Intracranial Metastasis from an Esophageal Gastrointestinal Stromal Tumor

Satoshi Hamada, Atsushi Itami, Go Watanabe, Shinya Nakayama, Eiji Tanaka, Masato Hojo, Akihiko Yoshizawa, Seiichi Hirota and Yoshiharu Sakai

Abstract

We report the case of a woman with intracranial metastasis from an esophageal gastrointestinal stromal tumor (GIST) with the mutation site in the 3’ end of exon 11. Frontal craniotomy was performed with complete resection of the mass, followed by postoperative stereotaxic radiotherapy (SRT). Intracranial metastasis from GISTs is extremely rare; we found only seven case reports in the literature.

Key words: gastrointestinal stromal tumor, brain metastasis, imatinib, mutation analysis

(Intermed 49: 781-785, 2010)
(DOI: 10.2169/internalmedicine.49.3124)

Introduction

Gastrointestinal stromal tumors (GISTs) account for at least 80% of all mesenchymal tumors of the gastrointestinal tract, where they arise from precursors of the interstitial cells of Cajal (1). Clinically, GISTs are usually diagnosed on the basis of KIT (CD117) expression on immunohistochemical analysis (2). About 70% of the GISTs are located in the stomach, 20% in the small bowel, and 5% in the rectum (3). Smaller portions of GISTs occur in the esophagus or outside the gastrointestinal tract. Recurrent disease arises mainly in the original site or via hematogenous metastasis or peritoneal dissemination. Intracranial metastasis is extremely rare, and our review of the literature revealed only seven reports (4-10).

The gain of function of the c-kit or platelet-derived growth factor receptor alpha (PDGFRA) genes plays a critical oncogenic role in GISTs (2, 11). Around 70% of mutations in c-kit gene are detected within exon 11, particularly the 5’ end. Some investigations of the relationship between the c-kit mutation site and clinical outcome have been reported (12-17). Imatinib mesylate is a competitive inhibitor of multiple tyrosine kinases, including KIT and PDGFRA. The clinical effectiveness of imatinib mesylate for advanced GISTs has been documented (18). We report the case of a woman with intracranial metastasis from an esophageal GIST with the mutation site in the 3’ end of exon 11, and systemic disease progression appeared to be controlled for two years after stopping imatinib mesylate prescribed for liver metastasis.

Case Report

A 54-year-old right-handed woman presented with an abnormality on a chest X-ray film at a routine medical checkup in July 2001. The chest X-ray showed loss of the descending aorta border. Abdominal computed tomography scan (CT) revealed a large complex lower esophagus mass (Fig. 1), and esophagography reveals no stenosis. Esophagectomy using a thoracotomy approach was performed, and the 11×7 cm mass was resected. Histopathological examination demonstrated a spindle-shaped cell tumor with a mitotic index of 2-3 per 10 high power fields (HPF). Immunohistochemical analysis was positive for c-kit, and the tumor was identified as a GIST.

The patient subsequently remained well, but multiple hepatic masses were detected on follow up abdominal CT in October 2003. Histopathological examination of the liver lesions revealed metastatic GISTs. Consequently, systemic...
treatment with imatinib mesylate 400 mg per day was administered from December 2003. The effectiveness of the drug was revealed by the change of tumor density on CT (data not shown). The dose was reduced to 300 mg per day in September 2005 because of adverse effects, including fatigue and edema. Eventually, the patient decided to stop treatment in December 2005.

The patient complained about new onset memory disturbance, communication difficulties, and other neurological symptoms around August 2007. These symptoms were slowly progressive and the patient was hospitalized in October 2007. CT of the brain revealed a 5 cm heterogeneous lesion in the left frontal lobe with significant perifocal edema and midline shift (Fig. 2). T1-weighted magnetic resonance imaging (MRI) of the head showed an isointense mass with ring enhancement. 18F-fluorodeoxyglucose positron emission tomogram (FDG-PET) showed no FDG uptake including in the liver (Fig. 3).

Frontal craniotomy was performed with complete resection of the mass, followed by postoperative stereotaxic radiotherapy (SRT). Histopathological examination of the resected mass showed a tumor with spindle-shaped cells with necrosis and a mitotic index of 1 per 50 HPF. Immunohistochemical analysis was positive for c-kit, confirming metastatic GIST (Fig. 4). Mutation analysis showed that six amino-acid residues corresponding to glutamine (Gln) followed by five amino acids codons 575-579 were inserted between codon 579 and codon 580 in exon 11 (Fig. 5). This finding was consistent with the mutation site of the patient’s...
Figure 5. DNA sequence of exon 11 of c-kit. DNA sequence of exon 11 of c-kit of control (upper) and patient (lower). Mutational analysis revealed a tandem duplication between codon 579 and 580. Six amino-acid residues corresponding to glutamine (Gln) followed by five amino acids codons 575-579 were inserted between codon 579 and codon 580 in exon 11.

Table. Seven Case Report of GIST with Intracranial Metastasis

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary site</th>
<th>Size of primary site</th>
<th>Mutation site</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>jejunum</td>
<td>7.5 cm</td>
<td>exon 9</td>
<td>surgery and imatinib</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>mesentery</td>
<td>no data</td>
<td>no analysis</td>
<td>imatinib</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>duodenum and jejunum</td>
<td>from 2.5 cm to 5 cm</td>
<td>no mutation in exon 11</td>
<td>imatinib and radiotherapy</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>mesentery</td>
<td>10 cm</td>
<td>no analysis</td>
<td>surgery</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>perisacrum</td>
<td>no data</td>
<td>no analysis</td>
<td>surgery</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>stomach</td>
<td>3.5 cm</td>
<td>no analysis</td>
<td>surgery</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>small intestine</td>
<td>no data</td>
<td>no analysis</td>
<td>radiotherapy</td>
<td>10</td>
</tr>
</tbody>
</table>

Discussion

We report the case of a woman with intracranial metastasis from an esophageal GIST with the mutation site in the 3’ end of exon 11, and systemic disease progression appeared to be controlled for two years after stopping imatinib mesylate prescribed for liver metastasis. The original tumor diameter was more than 10 cm, putting the patient in a high risk category for recurrent or metastatic disease according to NIH criteria (19); the detection of liver metastasis 2 years after esophagectomy was consistent with this. The patient was started on imatinib mesylate.

Assessment of small changes in tumor size or density on CT is a sensitive and specific technique for evaluating the response to imatinib mesylate (20). A change in density on CT was found in our patient (data not shown) and revealed that imatinib mesylate was effective in her case. Nevertheless, the patient decided to stop the drug after 2 years of treatment because of unacceptable side effects. Two years after imatinib mesylate cessation, intracranial metastasis occurred. Though the withdrawal of imatinib mesylate leads to rapid disease progression in most patients with advanced GIST (21), the present patient had stable disease (SD) for about 2 years.

Mutations in the 5’ end of exon 11, particularly deletions affecting codons 557-558, are associated with poor outcomes, whereas internal tandem duplications in the 3’ end of exon 11 are associated with a good clinical course (22). In our case, mutational analysis revealed a tandem duplication between codons 579 and 580. Long-term SD after imatinib mesylate termination is considered to be related to this mutation.

Eventually, the patient presented with brain metastasis. Intracranial metastasis of GIST is very rare. A review of the
literature revealed only seven case reports (Table) (4-10). Of these, four were treated surgically (4, 7-9) and one of these case received radiotherapy as an additional treatment (7). Another case was treated with radiotherapy alone to relieve pain (10). Only one case of the three cases treated with imatinib mesylate responded to treatment (5). It has been reported that imatinib mesylate apparently does not effectively cross the blood brain barrier and achieve adequate concentrations in the CNS, and this has been demonstrated in cases of chronic myeloid (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) (23, 24). Therefore for the present case, we decided on surgical treatment over imatinib mesylate, in the expectation of reducing the risk of local recurrence. Although radiation therapy is not a standard therapy for GIST, we performed SRT in hope of controlling micro residual cells. Our patient remained well after surgery and postoperative radiotherapy during six months of follow-up. Nevertheless, she remains in a high risk category and recurrences can be expected. Mutational analysis of the tumor in the esophagus and in the cerebral metastasis detected identical mutations, not a second mutation. One reason for the resistance to imatinib mesylate is a second mutation (25). Imatinib mesylate may, therefore, be effective as an adjuvant therapy in the event of a new recurrence.

The present case is very rare and interesting, both in terms of the metastasis and the mutation site. Analyzing the mutation site of GIST may help clinicians estimate the prognosis and select treatment.

Acknowledgement

The authors thank Dr. Toshiro Nishida for evaluating the sequence analysis of the esophageal and brain masses.

References

24. Takayama N, Sato N, O’Brien SG, Ikeda Y, Okamoto S-I. Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukemia due to poor penetration into cerebrospinal


© 2010 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html