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Case Report

Brain-Only Metastasis and 10-Year Survival after Curative Gastric Cancer Resection: A Case Report

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Keywords
Gastric cancer · Brain-only metastasis · Brain-blood barrier

Abstract
Gastric cancer (GC) usually metastasizes to locoregional lymph nodes, the peritoneum causing ascites, or to the liver and lungs but rarely to the brain. Few cases of brain-only GC metastases have been reported, and the prognosis is very poor. We present a case of brain-only metastasis 2 years after curative GC surgery and chemotherapy, who visited the ER due to a headache. The patient underwent operative tumor resection of the brain with additional chemotherapy and is still alive and disease free 10 years after initial curative treatment. This case shows that brain-only metastasis may have a better prognosis than that of systemic metastasis; thus, aggressive treatment with radiotherapy or surgery with chemotherapy may be needed.

Introduction

There are three routes of metastasis in gastric cancer (GC): hematogenous, direct peritoneal seeding, and lymphatics after the invasion of locoregional lymph nodes [1]. In most cases, multiple metastases are usually observed in various organs. In cases of hematogenous or lymph node metastasis, metastasis gradually spreads from the primary site to a more distant site, such as the brain.

Although skip metastasis may occur, it is rare in GC patients. In particular, extra-visceral metastasis alone without intra-visceral metastasis is rare, and its frequency is below 3% [2, 3].

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Reports show that extra-visceral metastasis with single or multiple intra-visceral metastases usually occurs in the thyroid, breast, skin, bone, and brain [4]. In these cases, the prognosis is poor despite various treatment modalities [5, 6].

Herein, we report a rare case of GC with a single metastasis to the brain, without intra-visceral metastasis 2 years after curative gastrectomy and adjuvant chemotherapy. The patient recovered successfully after tumorectomy of the brain and palliative chemotherapy and is disease free 8 years after completion of palliative chemotherapy treatment and 10 years after initial curative treatment.

Case Report

A 65-year-old Korean male with a history of GC underwent total gastrectomy with Roux-en-Y anastomosis and six cycles of adjuvant chemotherapy with tegafur/gimetacil/oteracil (TS-1, 60 mg/bid on days 1–21) + cisplatin (60 mg/m^2 on day 1) in a 28-day cycle. The patient was referred to our clinic having a headache that started a week ago. He had been diagnosed with GC 2 years prior; his cancer was located in the cardia of the stomach. The pathology diagnosis of the mass was poorly differentiated adenocarcinoma originating from the stomach; the staging was pT3N3aM0 (stage IIIb, AJCC 7th edition) as his tumor size had a diameter of 5.5 cm and had eight out of 74 lymph nodes positive for cancer, while the washing cytology was negative. The resection margin of 1 cm was tumor free, and there was no lymphovascular invasion or perineural invasion. The immunohistochemistry status of human epidermal growth factor receptor 2 (HER2) was zero out of three. The resection gross pathophysiology is shown in Figure 1a, the hematoxylin and eosin stain in Figure 1b, and HER2 immunohistochemistry in Figure 1c.

When the patient was admitted for headache, he started to vomit. Thus, brain computed tomography was performed, showing a brain mass of 3.5 cm in the right temporal region (Fig. 2a). To further evaluate metastasis to other organs, we performed positron emission tomography which showed no metastases other than those in the brain (Fig. 2b).

Thus, we performed a tumorectomy of the brain tumor, assuming that it was due to brain cancer. However, the brain tumor specimen was found to be metastatic adenocarcinoma originating from GC (hematoxylin and eosin stain in Fig. 2c) as it was positive for cytokeratin 7 (Fig. 2d) and negative for caudal type homeobox 2, cytokeratin 20, prostate-specific antigen, and thyroid transcription factor 1. The HER2 staining was zero out of three. As we were concerned about further metastasis, we performed palliative FOLFOX for 12 cycles (200 mg/m^2/day of leucovorin given as a 2-h infusion followed by a bolus of 400 mg/m^2 5-fluorouracil and a 22-h continuous infusion of 5-fluorouracil, 600 mg/m^2, repeated for two consecutive days). The patient had no metastasis to any other organs 8 years after the completion of chemotherapy (Fig. 2e). The patient is in complete remission and still alive, 10 years after the initial GC diagnosis. The treatment timeline is shown in Figure 3. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000530109).

Discussion

Recently, two retrospective studies by Harada et al. [2] and Brunner et al. [7] reported two common conditions and two common outcomes for isolated brain metastasis (BM) in GCs. First, the GC develops in the proximal portion of the gastroesophageal junction. Second, the cancer

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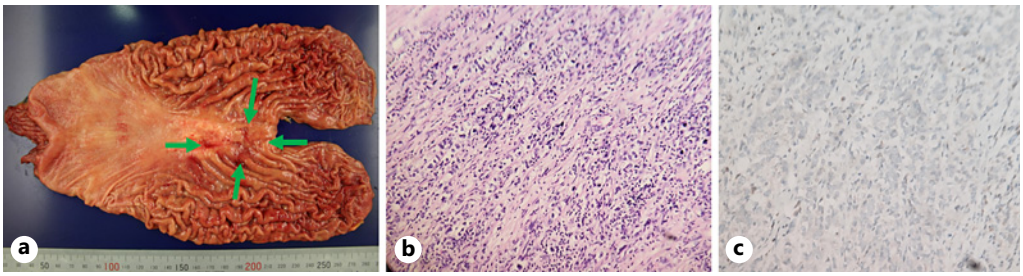

Fig. 1. Gross pathology of the resected stomach with green arrows indicating the tumor of 5.5 cm (**a**), the hematoxylin and eosin (H&E) stain of the original GC at ×200 magnification (**b**), and the immunohistochemical HER2 status of this specimen showing 0 out of 3 at ×200 magnification (**c**).

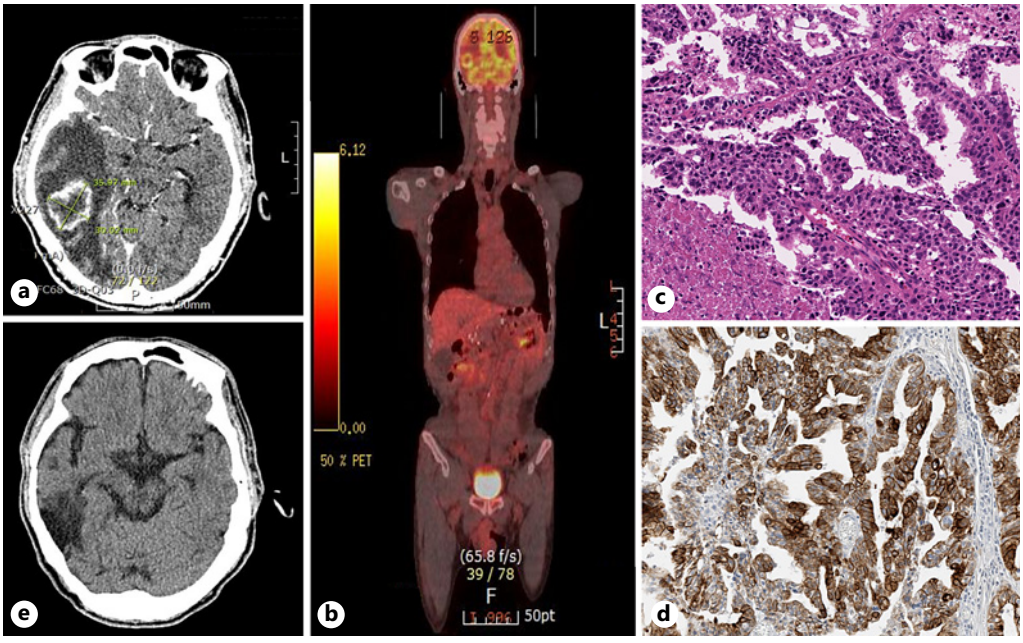

Fig. 2. **a** Computed tomography image of the brain showing a brain tumor of 35 mm. **b** A positron emission tomography image of the whole body shows no other tumor other than in the brain. **c** The biopsy of the brain was stained with H&E, demonstrating tubule-papillary structures lined by tumor cells within necrotic background at ×200 magnification. **d** Immunohistochemical staining for cytokeratin 7 is positive in tumor cells at ×200 magnification. **e** After 8 years, a follow-up brain CT computed tomography scan showed no tumor recurrence. H&E, hematoxylin and eosin.

type is adenocarcinoma. Third, the progression of BM was 14–20 months and the survival was better with isolated BM around 13–27 months after diagnosis of BM. Furthermore, Harada et al. [2] showed that lymph node metastasis had a higher rate of BM, whereas Brunner et al. [7] showed that male gender had a higher rate of BM. This case is similar in that the patient was a male with GC in the proximal area with adenocarcinoma type and had perigastric lymph node metastasis at the initial surgery. However, he did not have further lymph node metastasis detected along with BM and had a slightly longer progression-free disease.

Hence, this is a very rare case for two reasons. First, BM alone does not arise without hematogenic or lymphatic metastasis. Second, this patient had complete remission which lasted for 8 years after brain tumorectomy and palliative chemotherapy, which may be the

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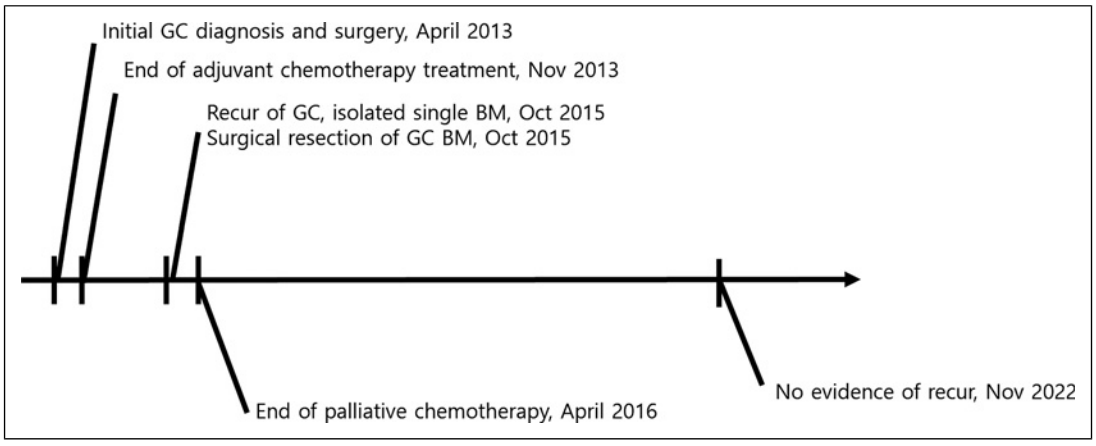

Fig. 3. Timeline of the treatment. The patient was diagnosed with gastric cancer (GC) in April 2013 by esophagogastroduodenoscopy. He underwent total gastrectomy surgery and 6 months of adjuvant chemotherapy of tegafur/gimetacil/oteracil with cisplatin. Two years later, he had a solitary brain mass, which was confirmed as a GC brain metastasis (BM) by a surgical resection in October 2015. Afterward, he had 12 cycles of chemotherapy (FOLFOX) treatment. Eight years after his chemotherapy treatment, he is still in remission.

first case report for long-term survival. Indeed, more articles have been published on the long-term survival of isolated BM in GC [8, 9].

BM originating from GC is thought to pass through the thoracic duct, which may arise from hematogenous and/or lymphatic metastases. Thus, intra-visceral metastasis is common in most cases of BM originating from GC. Hence, it is very rare for a single skip metastasis to occur without the involvement of intra-visceral metastases [10].

Systemic metastasis usually occurs within 1 year in most types of cancers. However, this patient had BMs only 2 years after complete remission, which may suggest three things. First, BM may have been present in the initial curative setting, and without brain magnetic resonance imaging and positron emission tomography, the brain tumor may not have been found. Second, the blood-brain barrier (BBB) may have been disrupted during the initial BM; however, it may have been intact after initial chemotherapy, hindering further BM [11]. Third, the tumor may have been dormant or slowly growing, until the patient developed neurological signs of headache and vomiting.

Furthermore, BM from GC is usually seen in terminal patients who have a fulminant GC diagnosis that is too advanced for treatment or in long-term survivors who had heavy treatment [12]. In most cases, BM is one of the multiple metastatic sites and is treated after multidisciplinary discussion, where intrathecal chemotherapy with methotrexate, radiotherapy, or radiosurgery and surgery are considered, all of which are standard modalities of treatment [13]. Usually, if it is a single metastasis, surgery is performed if it is approachable by the surgeon, while radiosurgery is preferred if the metastasis is too deep for surgery. Radiotherapy is preferred in oligometastatic settings (less than five metastatic lesions), while intrathecal chemotherapy is considered if radiotherapy causes excessive brain function loss rather than tumor reduction [3]. Usually, the prognosis of BM is poor, where the mean overall survival is known to be around 3 months for multiple BM in GC.

However, there are three limitations that need to be mentioned. First, as the primary tumor in this case was treated around 2010, there was no molecular diagnosis. Examining the brain tumor with whole-genome or -exome sequencing may have shed some insight into the method of brain-only metastasis. However, to date, there are no known molecular

markers for BM [14], while there is conflicting evidence on the role of HER2 in BM [2, 6, 7]. Second, the BBB may have been intact after BM and the metastatic cells were dormant, which may explain why solitary BM did not cause other BMs in an immune sanctuary nor did it cause systemic metastasis to other organs. This may explain why the prognosis may be better for this and other brain-only metastases in GCs in retrospective studies and the current literature [2, 7–9]. Furthermore, as most brain tumors do not have systemic metastasis, rare cases of brain tumors with systemic metastasis may provide insight into the BBB or tumor microenvironment [15]. Thus, we believe that chemotherapy may be an overtreatment for brain-only metastases. However, due to the excellent outcome of no other metastasis in the 8 years after brain tumorectomy and palliative chemotherapy, we believe that aggressive treatment may be needed. Third, if the initial brain cancer was known to be BM from GC, stereotactic radiotherapy or radiosurgery such as gamma-knife could have been used for the treatment, which is the standard treatment of care for BM. However, as we suspected a primary brain tumor such as glioblastoma due to a single brain mass after 2 years of GC treatment, a tumorectomy was performed for treatment and diagnosis purposes.

BM from GC is very rare and has a poor prognosis. However, as in the case of a single, isolated BM, as the prognosis may be better than that of systemic metastasis, aggressive treatment with radiotherapy or surgery with chemotherapy may be needed.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study was approved and monitored by the IRB of the Inje University Seoul Paik Hospital, Korea (IRB No. PAIK 2022-08-003).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, collection and assembly of data, data analysis and interpretation, manuscript writing, and writing – review and editing: Woo Yong Lee and Byung Woo Yoon.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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