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Dural Metastasis without Subdural Hematoma or Subdural Fluid Collection in a Patient with Signet Ring Cell Gastric Adenocarcinoma

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Female, 39-year-old

Final Diagnosis: Dural metastasis in signet ring cell gastric adenocarcinoma

Symptoms: Confusion • generalized seizure • headache

Medication: —

Clinical Procedure: —

Specialty: General and Internal Medicine • Oncology

Objective: Unusual clinical course

Background: Signet ring cell (SRC) gastric adenocarcinoma is an aggressive histotype associated with poor prognosis, especially in advanced gastric cancer. Dural metastasis is rarely described in the literature, and clinical manifestations are generally related to subdural hematoma. Here we present a case of advanced SRC gastric cancer with dural neoplastic involvement in the absence of subdural hematoma or subdural fluid collection.

Case Report: A 39-year-old woman presented with multiple episodes of confusion and headache. She had a history of SRC gastric adenocarcinoma that had been treated with neoadjuvant chemotherapy and total gastrectomy without evidence of disease relapse at follow-up. During hospitalization, she experienced persistent drowsiness and frequent generalized seizures that were nonresponsive to antiepileptic drugs. Brain computed tomography showed a dural right parafalcine nodular lesion suggestive of metastasis, and an SRC presence was detected in a cerebrospinal fluid sample. Cerebral magnetic resonance imaging showed isolated diffuse dural neoplastic involvement without evidence of subdural hematoma or subdural fluid collection. We considered palliative treatment with intrathecal chemotherapy, but it was not carried out because of clinical worsening and subsequent death.

Conclusions: In the very few case reports in the literature, dural metastasis in advanced gastric cancer is mainly associated with subdural hematoma. In our case, the absence of any subdural effusion, which is an even rarer condition, along with an unusual clinical presentation dominated by generalized seizures represented a diagnostic challenge. Given the aggressive course of the disease, a rapid diagnosis could allow a faster specific treatment to relieve a patient's symptoms.

MeSH Keywords: Carcinoma, Signet Ring Cell • Dura Mater • Neoplasm Metastasis • Stomach Neoplasms

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Background

Gastric signet ring cell carcinoma (SRCC) is a histological diagnosis that refers to particular microscopic characteristics [1], with weak cohesion among neoplastic cells and specific cytoplasmic and nuclear features [2]. Despite the overall decrease in gastric cancer incidence worldwide, partly related to eradication therapy for *Helicobacter pylori*, the incidence of SRCC is increasing. This increase could be related to other risk factors, based on comparison with non-SRCC gastric cancers. SRCC is known to be associated with distinct genetic mutations, particularly concerning the *CDH1* gene, which is frequently involved in familial forms of diffuse gastric cancer [3].

The stage of SRCC disease at the time of diagnosis has a key role in prognosis. In early gastric cancer, the SRCC histotype seems to have an equivalent or even better prognosis than other gastric adenocarcinomas, but at an advanced stage, the prognosis is generally poorer and has a worse survival rate [3].

Gastric cancer has the potential to metastasize, and the most frequently involved organs are the liver, peritoneal cavity, lymphatic glands, and lung; however, rare sites are also documented in the literature [4,5]. The meninges are generally a very unusual site of metastasis, but in such cases, leptomeningeal involvement is often present. Among the very few case reports of dural neoplastic involvement, clinical manifestations usually arise from spontaneous subdural hematoma. In the present report, we describe a case of advanced SRCC of the stomach with evidence of dural metastasis in the absence of any subdural hematoma or fluid collection.

Case Report

A 39-year-old woman presented at our Internal Medicine Department owing to multiple episodes of confusion and headache. Her medical history was positive for SRCC of the cardiac region with abdominal lymph node involvement, diagnosed 8 months before. It was treated with neoadjuvant chemotherapy (docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil) followed by total gastrectomy, D3 lymphadenectomy, and splenectomy. During the subsequent follow-up, positron emission tomography and computed tomography (CT) of the abdomen were negative for disease relapse. In particular, systemic metastasis was not detected.

On arrival, the patient was cachectic and reported several episodes of confusion and headache within the previous 10 days. No neurological deficits were found on physical examination except for left sixth cranial nerve palsy. Laboratory tests revealed moderate anemia (10.3 g/dL), while the platelet count and coagulation tests were within normal limits. After 3 days,

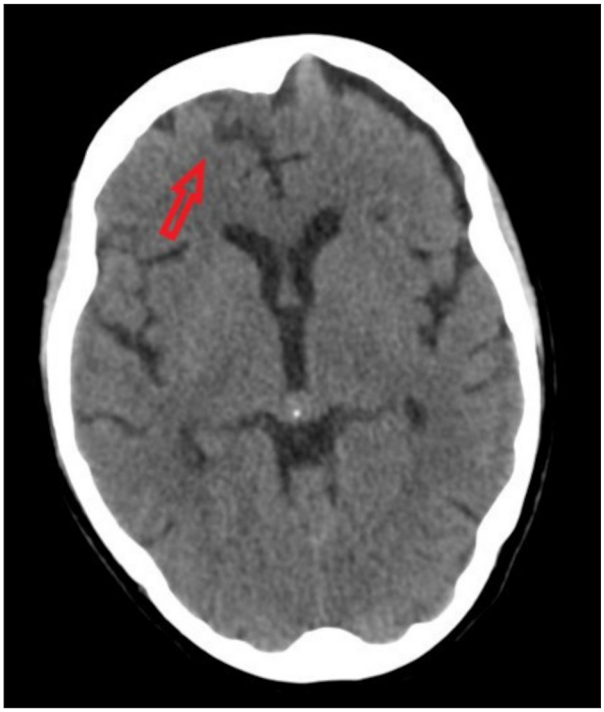

Figure 1. A direct brain computed tomography scan section showing the isodense right dural parafalcine nodular lesion (dimensions: 0.9×1.6 cm).

the patient experienced several progressively more frequent episodes of tonic-clonic generalized seizures alternating with absence seizures. No other neurological deficits were detected throughout the hospitalization. We therefore performed an electroencephalogram, which was positive for diffuse bilateral slowing without evidence of focal epileptiform abnormalities. We started intravenous levetiracetam, valproic acid, and lacosamide, with poor clinical improvement and progressive neurological worsening with persistent drowsiness. A worsening in headache intensity was also noted, along with emesis that did not respond to drugs (metoclopramide and ondansetron). These signs suggested possible intracranial hypertension, so intravenous dexamethasone and mannitol were started but without significant benefit. We simultaneously carried out a brain CT scan (Figure 1), which showed a right dural parafalcine nodular lesion (dimensions: 0.9×1.6 cm) that was highly suggestive of dural metastasis; no parenchymal lesions were found. Considering the clinical and radiological situation, we carried out a lumbar puncture with chemical-physical analysis of cerebrospinal fluid (CSF) on day 7. No evidence of a high-pressure CSF leak was found, so intracranial hypertension was not indicated. On microscopic examination of the CSF, signet ring cells were discovered (Figure 2A, 2B). On the same day, cerebral magnetic resonance imaging (Figure 3) confirmed the dural lesion already seen on CT scan. It also showed diffuse bihemispheric dural neoplastic involvement without evidence of leptomeningeal carcinomatosis, parenchymal lesions,

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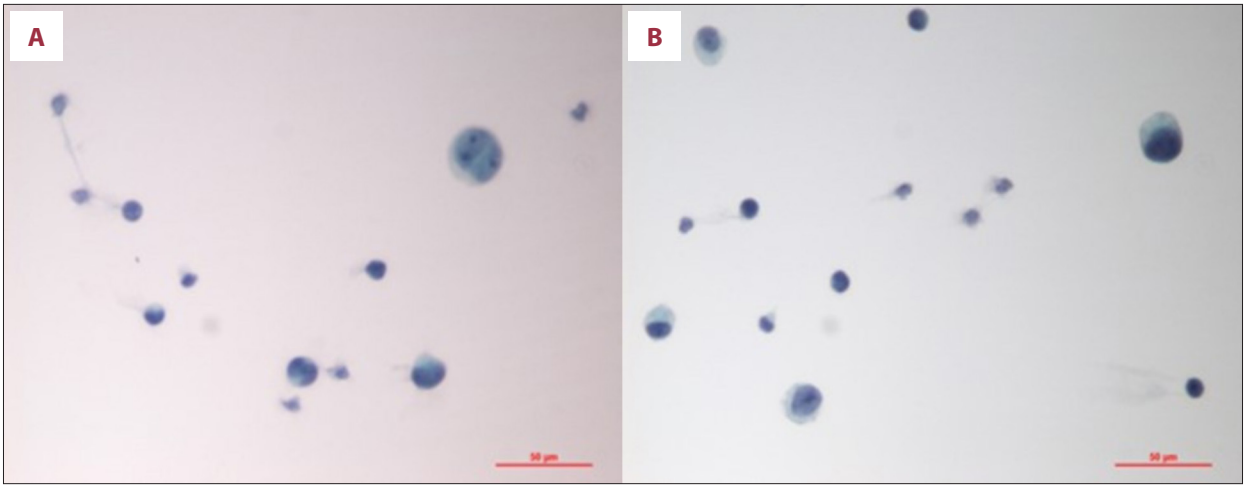

Figure 2. (**A, B**) Microphotographs from microscopic examination of the cerebrospinal fluid sample. Signet ring cells are clearly recognizable (method: liquid-based cytology, Papanicolaou stain).

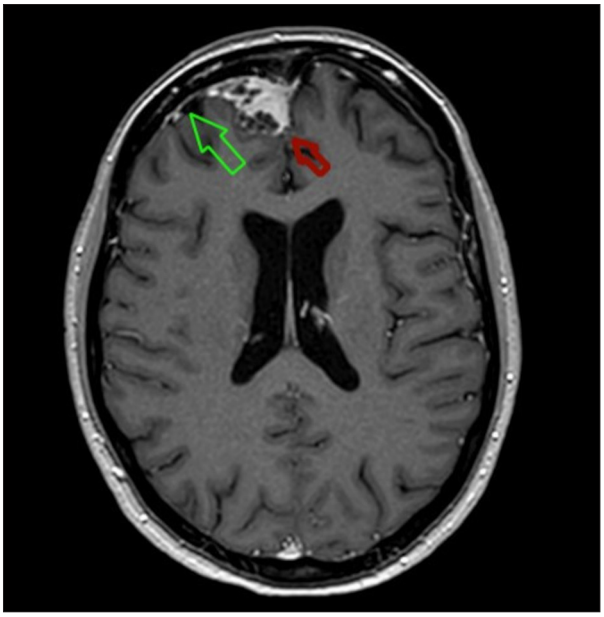

Figure 3. A contrast-enhanced cerebral magnetic resonance imaging section showing the right parafalcine nodular lesion already seen in the direct computed tomography scan (red arrow). Other dural areas of diffuse thickening and enhancement (known as "dural tail sign") are also visible (green arrow).

or subdural hemorrhage. Based on the clinical situation, we started a multidisciplinary discussion with the oncology team and, considering the advanced disease stage, we decided to initiate palliative intrathecal chemotherapy with methotrexate. Unfortunately, we were not able to start this treatment owing to further clinical worsening and could only continue supportive treatment with corticosteroids and antiepileptic drugs. The patient died 16 days after her arrival.

Discussion

In autopsies of patients with a history of malignant cancer from various primary sites, metastasis involving the dura mater was identified in only about 10% of cases, as previously described by Hirano and Hojyo [6]. The highest frequencies were found in connection to cancer of breast, lung, skin (particularly melanoma), gastroenteric tract, and prostate. Among the primary cancer sites, as described by Kunii et al. [7], the stomach appears to be the most frequent, followed by the prostate gland and breast, with adenocarcinoma being the most commonly detected histotype. However, cases of dural metastasis secondary to poorly differentiated cancer of unknown origin have also been described [8].

Owing to our case presented here, we performed a literature search and found that isolated dural involvement appears to be particularly rare in comparison with metastasis generally found in the central nervous system of patients with gastric cancer. Moreover, in the majority of the 12 case reports that we found [9–20], no hepatic metastasis was present.

In many of the cited case reports, subdural hematoma was present and, as described by Russell and Cairns [21], a possible underlying mechanism is the embolism of tumoral cells leading to the obstruction of draining veins in the dura mater. This obstruction can induce dilation and increase pressure in the capillary vessels, with subsequent breakdown and subdural hematoma development, although other hypotheses have also been proposed [22]. Nevertheless, these mechanisms alone are insufficient to explain subdural hematoma formation, and another contributing factor could be a concurrent congenital or acquired coagulopathy [23].

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Clinical presentation of these patients is frequently related to the mass effect of a hematoma on the brain, resulting in focal neurological deficits. Subdural hematoma was not detected in 3 of the 12 cases found [11,16,18]; instead, subdural fluid collection occurred in the absence of any bleeding sign. Given the cytological characteristics of signet ring cells and their secretion of mucin, this finding could be related to direct cellular fluid excretion combined with the increasing capillary perfusion pressure, as already described.

In contrast to all but one of the cited case reports on metastasis of the dura mater in gastric adenocarcinoma, it is notable in our case that diagnostic investigations did not demonstrate any kind of subdural bleeding or fluid collection. The exception was reported by Kim et al. [9], who also did not find subdural hematoma or subdural fluid collection. It is interesting to note that in our case, except for the left sixth cranial nerve palsy already present upon the patient's arrival, the main clinical signs were related to generalized seizures that were poorly responsive to conventional antiepileptic drugs. To our knowledge, this clinical manifestation is not frequently associated with dural metastasis. In addition, lumbar puncture did not show the increased output pressure that occurs with intracranial hypertension. The presence of a severe continuous headache and uncontrollable emesis in our patient could be explained by meningeal irritation by free neoplastic cells in the CSF.

Conclusions

The dura mater is a very rare site of metastasis in patients affected by advanced cancer of the stomach. Our patient represents one of the few described cases involving this rare manifestation of the aggressive disease. This case is notable owing to the absence of subdural hematoma or subdural fluid collection, which is an even rarer condition, and a clinical presentation dominated by generalized seizures. It serves as an example of a diagnostic challenge in light of other reports about patients with a similar medical and clinical history, which could delay correct diagnosis. A rapid diagnosis could enable starting an early specific treatment with radiotherapy or systemic and/or intrathecal chemotherapy (e.g., with methotrexate [9]). Such treatment is known to be palliative and can offer significant improvement in neurological symptoms and quality of life for eligible patients. However, the few reports found in literature are mainly related to advanced cancer of the stomach and concurrent leptomeningeal carcinomatosis. Currently, there are no criterion standard treatment guidelines available [24], and even less is known about dural metastasis and their best medical therapy.

Conflicts of interests

None.

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