffuse tumor infiltration of the bone marrow associated with hematological abnormalities, such as thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). Its incidence is very low, and only case reports have been described in the literature. Among its associated cancers, adenocarcinoma is the most common, of which gastric adenocarcinoma is the most common subtype, followed by breast cancer, colorectal cancer, and others [5].

We present the case of a patient with carcinomatosis of the bone marrow due to gastric adenocarcinoma who presented with thrombotic microangiopathy (TMA) and subsequently developed DIC, which required multiple transfusions and admission to the intensive care unit (ICU). Ultimately, the patient died during hospitalization.

CASE REPORT

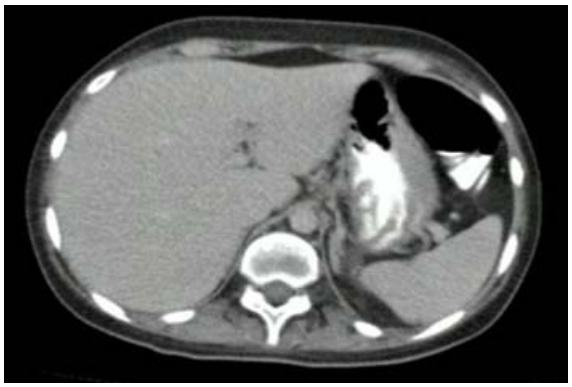
A 19-year-old female, who was previously healthy, presented with mucocutaneous pallor, asthenia, adynamia, and hematemesis that had persisted for two months; she consulted a local hospital where a complete blood count was performed with evidence of severe anemia and thrombocytopenia. An esophagogastroduodenoscopy led to a diagnosis of "Mallory Weiss syndrome." She received red blood cell and platelet transfusions and was discharged. However, she returned to the same institution with similar symptoms and a 14-kilogram weight loss and was given transfusional support. Further studies were performed: an abdominal tomography gave normal results, and immune hemolytic anemia was suspected. Steroid pulses were initiated. Finally, the patient did not continue hospitalization and left the health institution by her own means.

She then presented to our institution with a fever, and on admission, she was tachycardic and normotensive and had an area of phlebitis at the venipuncture sites of her previous hospitalizations. She also presented with marked mucocutaneous pallor, multiple ecchymoses in both upper limbs, and a systolic murmur in the aortic and mitral foci. Admission tests showed normocytic anemia (hemoglobin, 3.5 g/dL), severe thrombocytopenia (platelets, 17,500/mm^3), hyperbilirubinemia (total bilirubin, 2.9 mg/dL; direct bilirubin, 0.74 mg/dL; indirect bilirubin, 2.16 mg/dL), elevated lactate dehydrogenase (LDH) (LDH, 2394.14 U/L), a negative direct Coombs test, and a peripheral blood smear with schistocytes (++). The patient was diagnosed with TMA, and a PLASMIC score of 6 points was calculated (conferring a 72% risk of severe ADAMTS13 deficiency) [6]. This led to suspicion of TTP, and the patient was transferred to the ICU for hemodynamic monitoring and clinical surveillance due to a high risk of fatal complications. Considering the suspected diagnosis, plasma exchange therapy was initiated. Autoimmune diseases were ruled out (negative ANAs, ENAs, and ANCAs; negative rheumatoid factor; negative cardiolipin IgM and IgG; negative IgG and IgM beta 2 glycoprotein; and normal complement C3 and C4 levels of –123.43 and 19.85 mg/dL, respectively).

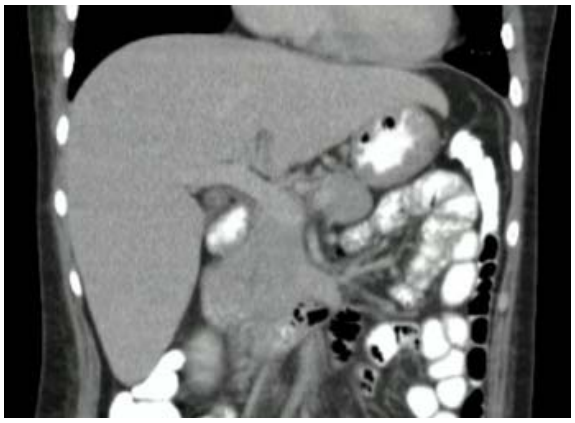
Subsequently, prolonged coagulation times, elevated D-dimer levels, and hypofibrinogenemia (fibrinogen, 137 mg/dL; control, 301 mg/dL) were obtained, which suggested DIC. In the search for organic compromise, uroanalysis was performed with findings of hematuria, pyuria, mild proteinuria, and creatinine levels within normal limits (0.43 mg/dL). During her stay in the ICU, methicillin-sensitive *Staphylococcus aureus* bacteremia was documented, and transthoracic echocardiography was performed for suspected bacterial endocarditis, but no vegetations were observed. Initial treatment with ceftriaxone and vancomycin was administered, which was then adjusted to oxacillin. Due to severe thrombocytopenia, transesophageal echocardiography was deferred, due to the high operative risk.

ADAMTS13 was reported within normal limits (68.2%), there was no improvement in hematological findings and catastrophic antiphospholipid syndrome (CAPS) was ruled out; therefore, plasma exchange therapy was suspended, and a bone marrow aspirate biopsy was performed. The patient continued to have a fever, and persistent bacteremia was documented. Hence, chest and abdominal tomographies were performed, which showed nonspecific thickening of the gastric walls (Figure 1a and 1b). Additionally, multiple generalized osteolytic lesions were present, which were compatible with metastatic disease (Figure 2). In the chest, centrilobular nodules, multilobular opacities in the process of consolidation suggestive of hematogenous infectious dissemination, were observed. The bone marrow biopsy confirmed diffuse infiltration by signet ring cells (Figure 3 a–h). Therefore, institutional esophagogastroduodenoscopy was performed, revealing a Borrman IV lesion in the gastric body (Figure 4) from where the biopsy samples were taken, but no malignancy was revealed (Figure 3 i–j).

1a



1b



Figures 1. Axial slices with axial (a) and coronal (b) reconstruction in the soft-tissue window of the stomach. The stomach is partially distended and presents with apparent thickening of the body in the greater curvature with apparent loss of the mucosal pattern. There is no alteration of the adjacent fat or presence of suspicious lymph nodes.



Figure 2. Bone window sagittal section of the lumbosacral spine showing multiple diffuse soft lesions compromising all the bony structures visualized.

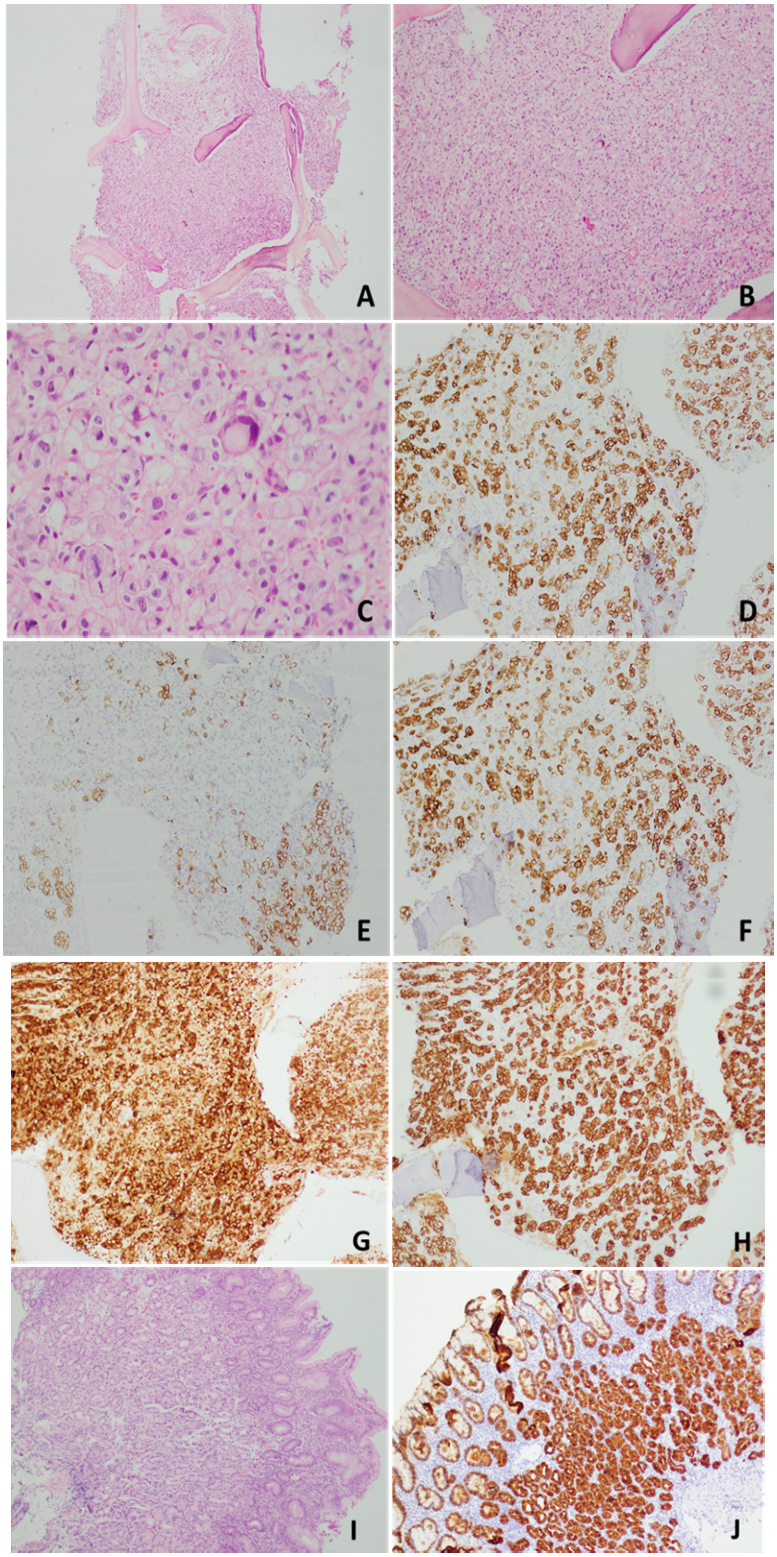
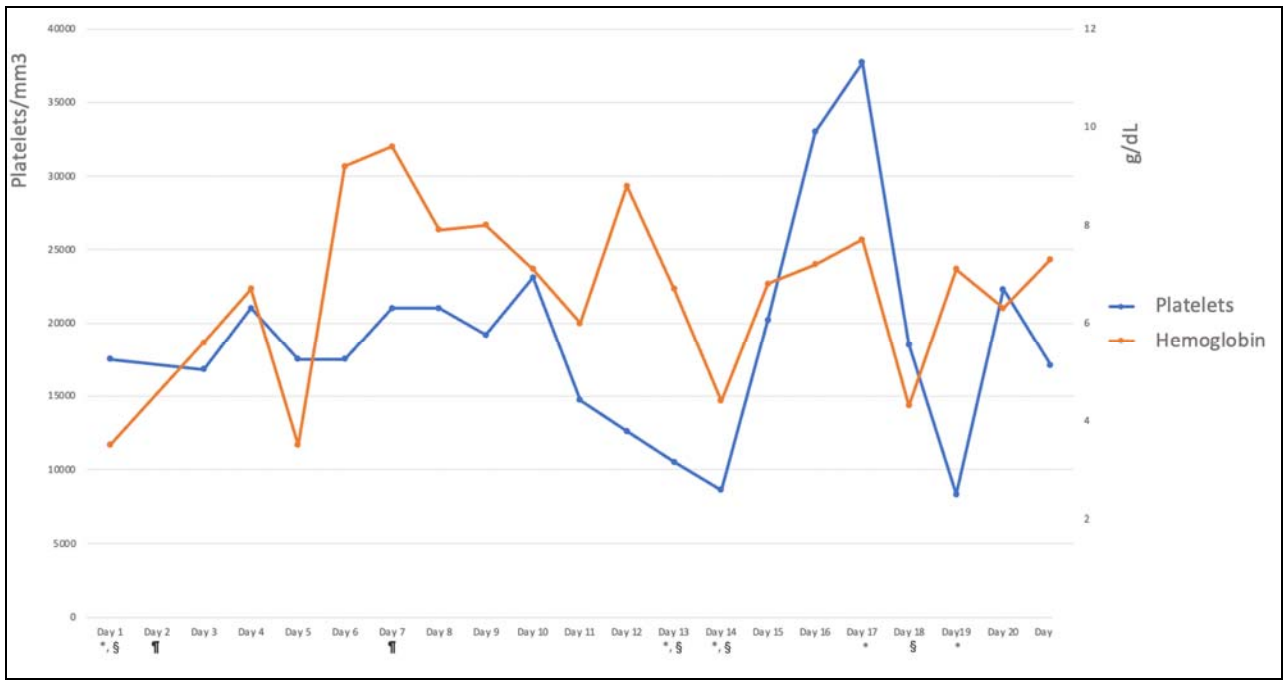


Figure 3. Bone marrow biopsy. **A, B and C**: Hematoxylin–eosin (HE) staining. Diffuse infiltration by epithelial cells arranged in nests that are discohesive, with clear, vacuolated, and broad cytoplasm; round nuclei; and some peripheral features giving a "signet ring" appearance. No residual hematopoiesis was identified. There were areas of extensive necrosis and thinned bone trabeculae (data not shown). **D, E, F, G, and H**: Immunohistochemical markers for CKAE1/AE3, CK7 (focal), CK20, CEA, and CK19, respectively, show positivity in neoplastic cells. Ca125, CDX2, and GATA3 markers were negative (not shown). **I and J**: Biopsy of gastric body mucosa. **I**: HE staining. Changes in the gastric mucosa due to chronic gastritis with mild inflammatory activity. No evidence of atrophy, intestinal metaplasia, dysplasia, or malignancy was found. **J**: Immunohistochemistry for CKAE1/AE3. Highlights the normal epithelial component without evidence of infiltrating cells.



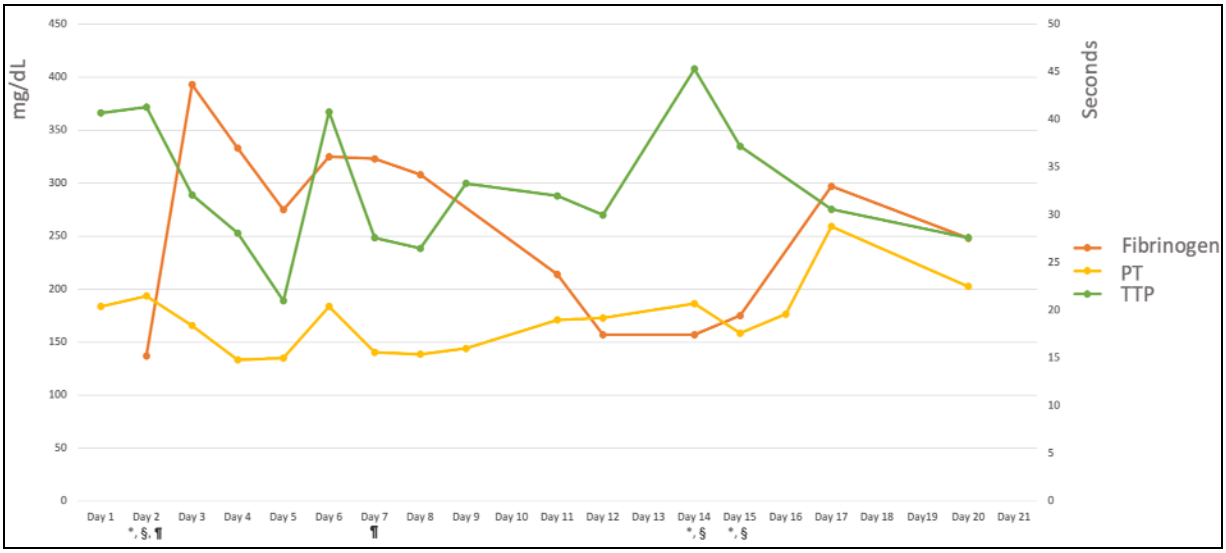
Figure 4. From the midbody to the proximal antrum, mucosa with an infiltrated appearance is observed with thickened gastric folds that do not distend despite maximal insufflation.

Chemotherapy was proposed with palliative intent; however, due to persistent bacteremia, it was not possible. Given the evidence of progressive deterioration and the impossibility of offering medical treatment, therapeutic efforts were redirected at ensuring well-being and comfort; therefore, she was discharged from the ICU to general hospitalization in the internal medicine department to optimize symptom control. Ultimately, the patient died during hospitalization. Graphics 1 and 2 show hemoglobin, platelets, coagulation times, and fibrinogen monitoring during the hospital stay.



* Transfusion of 2 units of packed red blood cells.
§ Transfusion of two single platelet concentrates.
¶ Initiation and completion of plasmapheresis.

Graphic 1. Platelet (mm^3) and hemoglobin (g/dL) monitoring during hospital stay.



* Transfusion of 10 cc/kg of cryoprecipitates.
§ Four units of plasma transfusion.
¶ Initiation and completion of plasmapheresis.

Graphic 2. Monitoring of prothrombin time (PT), thromboplastin (TTP), and fibrinogen during hospital stay.

DISCUSSION

We present the case of a 19-year-old female patient with no previous medical history who presented with non-immune microangiopathic hemolytic anemia and severe thrombocytopenia associated with DIC. She was found to have a Borrmann type IV gastric body lesion associated with diffuse infiltration of the bone marrow with signet ring cells.

The most common tumors that metastasize to the bone marrow are carcinomas originating from the breast, lungs, and prostate. Bone marrow metastasis from gastric adenocarcinoma is rare, with an incidence of less than 1%. In carcinomatosis of the bone marrow, a rare subtype of bone marrow metastasis with malignant cells, tumor cells diffusely infiltrate the bone and bone marrow, causing bone destruction and systemic hematological disorders. Metastatic tumors are best classified and diagnosed in specimens from their primary site of origin; however, immunohistochemical studies, in correlation with morphology, can indicate the primary origin in cases of tumors of unknown origins. In this patient, the tumor expressed pan-cytokeratin, CEA, CK20, and CK7 [5, 7].

TTP is a disseminated form of TMA in which there is a marked activation and consumption of platelets, resulting in excessive microvascular thrombosis, which leads to thrombocytopenia and non-immune hemolytic anemia. The majority of TTP cases are idiopathic, but there are secondary causes, including cancers (mainly gastric carcinoma), in approximately 50% of cases. Cancer-related microangiopathic hemolytic anemia was first described in 1970 by Brain *et al.* in 12 patients with metastatic mucin-secreting adenocarcinomas, of which six were of gastric origin. DIC is a serious condition that causes microvascular thrombosis due to activation and consumption of the coagulation system followed by activation of secondary fibrinolysis, which causes thrombocytopenia and a tendency to bleed. Common causes of DIC include sepsis, infection, trauma, malignancy, and liver disease. Clinical findings of cancer-associated TMA are difficult to distinguish from those of DIC because they have various similarities [8–12].

Both DIC and TMA can cause bleeding and organ failure, and during paraclinical tests, both can cause thrombocytopenia. Paraclinical tests are essential for differentiating between these conditions; prolongation of coagulation times, elevated fibrin degradation markers and hypofibrinogenemia are observed in patients with DIC and not typically seen in patients with TMA. Anemia and increased levels of creatinine, total bilirubin, and LDH are more frequently observed in patients with TMA; however, it is important to note that these abnormalities can be observed in up to 15% of patients with DIC. Additionally, schistocytes are commonly observed in TMA, since in DIC,marked fibrinolysis may dissolve microthromboses. Based on these considerations, we suspect our patient had coexisting TMA and DIC because she had

prolonged coagulation times, elevated D-dimer levels, hypofibrinogenemia, thrombocytopenia, and non-immune microangiopathic hemolytic anemia. The coexistence of these hematological disorders in patients with gastric carcinoma is exceptional; to our knowledge, only one case has been reported in the literature [12, 13].

This is an unusual presentation that occurred in a young woman with no comorbidities, no history of risk for neoplasms, and no positive findings on physical examination. Thus, the initial suspicion was TTP, and targeted treatment with therapeutic plasma exchange was initiated. The treatment was suspended when ADAMTS13 activity was found to be normal, ruling out autoimmune pathologies such as CAPS, which were the most likely differential diagnoses in this case.

Linitis plastica is a gastric cancer of diffuse histology that causes thickening of the gastric walls by diffuse infiltration and involves at least one-third of the stomach circumference. It represents 3%–19% of gastric adenocarcinomas and is more common in women and in those under 40 years of age. Generally, linitis plastica infiltrates the submucosal layer without destroying the structure of the stomach walls; however, findings in the mucosal layer are still insufficient to make a diagnosis because up to 30% of patients with linitis plastica produce negative results for malignancy on tissue biopsy [14–16], as in the present case.

The only treatment available for cancer-related TMA is treatment of the underlying neoplasm; even then, the prognosis is very poor [9–11]. This highlights the need for timely diagnosis of this disease, as well as an accurate method of distinguishing it from other forms of TMA, to decrease the time to systemic antitumor treatment and avoid inappropriate therapies.

In this patient, there were multiple difficulties during the therapeutic process, mainly due to hematological compromise (severe anemia and thrombocytopenia) requiring multiple transfusions, as well as infectious involvement (persistent bacteremia caused by *Staphylococcus aureus*). However, the high index of suspicion of a secondary etiology (in this case, cancer) of TMA allowed a definitive diagnosis, even with a negative histopathological result at the site of origin.

CONCLUSION

TMA secondary to carcinomatosis of the bone marrow as the initial manifestation of advanced gastric adenocarcinoma is extremely rare. A multisystem diagnostic approach in patients with coexisting TMA and DIC, especially if initial therapy has failed, could reduce the time to a definitive diagnosis in patients who have poor prognoses in the short and medium term.

Carcinomatoza medulară este rară fiind caracterizată prin infiltrat tumoral difuz în maduva hematogenă ce asociază modificări hematologice inclusiv microtrobi și CID. La pacienții cu cancer gastric această asociere un este frecventă. Prezentăm cazul unei paciente de 19 ani fără istoric cunoscut ce s-a prezentat cu hemoragie digestivă superioară. La examenul clinic s-a observat anemia și trombocitopenie, cu schizocite pe frotiul de sânge periferic și prelungirea timpilor de coagulare. Examenul endoscopic a decelta o leziune în corpul gastric Borrmann IV iar la biopsia medulară s-au observat celule în inel cu pecete. Pacienta a decedat în timpul spitalizării.

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Ethical considerations: We had the express authorization and signed informed consent of the patient to publish this case report.

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