Case report

Leptomeningeal carcinomatosis in gastric cancer: a case report of a rare yet aggressive entity

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Abstract

Leptomeningeal carcinomatosis (LMC) is exceedingly rare in gastric cancer. It is most commonly seen in breast, lung cancer and melanoma, and is associated with an extremely poor prognosis. If untreated, median overall survival is four to six weeks. No standard treatment for LMC exists and published data are scarce. We present two cases of gastric carcinoma diagnosed with LMC that exemplify how aggressive this condition is and how short the time lapse is to perform any targeted therapy. This report aims to raise awareness of this rare metastatic possibility in gastric cancer and its diagnostic and therapeutic challenges.

Keywords: *leptomeningeal carcinomatosis; gastric cancer; advanced cancer; intrathecal chemotherapy*

Introduction

Leptomeningeal carcinomatosis (LMC), also known as carcinomatous leptomeningitis, is defined as diffuse infiltration of carcinoma into the meninges. Occurring in 3-8% of all cancer patients, it is associated with major neurologic complications and high mortality [1]. LMC is frequently found in patients with breast cancer, lung cancer, melanoma and hematologic malignancies [2]. The prevalence of LMC in gastric cancer (GC) patients is as low as 0.16-0.69% [3].

Common neurological symptoms include headache, nausea, vomiting, altered mental status and cranial nerve palsies. Definitive diagnosis is established by the presence of neoplastic cells in the cerebrospinal fluid (CSF) or by meninges biopsy. Prognosis of LMC is poor because most treatments are only for symptomatic control [4, 5]. Central Nervous System (CNS) metastasis in gastrointestinal cancer is not common, and LMC is even rarer. There are reports of gastrointestinal-origin LMC [1, 6], although clinical features and the best treatment strategies have yet to be determined.

We herein report two cases of LMC in GC. We underline the rarity of this condition. Neurological symptoms in GC patients should raise suspicion of CNS spread metastasis, including LMC; this may help to secure timely and safe patient care.

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Case report

Case 1

A 46-year-old man was diagnosed with advanced poorly cohesive signet ring cell gastric adenocarcinoma (cT3N2M1), human

epidermal growth factor receptor 2 (HER2) negative, in November 2017. He was initially treated with modified DCF regimen (Docetaxel 40 mg/m2 on day 1, Cisplatin 40 mg/m^2 on day 3 and 5-Fluorouracil 2000 mg/m^2 continuous infusion over 48h, every two weeks). He completed six cycles with good clinical response and partial radiological response.

Two months later, he presented to the emergency department (ED) with a 6-day history of severe persistent headache, diplopia and abnormal gait. Besides ataxia, his neurological examination was unremarkable. Initial blood workup and head CT scan showed no abnormalities. Subsequently, a lumbar puncture was performed and CSF analysis was compatible with LMC (Figure 1). He was then admitted to the neurology department for further evaluation and initiated dexamethasone (16 mg/day), with partial resolution of symptoms. Brain magnetic resonance imaging (MRI) was performed, showing leptomeningeal enhancement as well as malignant infiltrates at the entire cerebrum (Figure 2).

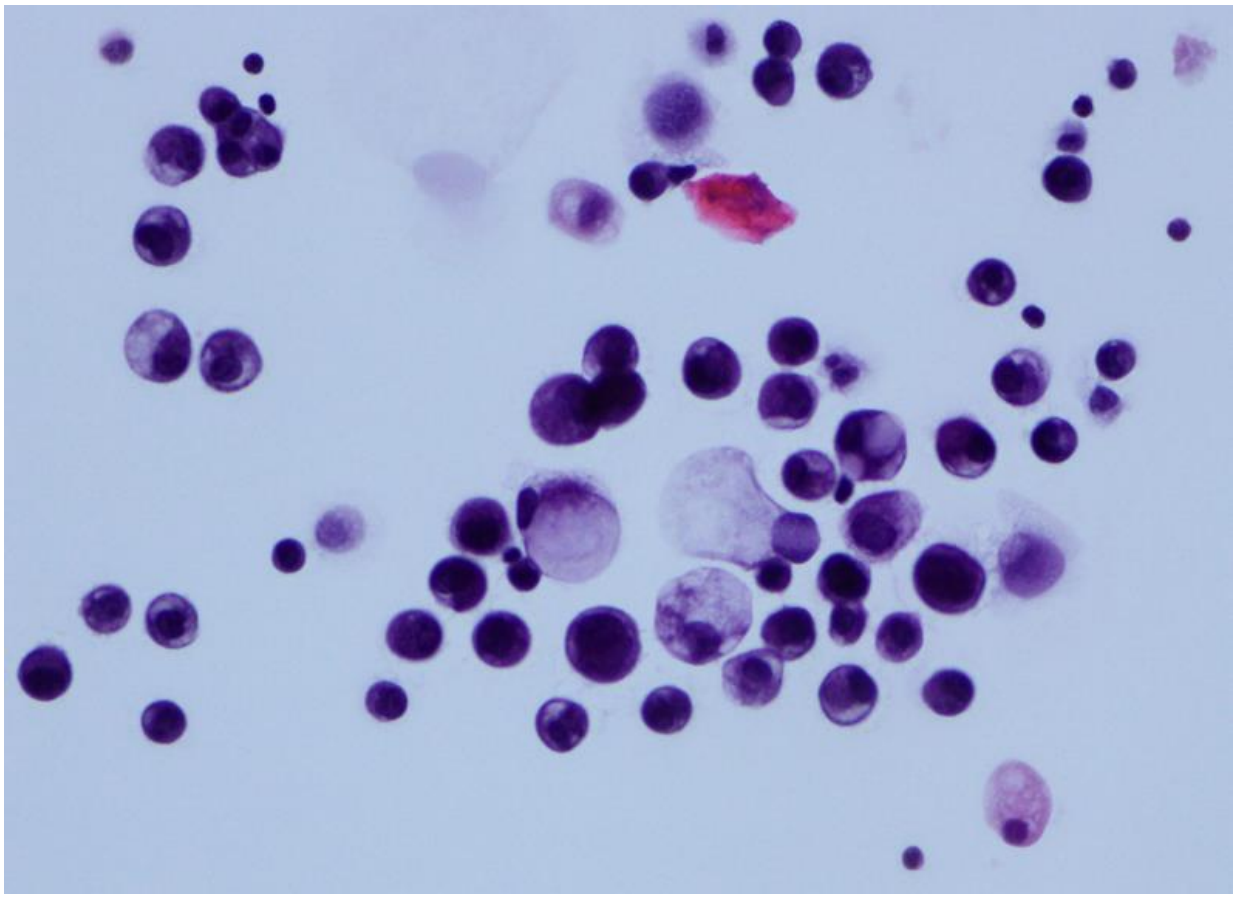

Fig. 1. Cytopathologic finding of cerebrospinal fluid revealing large malignant cells, some with a signet-ring appearance.

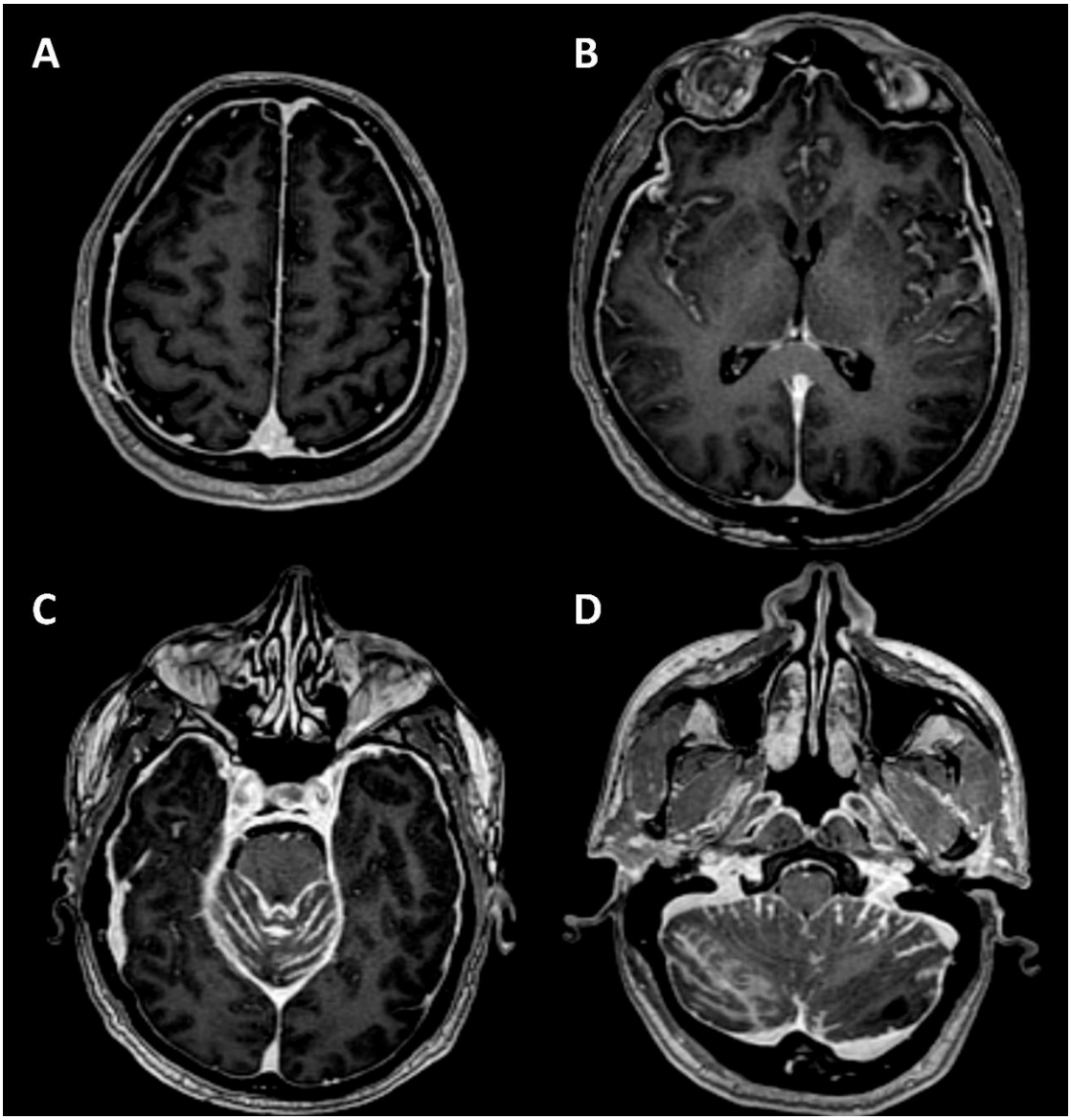

Fig. 2. A, B, C: T1-weighted gadolinium-enhanced MRI scan showing brain meningeal enhancement with involvement of the subarachnoid space; **D**: T1-weighted gadolinium-enhanced MRI scan showing cerebellar and bulbar meningeal enhancement.

Case 2

A 50-year-old man was diagnosed with localized poorly cohesive gastric adenocarcinoma (cT2N2M0) in February 2015 and was treated with perioperative chemotherapy and surgery (total gastrectomy), according to the MAGIC trial [7].

One month after the surgery, he presented to the ED with a 4-day history of nausea, epigastric abdominal pain and acholic stools. Laboratory data revealed elevated serum lipase (1980 U/L) and amylase (215 U/L), but the abdominal ultrasound was unremarkable. A postoperative acute pancreatitis was assumed but on day 3, he developed two brief episodes of clonic left hemi-body seizures with Jacksonian march without loss of consciousness. Head CT scan revealed a hyperintense right frontoparietal lesion with surrounding oedema, suggestive of malignancy on brain MRI (Figure 3). He suddenly began with persistent unrelieved headache, nausea and vomiting. CSF analysis revealed atypical malignant signet-ring cells and gastric adenocarcinoma LMC was assumed (Figure 4).

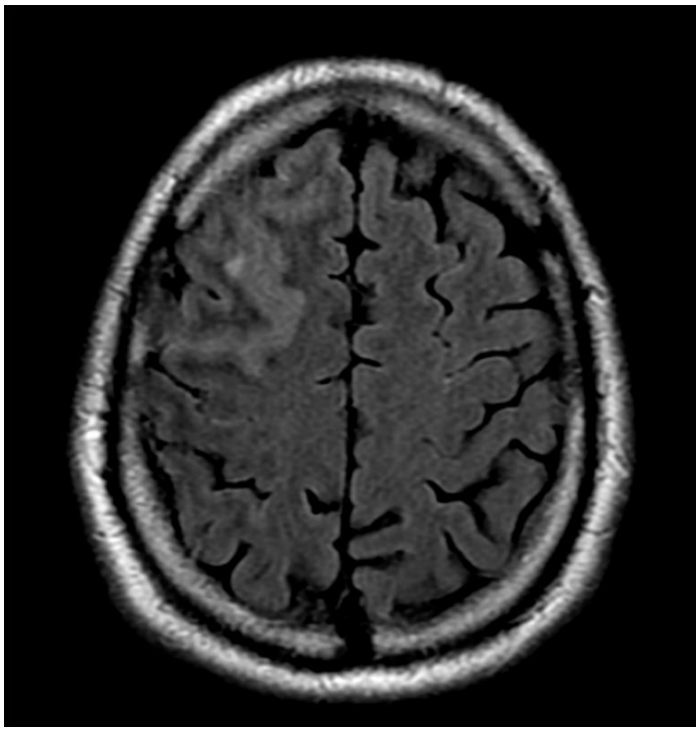

Fig. 3. Brain MRI, axial FLAIR, revealing hypersignal and locoregional thickening of the superior frontal sulcus.

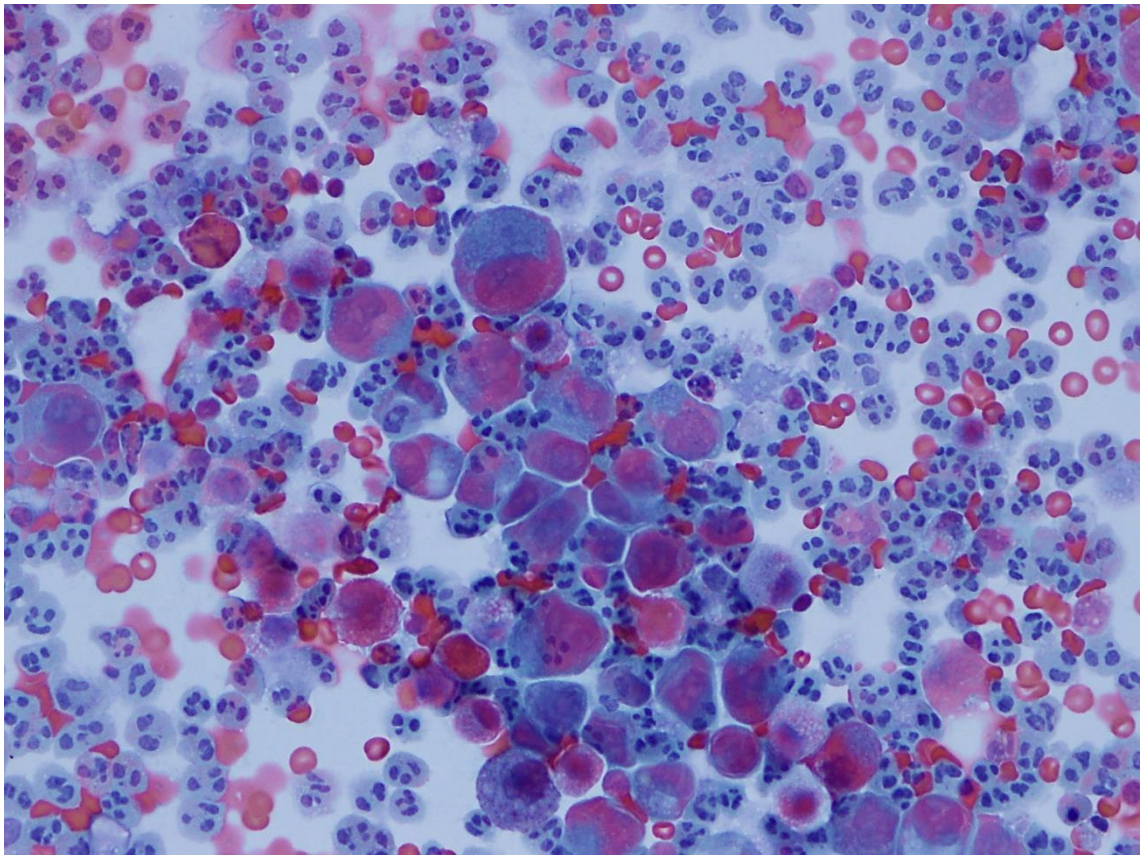

Fig. 4. Neoplastic cells in the CSF with pleomorphic nuclei and prominent nucleoli.

After discussion at the multi-disciplinary tumor board, the patient started intrathecal (IT) chemotherapy with methotrexate (12 mg) and dexamethasone (4 mg), once a week. After two cycles of IT his neurological symptoms aggravated and its performance status degraded and he was referred to palliative care, were he died two months later.

Discussion

LMC is the third most common metastatic complication of the central nervous system affecting approximately 5% of patients with cancer. LMC has been rarely reported in GC, it seems more often in advanced poorly differentiated adenocarcinoma with signet ring cell features, as seen in one of our patients [8].

The clinical manifestations of LMC are commonly nonspecific and lead to multifocal neurological deficits, associated with obstructive hydrocephalus and meningeal infiltration of cranial and spinal nerve roots or cord. As a result, headache, nausea, vomiting, as well as altered mental status, cranial nerve palsy and radicular complaints may occur, disturbing life quality [9]. The possibility of metastatic disease should be investigated in patients featuring new headache onset or cranial nerve symptoms in the setting of GC.

Currently, there is no acknowledged diagnostic test for LMC and diagnosis is based on cytological examination of the CSF along with a gadolinium-enhanced MRI. Although CSF cytology is required for definite diagnosis, it has low sensitivity for LMC, around 54% [10]. Similarly, MRI with gadolinium enhancement only shows abnormalities in 67% of patients with LMC [10]. The low sensitivity of both exams can delay the LMC recognition until the emergence of neurological symptoms. The definitive diagnosis of LMC can only be ascertained by the presence of malignant cells in the CSF. Both MRI and CSF analysis proved leptomeningeal carcinomatosis in both cases.

Gastric LMC is associated with an extremely poor prognosis, with median overall survival of only four to six weeks if untreated and two to four months with therapy [11]. The survival of our patients since presentation of the first neurological symptoms is consistent with the one described in the literature.

There is no established standardized therapeutic approach to LMC from gastrointestinal origin [12]. Most chemotherapeutics agents do not penetrate the blood-brain barrier. For this reason, whole-brain radiotherapy (RT) and intrathecal chemotherapy, alone or combined with systemic chemotherapy, have been attempted. Although overall palliative treatments show disappointing results in LMC, they can improve symptoms of meningeal irritation or CSF obstruction to some degree, leading to a better quality of life. One of our patients deteriorated rapidly and we had no time to carry out any of those options.

Methotrexate, cytarabine and thiotepa, in combination with corticosteroids, are the most common agents used in IT chemotherapy [13]. Previous reports suggested that patients receiving IT chemotherapy live longer than those treated with best supportive care [14]. However, there is scarce and conflicting data showing that IT chemotherapy prolongs survival. Methotrexate is the most used agent for IT chemotherapy and in high doses has shown some encouraging results [15]. In cases of bulky LMC, radiotherapy has shown better results regarding local progression and symptomatic control. RT improves CSF flow, rendering intrathecal chemotherapy more effective [16]. Anticonvulsant therapy as primary prophylaxis for seizures is not usually recommended [17]. Ventriculoperitoneal shunt may benefit some patients with refractory intracranial hypertension; however, there are concerns about neurotoxicity and intraperitoneal toxicity [18].

Therapeutic alternatives are still lacking. Intrathecal administration of trastuzumab in HER2-positive metastatic breast cancer with LMC seems to be safe and effective [19]. Testing for HER2 overexpression might be appealing for gastric LMC. In fact, some studies have already evaluated lapatinib and trastuzumab efficacy in metastatic HER2-positive GC, but patients with LMC were excluded from such trials, so conclusions regarding safety and efficacy cannot be determined [20, 21].

Conclusion

In summary, we report two cases of LMC from gastric origin that show how aggressive this condition is. Available therapies are rather unsatisfactory, though they may improve or, at least, stabilize LMC's symptoms. Clearly, a high index of clinical suspicion is required and further research on the disease's pathogenesis is necessary to ameliorate outcomes.

Acknowledgements
Written informed consent was obtained from the patients' families for publication of this case report.

Conflicts of interest
The authors declare that they have no competing interests.

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