Parésia Paraneoplásica do Nervo Abducente como Apresentação Inicial de Cancro Gástrico com Metastização para a Medula Óssea

Gastric Cancer with Disseminated Bone Marrow Carcinomatosis Initially Presenting with Paraneoplastic Abducens Nerve Palsy

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Resumo:

Aproximadamente 5%-10% dos acidentes vasculares cerebrais (AVC) criptogénicos têm uma neoplasia subjacente. A parésia do nervo abducente em doentes com neoplasia encontra-se geralmente relacionada com compressão tumoral, hipertensão intracraniana ou metastização.

Os autores reportam um caso de um doente com 65 anos com AVC multiterritório que se apresentou com uma parésia do sexto nervo unilateral e isolada cuja etiologia foi extensamente estudada. Admitiu-se o diagnóstico final de síndrome paraneoplásico, que foi a apresentação inicial de um carcinoma gástrico oculto provavelmente relacionado com a hipercoagulabilidade associada à malignidade.

Este caso enfatiza a importância de considerar um estudo adicional em casos selecionados de AVC criptogénico ou parésia do abducente.

Palavras-chave: Acidente Vascular Cerebral; Doenças do Nervo Abducente/complicações; Neoplasias; Metástases Neoplásica; Neoplasias do Estomago.

Abstract:

Approximately 5%–10 % of the patients with cryptogenic stroke have an underlying malignancy. Abducens nerve palsy in cancer patients is usually related to tumor compression, intracranial hypertension, or metastasis.

We report a case of a 65-year-old patient with multiple cerebral infarctions who presented with an isolated unilateral sixth nerve palsy and multi-territory cerebral ischemic lesions whose etiology was extensively investigated. The final diagnosis was a paraneoplastic syndrome, which was the initial presentation of an occult gastric cancer probably related to hypercoagulability associated with malignancy.

This case emphasizes the importance of considering additional workup in selected cases of cryptogenic stroke or abducens palsy.

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Keywords: Abducens Nerve Diseases/complications; Neoplasm Metastasis; Neoplasms; Stomach Neoplasms; Stroke.

Learning points

1. The report emphasizes that cranial nerve palsies, specifically unilateral abducens nerve palsy, can be a rare initial presentation of malignancies, including gastric cancer. This underscores the importance of considering a wide differential diagnosis in patients presenting with neurological symptoms.
2. Bone marrow metastasis in gastric cancer is uncommon but can occur, often associated with poor prognosis. This case serves as a reminder of the potential for atypical metastatic sites and their implications on patient outcomes.
3. Comprehensive evaluation involving various specialties and multiple diagnostic modalities is essential for accurate diagnosis and management.
4. This report highlights how acute complications, such as multiple strokes, can significantly worsen the prognosis of already compromised cancer patients, emphasizing the need for timely diagnosis and intervention.

Introduction

Patients with cancer have a substantially increased risk of stroke, generally related to cancer-associated hyper¬coagulation.[1-6] However, gastric cancer is not consistently listed as one of the cancers with the highest risk of stroke.[4,7,8]

Cancer-related cerebral embolism was never reported in the literature as a cause of an isolated abducens palsy. Generally, mononeuropathy of the abducens nerve in cancer patients is associated with tumor compression, increased intracranial pressure, or metastasis.[9,10]

Bone marrow is a rare local for metastasis in gastric cancer and its co-occurence with embolic phenomena as initial presentation is even rarer.[11]

We describe a rare case of unilateral abducens nerve palsy associated with metastasized gastric carcinoma to bone marrow.

Case Report

A 65-year-old man presented to the emergency department (ED) complaining of headaches, diplopia, and gait disturbance since 4 days ago. By this time, the patient had already visited the ED 3 times in the last month. He had general complaints of dry cough, anorexia, asthenia, and nausea generally after meals with 3 months of evolution. Additionally, he experienced a 5% weight loss, and more recently, he noticed fever, especially in the evening. He also had a history of contact with family members who had pulmonary tuberculosis. During the last ED visits, pleural effusion was investigated and a pleural exudate was identified, and an appointment was scheduled.

The patient worked at that time in railway construction in Norway. He has a history of hypertension and hypothyroidism as a consequence of hemithyroidectomy for benign nodular goiter. Previous medication includes levothyroxine and indapamide. No family history of cancer was noticed.

On present admission, the patient was 160 cm tall and weighed 56 kg. His pulse rate was 124 min, blood pressure of 158/94 mmHg and axillar temperature of 37.2°C. On physical examination decreased breath sounds were detected in the left lung base with no other abnormalities, including palpations of the lymph nodes, chest and abdomen. A full neurological examination revealed right palsy of the sixth cranial nerve and gait instability. No further alterations were detected.

The patient's laboratory data showed pancytopenia with hypoproliferative normocytic and normochromic anemia, with no deficit in hematin factors or changes in the peripheral blood smear (hemoglobin 9.1 g/dL, 1.28 x109/L lymphocytes and 88 x 109/L platelets), prolonged international normalized ratio (1.38) and mildly elevated levels of C-reactive protein (137.4 mg/dL) and erythrocyte sedimentation rate (80.0 mm/h). The D-dimer levels were elevated (27148 ng/mL), and lactate dehydrogenase was 239 UI/L. No other significant abnormalities were observed in the blood analysis, including liver enzymes and fibrinogen.

Electrocardiography showed sinus tachycardia, and brain computed tomography (CT) scan was normal. On lumbar puncture, cerebrospinal fluid (CSF) was clear and exhibited normal pressure. Analysis of the the CSF disclosed absence of pleocytosis or proteinorrachia, nor glucose consumption.

Brain magnetic resonance imaging (MRI) revealed "multiple foci of reduced diffusibility, one left posterior periventricular, one subcortical in the left parieto-occipital transition, two cortico-subcortical foci in left parietal and right medial occipital topography, and also a right parietal cortical focus, acute/recent ischemic lesions in multiple territories, evoking a possible embolic source or possible vasculitis" (Fig. 1). No leptomeningeal enhancement was reported.

The patient was hospitalized for further investigation. Initially, a stroke work up was performed to rule out embolic or

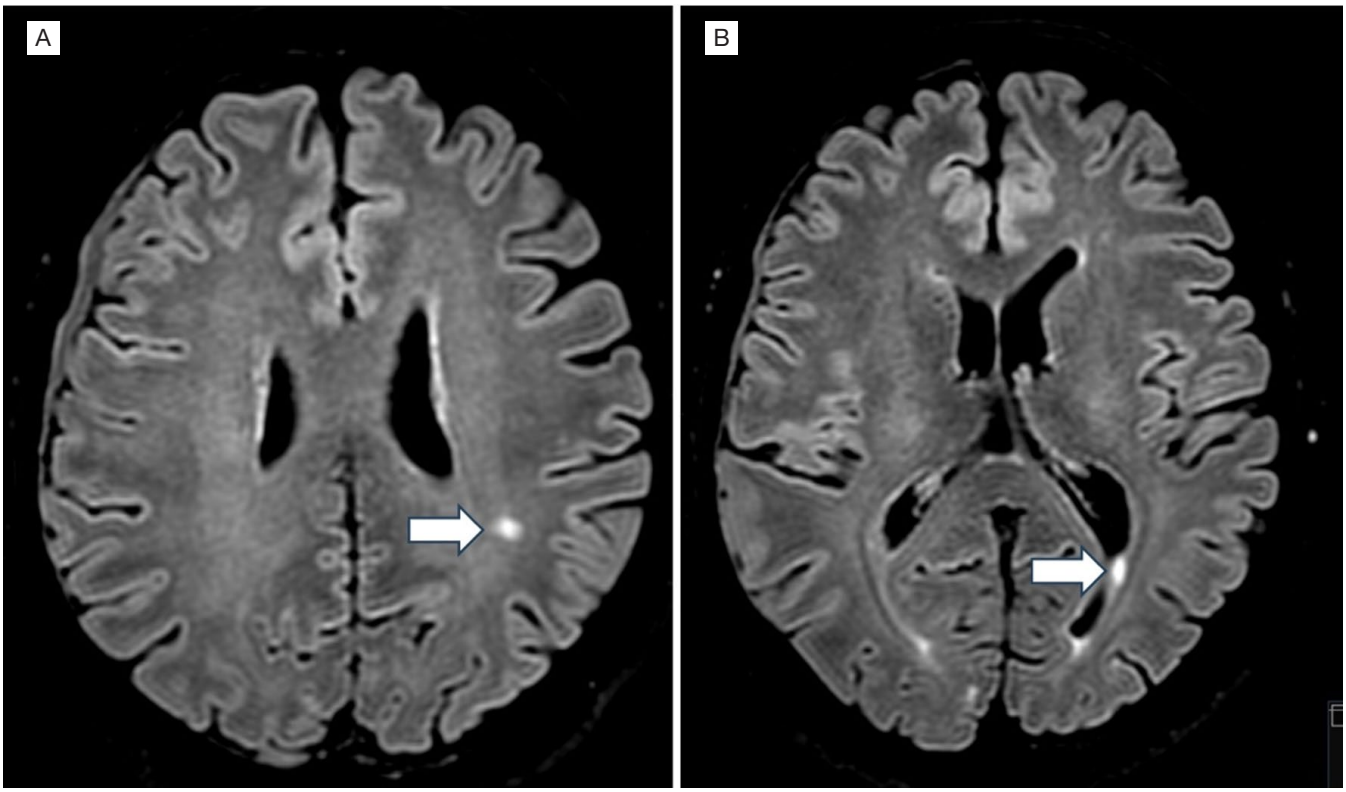

Figure 1: Axial FLAIR-weighted brain magnetic resonance images – **(A)** Evidence of a left parietal subcortical hypersignal focus (arrow). **(B)** Evidence of a left posterior periventricular hypersignal focus (arrow).

atherosclerotic causes. A CT angiography, transthoracic and transesophageal echocardiography, Doppler ultrasound of neck vessels and 24-hour electrocardiogram (ECG) test did not reveal a source. The Doppler ultrasound of the neck vessels showed a stenosis without hemodynamic significance (<50%) of the right internal carotid artery.

The possibility of an infectious, neoplastic, or auto-inflammatory cause was also investigated.

Microbiological blood analysis was negative as well as serologies for human immunodeficiency virus, hepatitis virus (**B**, **C**), *Toxoplasma gondii, Coxiela burnetti, Borrelia (burgdorferi, afzelii, garinii), Francisella tularensis, Legionella pneumoniae, Aspergillus fumigatus, Mycobacterium tuberculosis complex*. The Venereal Disease Research Laboratory (VDRL) test yielded a negative result. Additional results from de CSF were obtained during hospitalization. The CSF exams yielded negative findings for cryptococcus antigen and VDRL tests. Testing for Mycobacterium tuberculosis DNA returned negative results. Additionally, CSF cytology and cultures for bacteria, acid-fast bacilli, and fungi were all negative.

Screening for vascular risk factors and immunological disorders (antinuclear antibodies, antineutrophil cytoplasmic antibodies, anticardiolipin antibody, rheumatoid factor, C3, and C4) as well as thyroid function and prostate-specific antigen test were normal.

Proteinogram showed an inflammatory pattern with an increased immunoglobulin A (698 mg/dL)

A chest, abdominal, and pelvic CT revealed bilateral pleural effusion and intercavoaortic lymphadenopathy, the largest measuring 20x17 mm. No other abnormalities were detected, including the gastrointestinal tract without wall thickening.

An 18F-fluorodeoxyglucose positron emission tomography (18-FDG-PET) was performed in the absence of a definitive diagnosis and suspicion of a lymphoproliferative disorder. It showed hypermetabolic involvement medullary/bone (involving much of the skeleton, more evident in the humerus and femurs); foci of anomalous and significantly increased uptake of fluorodeoxyglucose (FDG) in adenopathies on the lesser gastric curvature, in the region of the hepatic hilum/next to the pancreatic head, in the intercavoaortic chain at the level of the L2 vertebral body and in small left supraclavicular nodes; increased uptake of FDG in the stomach; and bilateral pleural effusion, larger on the left, with very discreet and diffuse uptake of FDG (Fig. 2).

A dry tap was obtained on bone marrow aspiration and a bone marrow biopsy was done. An upper gastrointestinal endoscopy was performed and demonstrated an extensive

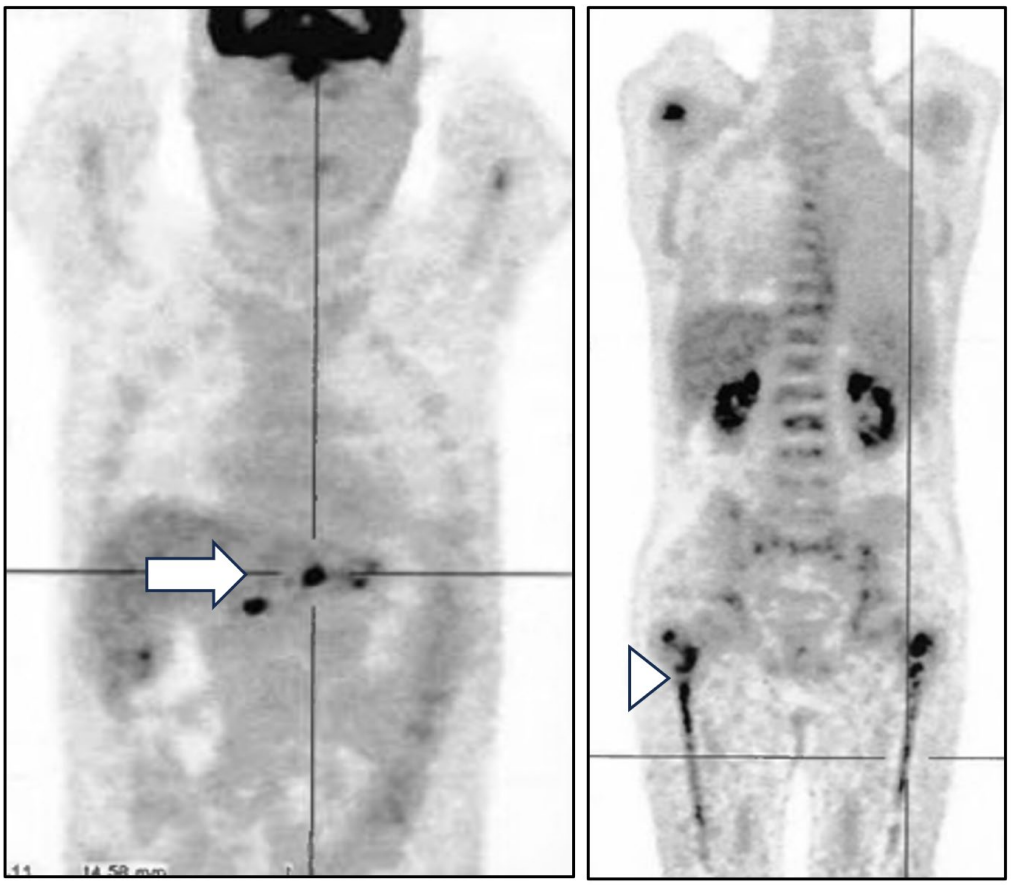

Figure 2: 18-FDG-PET coronal images - Focal FDG uptake in the stomach and surrounding adenopathies (arrow), and in the skeleton (more evident in femurs - arrowhead).

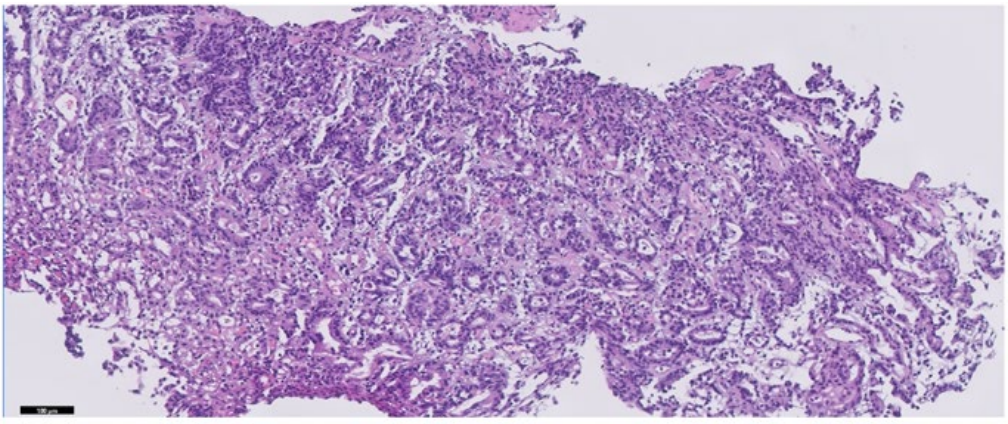

Figure 3: Gastric biopsy (HE, 20x): Gastric mucosa infiltrated by a poorly differentiated carcinoma.

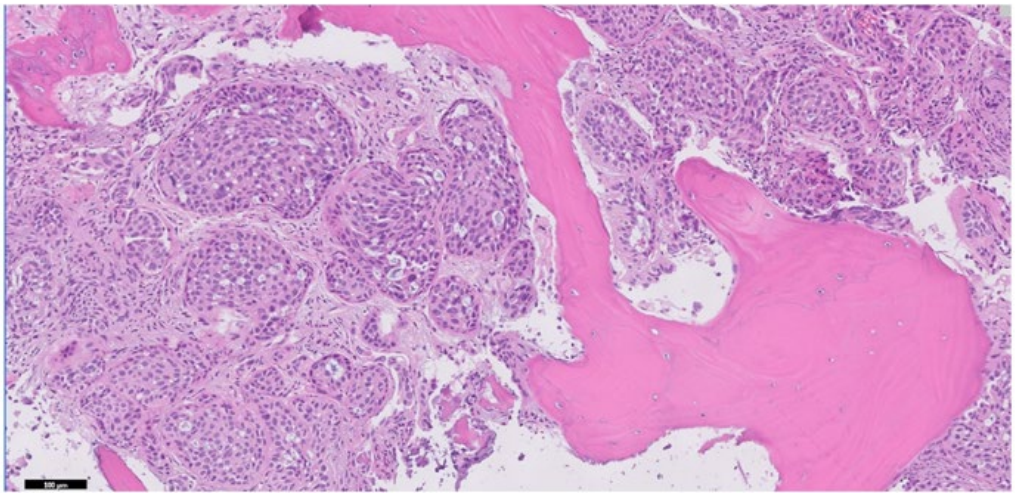

Figure 4: Bone marrow biopsy (HE, 20x): Metastatic infiltration of bone marrow by adenocarcinoma cells.

infiltrative-type lesion on the lesser curvature of the body and antrum, which biopsy confirmed a poorly differentiated gastric carcinoma (Fig. 3).

His inpatient stay was complicated by new cerebral ischemic lesions with ataxia, left hemiparesis and of visual field loss and acuity. He developed severe pancytopenia, gastrointestinal bleeding, and refractory fever in his last week.

The final diagnosis came from gastric mass and bone marrow biopsies that showed a poorly prognostic gastric carcinoma with bone marrow infiltration (Fig. 4), with association of multiple cerebral infarctions due to hypercoagulability state due to malignancy.

The worsening consciousness levels, and poor performance status disabled any active management. Best supportive care was done, and the patient died.

Discussion

The authors present the first case report of unilateral abducens nerve palsy caused by a paraneoplastic syndrome as the initial presentation of an occult gastric cancer.

The initial diagnostic hypothesis was pleural tuberculosis in view of the nonspecific complaints with 3 months of evolution, pleural exudate, and history of contacts with family members with pulmonary tuberculosis, the reason why the diagnostic march was suspended. It is only when the patient presents with sixth nerve palsy and multi-territory cerebral ischemic lesions that diagnostic doubt is renewed. An extensive stroke workup was done with no etiology found. Thus, in the presence of a cryptogenic stroke, a larger investigation was done.

Etiological diagnosis of sixth cranial nerve palsy can be at times quite challenging, with a vast list of possible causes. In an older adult with vasculopathic risk factors as our patient, a neurologically isolated cranial nerve (CN) VI palsy is most commonly due to a microvascular ischemic cause, but other serious etiologies should be excluded.[9,10] In fact, isolated CN VI paresis has been reported previously as the presenting sign of neoplasms and its occurrence was related to tumor compression, increased intracranial pressure, or neoplastic infiltration.[12-15] In the etiological investigation of this case, possible causes for abducens palsy were reasonably excluded based on clinical data, laboratory analysis, and brain scan findings, namely infections, inflammatory diseases, and thyroid eye

disease. Brain MRI showed an unexpected cause for sixth--pair mononeuropathy, namely embolic cerebral infarctions. Echocardiography was performed and ruled out the presence of intracardiac mass, putting aside the hypothesis of nonbacterial thrombotic endocarditis and infective endocarditis. The presence of constitutional symptoms and moderately high inflammatory biomarkers alerted us to the possibility of an underlying neoplastic disease and directed further workup until the diagnosis of gastric cancer. Some isolated cases of sixth pair paresis associated with metastasis from gastric cancer have been reported.[13] However, to the best of our knowledge, there are no documented cases of abducens palsy caused by tumor brain embolism as a manifestation of cancer.

It is known that stroke is a serious complication of malignancy, significantly aggravating their condition and prognosis, and it can occur either at the beginning or during the cancerous disease.[1-3,5] In the pathogenesis of stroke in cancer patients a plethora of mechanisms are evolved, and cancer--associated hyper¬coagulation seems to be the most relevant stroke etiology.[4,6] Several studies have attempted to elucidate which cancer types present a stronger association with the occurrence of stroke and gastric cancer is not consistently listed as one of the principal contributors.[4,7] No increased stroke risk for gastric cancer was reported by Lindvig *et al.*[7] In 2014, Navi *et al* study showed that cancers with the highest incidences of stroke are lung, pancreatic, colorectal, breast and prostate.[4] A retrospective analysis, including 1274 stroke patients admitted to a stroke unit, showed that 12% had an additional diagnosis of cancer, with urogenital, breast and gastrointestinal being the most frequent cancer types.[8] Some studies found evidence that patients with cancer have significantly higher prevalence of infarction in multiple vascular territories suggesting an embolic origin, more frequentlycryptogenic strokes, more elevated inflammatory markers, and lesser vascular risk factors compared with non-cancer groups, which is consistent with our case findings.[3,16,17]

There is yet another rare finding in this case. The observed hematologic alterations were initially interpreted as an acute response to the inflammatory context. However, PET and bone biopsy confirmed an extensive medullary infiltration by cancer. Bone marrow involvement in gastric cancer is not a frequent expected finding, in fact is a rare local of metastization and is not usually seen in the initial presentation.[11] We found in the literature only a case of gastric cancer with bone marrow metastases and embolic phenomena as initial presentation.[18] Bone marrow metastasis in gastric cancer is usually related to poorly differentiated subtypes, younger ages at presentation and it is a disease with worse prognosis, their median survival is less than 3 months.[19,20] In our patient, the multiple strokes beyond decreasing the performance status of the patient also contributed to worsen prognosis of the underlying oncological condition. The role of bone marrow carcinomatosis in the development of cerebral infarction was unclear in our patient.

Conclusion

In summary, we present a rare clinical presentation of a gastric cancer. In our patient, abducens nerve palsy of thromboembolic origin was the initial presentation of a metastasized gastric cancer. Bone marrow is an unusual site of metastasis in gastric cancer and its co-occurrence with paraneoplastic embolic phenomena in its initial presentation is even rarer. ■

Presentation

The clinical case was presented at the 29th National Congress of Internal Medicine.

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TP, AP, ST – Revisão da literatura e elaboração do manuscrito
LP – Revisão critica do manuscrito e aprovação da versão final do artigo
Todos os autores aprovaram a versão final a ser publicada

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TP, AP, ST - Literature review and drafting of the manuscript
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