

Leptomeningeal carcinomatosis of gastric adenocarcinoma

Gülcan BULUT¹, Asuman ERDEN¹, Burçak KARACA², Erdem GÖKER²

Departments of ¹Internal Medicine and ²Medical Oncology, Ege University Faculty of Medicine, İzmir, Turkey

Gastric cancer is the third most common malignancy among gastrointestinal malignancies. With the advance of new treatments, overall survival in gastric cancer is extending, and metastasis to atypical sites is seen more commonly. Leptomeningeal metastasis is one such atypical metastasis for gastric cancer. We report a case of gastric adenocarcinoma with leptomeningeal metastasis as an atypical involvement. A 39-year-old female, presenting with headache, vertigo, horizontal gaze palsy, visual disturbances, and seizures, was admitted to our hospital in August 2009. The fundoscopic examination revealed the presence of bilateral papilledema. Magnetic resonance imaging of the brain showed diffuse leptomeningeal enhancement and biventricular dilatation. Cytological examination of the cerebrospinal fluid revealed malignant cells. These findings were consistent with leptomeningeal carcinomatosis. Six months before, she was diagnosed as having gastric cancer by upper gastrointestinal tract endoscopy, which was performed as a part of the diagnostic work-up to clarify the cause of her abdominal ascites. She received six cycles of docetaxel-cisplatin-5-fluorouracil for metastatic gastric cancer, and she developed the above-mentioned symptoms under chemotherapy. She was included in a craniospinal radiotherapy program and received intrathecal methotrexate treatment. We present this case report since leptomeningeal carcinomatosis of gastric cancers is a rare clinical entity, and treatment strategies remain challenging for clinicians.

Key words: Gastric adenocarcinoma, leptomeningeal metastasis, intrathecal treatment

Gastrik adenokarsinomda leptomeningeal tutulum: Nadir görülen bir metastatik odak

Mide kanseri gastrointestinal maligniteler içinde üçüncü en sık görülenidir. Yeni tedaviler geliştikçe sağkalım uzamakta ve atipik metastaz görülme sıklığı artmaktadır. Leptomeningeal metastaz da mide kanseri için atipik bir metastazdır. Mide adenokarsinomu için atipik bir tutulum olan leptomeningeal metastazlı bir olguyu sunuyoruz. Ağustos 2009'da otuz dokuz yaşında kadın hasta; baş ağrısı, baş dönmesi, dışa bakış kısıtlılığı, görme kaybı ve nöbet yakınmaları ile hastanemize başvurdu. Fundoskopik bakıda, bilateral papil ödemi saptandı. Yapılan kranial manyetik rezonans görüntülemesinde diffüz leptomeningeal kontrast tutulumu ve ventriküler dilatasyon saptandı. Beyin-omurilik sıvısının sitolojik incelemesinde malign hücreler görüldü. Bulgular leptomeningeal karsinomatozis ile uyumlu olarak değerlendirildi. Hastanın altı ay önce abdominal asit nedeni aydınlatılmaya çalışılırken tanı için yapılan üst gastrointestinal endoskopisiyle mide kanseri tanısı aldığı ve metastatik mide kanseri için dosetaksel, cisplatin, 5-fluorurasil kemoterapisi aldığı saptandı. Mide adenokarsinomunun leptomeningeal tutulumu olarak kabul edilen hasta kraniospinal radyoterapi programına alındı ve intratekal metotreksat tedavisi uygulandı. Leptomeningeal karsinomatozis, mide kanseri için nadir bir metastatik saha olduğundan ve tedavi stratejisi halen tartışmalı bulunduğu için vakayı sunmaya değer bulduk.

Anahtar kelimeler: Mide adenokarsinomu, leptomeningeal tutulum, intratekal ilaç uygulama

INTRODUCTION

The most common neoplasms metastasizing to leptomeninges are carcinoma of the breast, lymphomas and leukemia. The incidence of lepto-

meningeal carcinomatosis (LMC) is 3-8% of all solid cancers (1). Development of LMC from a gastric cancer is very rare. Kim et al. (2) reported that the

incidence of LMC from a gastric cancer was 0.06% of all cases of gastric cancer. The diagnosis is confirmed by examination of the cerebrospinal fluid (CSF). Findings may include elevated CSF pressure, pleocytosis, increased protein and lactate dehydrogenase (LDH) concentration, and decreased glucose concentration. Cytological studies may indicate the presence of malignant cells.

Treatment is by radiotherapy combined with intrathecal methotrexate (IT-MTX). The long-term prognosis is very poor, and palliative care is therefore important.

CASE REPORT

A 39-year-old female patient was first admitted to the hospital with back pain in March 2009. Abdominal ultrasonography revealed ascites and free fluid in the Douglas space. Her CA-125 level was elevated, at 167.5 U/mL (0-35 U/mL), and the pre-diagnosis was ovarian cancer based on these findings. The cytological examination of the ascites showed the presence of malignant cells. With further diagnostic research, pleural effusion was detected in the computerized tomography (CT) of the chest. Thoracentesis revealed the presence of malignant cells, which were cytologically consistent with adenocarcinoma, and the pathological comment was to search the primary lesion in the gastrointestinal tract. Positron emission tomography (PET/CT) was then performed to determine a primary site of metastatic lesions, and her PET/CT examination showed multiple metastatic lesions, which were described as a soft tissue mass in the right adnexa, lymphadenopathies in the mediastinum, and lytic lesions in bones, all having elevated standard uptake values (SUV). Based on the pathological suggestion, an upper gastrointestinal system endoscopy was performed even though PET/CT did not demonstrate any lesion (Figure 1). The appearance of the gastric corpus was consistent with chronic gastritis, and the pathological examination of the biopsy specimen was reported as poorly differentiated adenocarcinoma. The patient was scheduled to receive docetaxel 75 mg/m²/day, cisplatin 75 mg/m²/day, 5-fluorouracil 750 mg/m²/5-days infusion (DCF regimen) for metastatic disease. After three cycles of chemotherapy, she was evaluated for tumor response and stable disease was achieved. Six months after the diagnosis of gastric cancer, just a few days after the sixth course of her chemotherapy, she had generalized tonic-clonic seizure and sudden bilateral

visual loss. The fundoscopic examination revealed the presence of bilateral papilledema. Magnetic resonance imaging (MRI) of the brain showed leptomeningeal gadolinium enhancement and mildly dilated lateral ventricles; no space-occupying mass was detected (Figure 2). The CSF examination showed an elevated protein (89.4 mg/dl) and decreased glucose levels (5 mg/dl), and cytological study revealed the presence of malignant cells in the CSF. All these findings were consistent with LMC. She received palliative craniospinal radiotherapy, systemic steroids and antiepileptic medications, and regular IT-MTX treatment was scheduled, as 12.5 mg twice a week. Radiologic imaging of the spine was normal and IT port catheter was placed for further treatment. The follow-up of

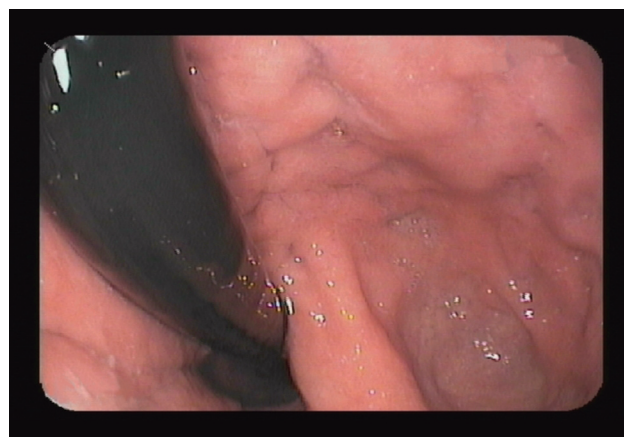


Figure 1. The endoscopic view of infiltrative adenocarcinoma in cardia.

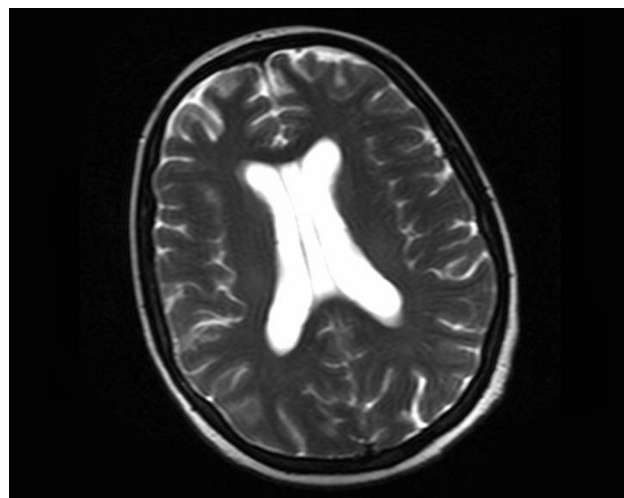


Figure 2. Leptomeningeal gadolinium enhancement in bilateral temporal lobes, and mildly dilated lateral ventricles in T2 section images of cranial MRI.

the patient included administration of regular IT-MTX treatment 12.5 mg twice a week, until benign cytology was detected on three consecutive CSF samplings, and then the therapy was switched to monthly IT-MTX treatment. All her neurological symptoms except for visual loss recovered and her CSF protein levels decreased to 18.5 mg/dl. She is still receiving IT-MTX treatment monthly.

DISCUSSION

Leptomeningeal carcinomatosis (LMC) was first described by Eberth in 1870. The overall incidence of LMC for all types of cancer was reported as 3-8%, but in autopsy series this incidence increases up to 20% (3).

Leptomeningeal carcinomatosis (LMC) mostly appears with leukemia, lymphoma, malignant melanoma, breast cancer, and lung cancer. However, LMC from a gastric cancer is extremely rare, and the histopathologic type of gastric cancer is signet ring cell carcinoma in most cases (1,4). In our case, the histopathologic type was adenocarcinoma.

Leptomeningeal carcinomatosis (LMC) mostly appears in the advanced stages of cancer (3). Most cases have multiple metastatic lesions outside the nervous system, including the liver, lungs and bone (5). Our patient had multiple metastases including bones and mediastinal and iliac lymph nodes at the time of the diagnosis of gastric cancer. In studies, the time lapse between the first recognition of cancer and establishing the diagnosis of LMC presenting with heavy neurological symptoms is approximately 12 months (6). However, in our case, the interval was much shorter, at only six months. This could be explained by the heavy tumor burden present at the time of the diagnosis.

After the diagnosis of LMC, the median survival is around 8 weeks (range: 4 to 11 weeks) for patients with solid tumors (3,7). Because the life expectancy is very short, the earlier the diagnosis is made and the treatment started, the better the quality of life achieved.

Leptomeningeal carcinomatosis (LMC) may lead to multifocal neurologic deficits, which may be associated with infiltration of cranial and spinal nerve roots, direct invasion of the brain or spinal cord, obstructive hydrocephalus, or some combination of these factors. As a consequence, the patient may complain of nausea, vomiting, headache, diabetes insipidus, changes in mental status, diplopia, facial numbness, hearing loss, loss of visual acuity,

paresthesias, pain in the back or neck, weakness of the legs, and bladder and bowel dysfunction, and may have a variety of other neurologic deficits. In our case, the patient's first neurologic symptom was a generalized tonic-clonic seizure following sudden bilateral visual loss, which was a result of papilledema.

Radiologic imaging techniques play an important role in the diagnosis of LMC, but unfortunately do not always clearly identify LMC. The meningeal gadolinium enhancement is a meaningful but not specific finding on cranial MRI. Infectious or inflammatory conditions of the meninges may show a similar contrast enhancement pattern. In the literature, the sensitivity of cranial MRI in the diagnosis of LMC had been reported as between 65% and 75% (6).

Elevated CSF pressure is another important finding for LMC diagnosis. However, the incidence of this finding has varied in different studies in the literature (8-10). These studies have shown that the symptoms of elevated pressure can be seen in LMC cases, and most of these symptoms were due to hydrocephalus, although rarely, symptoms of CSF pressure elevation can be seen without the presence of hydrocephalus. Our patient had symptoms of CSF pressure elevation, and her cranial MRI showed the presence of biventricular dilatation and leptomeningeal contrast enhancement, and findings that were consistent with communicating hydrocephalus.

The definitive diagnosis of LMC can only be done by documenting the presence of malignant cells in the CSF. However, in one-third of the patients, the CSF cytology is not diagnostic (11). Wasserstrom et al. (5) had reported that the first CSF sampling has a diagnostic sensitivity of 54%, and with repeated samplings, this ratio increases up to 91%. In our case, the first CSF sampling documented the presence of malignant cells. In cases in which the cytological examination of the CSF is negative for malignant cells, one should not hesitate to repeat the procedure, because the likelihood of detecting malignant cells increases in repeated samplings.

There are several treatment options for patients with LMC, including IT chemotherapy with or without radiotherapy. Most chemotherapeutic agents do not penetrate the blood-brain barrier (BBB), and are given by direct IT administration. Agents that can be used for IT chemotherapy include

MTX, cytarabine, thiotepa, and steroids. The benefit (i.e. prolongation of survival) achieved with IT chemotherapy (single or multiple regimens) in LMC patients continues to be debated, and is still an important challenge in daily oncology practice. MTX is one of most useful agents for IT chemotherapy. The median survival of LMC is reported to be four to six months, despite systemic or IT treatment (10), and whether intra-CSF chemotherapy offers any advantage over systemic treatment remains to be established (12). Our patient received both craniospinal radiotherapy and regular IT-MTX, since her symptoms were intense and she needed urgent palliation. After the initiation of

treatment, all her neurological symptoms regressed except visual disturbance. She remains on monthly IT- MTX therapy.

In conclusion, LMC is a rare entity and unfortunately has catastrophic outcomes. Its ultimately poor prognosis raises the urgency of early diagnosis and treatment. Although these patients had a fatal clinical course, cytologic negative conversion of CSF may improve survival (13). In disseminated malignancies, newly onset neurological symptoms should alert the physician to any central nervous system involvement, and the appropriate diagnostic and therapeutic work-up should be established immediately.

REFERENCES

1. Lee JL, Kang YK, Kim TW, et al. Leptomeningeal carcinomatosis in gastric cancer. *J Neurooncol* 2004; 66: 167-74.
2. Kim M. Intracranial involvement by metastatic advanced gastric carcinoma. *J Neurooncol* 1999; 43: 59-62.
3. Pavlidis N. The diagnostic and therapeutic management of leptomeningeal carcinomatosis. *Ann Oncol* 2004; 15(Suppl): iv285-iv291.
4. Giglio P, Weinberg JS, Forman AD, et al. Neoplastic meningitis in patients with adenocarcinoma of the gastrointestinal tract. *Cancer* 2005; 103: 2355-62.
5. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 1982; 49: 759-72.
6. Lisenko Y, Kumar AJ, Yao J, et al. Leptomeningeal carcinomatosis originating from gastric cancer. *Am J Clin Oncol* 2003; 26:165-70.
7. Jayson GC, Howell A. Carcinomatous meningitis in solid tumours. *Ann Oncol* 1996; 7: 773-86.
8. Herrlinger U, Förchler H, Küker W, et al. Leptomeningeal metastasis: survival and prognostic factors in 155 patients. *J Neurol Sci* 2004; 223: 167-78.
9. Jayson GC, Howell A, Harris M, et al. Carcinomatous meningitis in patients with breast cancer. *Cancer* 1994; 74: 3135-41.
10. Omuro AMP, Lallana EC, Bilsky MH, DeAngelis LM. Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. *Neurology* 2005; 64: 1625-7.
11. Rudnicka H, Niwinska A, Gruszczyk A, Pienkowski T. Diagnosis and treatment of carcinoid meningitis: a challenge to the neurologist and oncologist. *Neurol Neurochir Pol* 2003; 37: 811-24.
12. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained release cytarabine (DepoCyt) to intrathecal methotrexate in the patients with neoplastic meningitis from solid tumors. *Clin Cancer Res* 1999; 5: 3394-402.
13. Oh SY, Lee SJ, Lee J, et al. Gastric leptomeningeal carcinomatosis: multi-center retrospective analysis of 54 cases. *World J Gastroenterol* 2009; 15: 5086-90.