Uncommon presentation of leptomeningeal carcinomatosis from gastric cancer: a case report

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Abstract: Leptomeningeal carcinomatosis in gastric adenocarcinoma is very rare (0.16–0.69%). Breast cancer, lung cancer, melanoma and hematologic malignancies are the most common causes of leptomeningeal carcinomatosis. The diagnosis is usually established by the presence of malignant cells in cerebrospinal fluid along with magnetic resonance imaging. There are few published studies about this condition and prognosis is very poor. We present a case of a 67-year-old man with a localized gastric cancer adenocarcinoma treated with perioperative chemotherapy and total gastrectomy with D2 lymphadenectomy. During the post treatment surveillance, recurrence occurred after a year, with exclusive leptomeningeal location. Clinical presentation consisted of bilateral optic peri neuritis, a peculiar manifestation which required an extensive differential diagnosis including inflammatory, infectious, autoimmune diseases, genetic and toxic neuropathies. Treatment strategy of this condition is not established. Besides symptomatic therapy, chemotherapy or radiotherapy are treatment options, even though these are palliative treatments and results are disappointing. This patient died 3 months after diagnosis of leptomeningeal involvement. We underline the rarity of this condition, the need for a high level of clinical suspicion and the difficulty in the diagnostic and treatment process. Late diagnosis and shortage of prospective randomized trials may be the reason for poor prognosis. Further studies are needed to better improve gastric leptomeningeal carcinomatosis treatment.

Keywords: Leptomeningeal carcinomatosis (LMC); gastric cancer (GC); optic perineuritis; intrathecal chemotherapy; case report

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Introduction

Leptomeningeal carcinomatosis (LMC) from solid tumors is an important neurological complication of systemic cancer (1). The prevalence of LMC in gastric cancer (GC) patients is very low (0.16–0.69%) (2). Prognosis of LMC is poor and published data are scarce. No standard treatment for LMC exists and median survival of patients with LMC from gastrointestinal tract adenocarcinoma is 3–4 weeks (3,4).

We report a case of gastric adenocarcinoma LMC that presented with bilateral optic perineuritis. This condition is very similar to inflammatory optic neuropathy, having a broad differential diagnosis (5).

We present the following study in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/dmr-21-18).

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Case presentation

We present a case of a 67-year-old man with a history of controlled arterial hypertension and former smoking habits. He was diagnosed with localized gastric adenocarcinoma of diffuse type (signet ring cell) human epidermal growth factor receptor 2 (HER2) negative, in September 2017. The patient was treated with perioperative chemotherapy and surgery (gastrectomy with D2 lymphadenectomy) according to the MAGIC trial (6). In June 2018, post-treatment computed tomography (CT) scan was unremarkable.

In June 2019, he presented to the emergency department with a 1-month history of blurred vision. The neurological exam revealed left pupillary afferent defect and ophthalmologic evaluation showed bilateral optic disk edema with papillary hemorrhages along with marked decrease in bilateral visual acuity. There was no history of glaucoma, trauma, uncontrolled high blood pressure or toxic exposure. Initial blood workup was unremarkable. Head CT scan showed possible communicating hydrocephalus, but venous scan was normal. Cerebrospinal fluid (CSF) analysis, opening pressure measure, vitamin blood levels, infectious and autoimmune disease's panel were all unremarkable, including negative anti myelin oligodendrocyte glycoprotein (MOG) and anti-aquaporin (AQ4) antibodies. Optic coherence tomography confirmed bilateral optic disk edema and brain magnetic resonance imaging (MRI) showed bilateral optic nerve T2 hypersignal with gadolinium enhancement. The patient started treatment with prednisolone, assuming an inflammatory etiology, with partial resolution of symptoms.

Two months later he began with behavior changes, headache and transient episodes of loss of consciousness with bilateral forced downward gaze deviation. Intracranial angiography and electroencephalogram were normal. Repeated lumbar puncture (LP) disclosed high opening pressure, pleocytosis and presence of circulating neoplastic signet cells. Body CT scan did not reveal extracranial neoplastic disease. The patient was started on intrathecal chemotherapy with a protocol consisting of an evacuating LP (70 mL) and administration of 15 mg hydrocortisone, 10 mg methotrexate and 5 mL of sodium chloride. After 3 cycles he had poor clinical response, with degrading performance status. It was decided to stop therapy and he was referred to palliative care. He was medicated with acetazolamide and antiemetics to improve symptoms of intracranial hypertension. Neurological deterioration progressed with the installation of catatonic state and left hemiparesis, with head CT scan showing cortical left parietal and cerebellar lesions and active hydrocephalus. He died 3 months after diagnosis of leptomeningeal involvement.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family.

Discussion

LMC is one of the most common metastatic complications of the central nervous system and occurs in approximately 5–8% of all cancer patients. Types of cancer more commonly associated with LMC are leukemia, lymphoma, melanoma, breast and lung. Nevertheless, LMC can virtually complicate any kind of neoplastic process. Brain metastasis are uncommon in GC and LMC is extremely rare (7). Our patient had a poorly cohesive signet ring cell gastric adenocarcinoma, which is the histopathologic type more frequently associated with LMC, among GC (8).

LMC may lead to multifocal neurologic deficits, associated with infiltration or direct invasion of cranial and spinal cord meninges and obstructive hydrocephalus. As a result, the presenting manifestations are usually headache (39%), nausea and vomiting (25%), encephalopathy (16%), seizures, cranial nerve symptoms (9.8%) and spinal nerve complaints (8.5%) (9-11).

Patients with new headache onset or cranial nerve dysfunction (namely with visual complaints or deafness) in the setting of GC should be assessed for possible metastatic disease while excluding other diagnosis, particularly: intracranial hypertension from venous cerebral thrombosis related to the prothrombotic effect; vitamin A and B12 deficiency due to the diminished absorptive state after surgery and iatrogeny to chemotherapy, like infections or neuropathies. The work-up panel for these symptoms may include autoimmunity and infectious laboratory panel, LP with opening pressure measurement, head CT and MRI with venography.

There is no established diagnostic test for LMC, although CSF cytology and MRI are useful. Meningeal gadolinium enhancement may aid in diagnosis of LMC, although it is not a specific finding. Differential diagnosis includes infectious or inflammatory meningeal affections. Reported sensitivity of cranial MRI in diagnosing LMC ranges from 65% to 75% (12). In contrast to MRI, CSF cytology is quite specific but has low sensitivity for LMC,

around 54% (13). The final diagnosis of LMC can only be documented by the presence of malignant cells in the CSF. Combining MRI with CSF cytology improves sensitivity to 91% (13). MRI of our patient showed bilateral optic nerve T2 hypersignal with gadolinium enhancement, suggestive of optic perineuritis. First CSF sample was normal but the following had high opening pressure, pleocytosis and circulating signet ring cells.

No standard treatment for LMC from gastric origin is established (4). Chemotherapy or radiotherapy (RT) are treatment options, even though these are palliative treatments and results are disappointing (14). Although systemic chemotherapy is an essential treatment for metastatic patients, most anti-cancer agents do not penetrate the blood-brain barrier. For this reason, whole brain RT and intrathecal chemotherapy have been attempted, alone or in combination with systemic chemotherapy. In our patient, systemic chemotherapy and RT were not performed due to rapid degradation of performance status. RT is an important treatment modality for symptomatic and bulky LMC due to its capacity to improve CSF flow, making intrathecal chemotherapy more effective and relieving neurologic symptoms (3,9). Drugs usually used for intrathecal chemotherapy include methotrexate, thiotepa and cytarabine in combination with steroids but there are no randomized studies comparing the benefit of these three drugs (4,15,16). Some reports suggested that patients receiving intrathecal chemotherapy have prolonged survival compared with those treated with best supportive care (15). Intraventricular administration compared with intralumbar administration of chemotherapy seems to provide less variability of the drug's distribution and to improve the drug's level in CSF (4,15). Also, some evidence suggests that intraventricular administration of chemotherapy leads to a survival benefit (15). Despite this fact, LMC patients are frequently very debilitated, as our patient was, so a surgical intervention, exposing the patients to further complications, might not be appropriate and raise ethical questions. High dose intravenous methotrexate (3.5 g/m^2) showed a 28% partial response, 28% stable disease and 44% progressive disease (16).

Multidisciplinary team approach is important as there is no standard treatment and multiple interventions may be needed in order to obtain best clinical benefit, including chemotherapy, RT and neurosurgical techniques. Adequate clinical neurology and neuroimaging follow-up to assess clinical benefit are also essential. Also, palliative care is an urgent need since a rapid neurological decline is expected. Treating symptoms derived from intracranial hypertension is important. Analgesics to treat headache, steroids as dexamethasone, antiemetics and diuretics might not be sufficient to improve symptoms. Ventriculoperitoneal shunt may benefit some patients with intractable pharmacologic intracranial hypertension as this poses an imminent life threat, however there are concerns about neurotoxicity and intraperitoneal toxicity due to frequent coexisting CSF flow disturbances (10,11). Therapeutic alternatives are still lacking. Metastatic GC HER2 positive can be treated with systemic monoclonal antibody trastuzumab but so far, intrathecal administration is only demonstrated in breast cancer (17). Capecitabine is also being used in patients with brain metastasis and LMC from breast cancer based on some reports, even though there is no pharmacokinetic data showing efficacy of capecitabine in the central nervous system (4). Studies that evaluate lapatinib and trastuzumab efficacy in metastatic HER2 positive GC do not include patients with LMC, so we cannot determine how effective these medications are in treating these patients (18-20).

In some reports of gastric LMC, median survival since LMC diagnosis was 5.6 weeks (2). Our patient survived for approximately 20 weeks since presentation of the first neurological symptoms and 12 weeks since LMC diagnosis. Our patient presented with a peculiar LMC manifestation and had no evidence of extracranial neoplastic recurrence, which may have led to delayed diagnosis. In fact, the patient presented with bilateral optic perineuritis, which requires an extensive differential diagnosis along with typical and atypical symptoms of intracranial hypertension (5). Optic nerve sheath enhancement, adjacent tissue involvement, weak response to steroids and encephalopathy were strong points against a demyelinating disease or other immune conditions, supporting a neoplastic process.

Late diagnosis and shortage of prospective randomized trials may be the reason for poor prognosis. In our patient, repeated LPs were crucial for correct diagnosis and clinical monitoring was essential to avoid futile treatment.

Further case reports and studies focusing on the disease's pathogenesis are needed to better improve gastric LMC treatment.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-21-18). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family.

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