

Long-term progression-free survival achieved in the skull base metastasis of gastrointestinal stromal tumor with introduction of tyrosine kinase inhibitor: illustrative case

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BACKGROUND Gastrointestinal stromal tumors (GISTs) are common subepithelial tumors that rarely metastasize to the intracranial space. Because the standard treatment for metastatic intracranial GISTs has not been established, multimodal therapies are needed, especially in the case of skull base metastasis. However, its outcome has not always been favorable. The authors report the longest known surviving case of skull base metastasis of GIST treated with imatinib only.

OBSERVATIONS A 52-year-old male with a history of GIST presented with left facial swelling and numbness. Examinations revealed a 70-mm tumor occupying the left middle cranial fossa and the orbit. The authors performed transnasal endoscopic tumor biopsy for definitive diagnosis and reintroduced imatinib treatment. The tumor significantly decreased in size early after the introduction of imatinib, and symptoms completely disappeared within several weeks. The lesion has remained shrunk radiologically for 63 months, and the patient is continuously being followed up under imatinib treatment.

LESSONS The authors reported a rare case of skull base metastasis of GIST successfully treated solely with systemic therapy with a tyrosine kinase inhibitor, achieving tumor control for over 5 years. This case suggests that tyrosine kinase inhibitors might play a key role in the multidisciplinary treatment for skull base metastases of GIST.

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KEYWORDS gastrointestinal stromal tumor; tyrosine kinase inhibitor; intracranial metastasis; skull base; oncology; neurosurgery

Gastrointestinal stromal tumors (GISTs) are the most common subepithelial tumors of the gastrointestinal tract, arising from precursors of connective-tissue cells in the gastrointestinal tract.¹ GISTs occur most commonly in the stomach (50%–60%), small intestine (30%–35%), colon (5%), and less frequently in the esophagus, omentum, mesentery, or the retroperitoneum.² GISTs are defined and diagnosed by the expression of a proto-oncogene protein called KIT (CD117) detected by immunohistochemistry. Complete resection is the standard treatment for localized primary lesions of GIST, and

tyrosine kinase inhibitors (TKIs) such as imatinib are generally used for invasive inoperable and/or metastatic lesions.³

Metastases of GIST are commonly detected in the liver, omentum, peritoneum, and other intraperitoneal areas; meanwhile, metastases outside the peritoneal cavity, especially intracranial metastases are known to be quite rare.^{2,4} Although TKIs are the standard treatment for metastatic lesions, in cases in which metastases are localized and symptomatic, such as intracranial metastases, multidisciplinary treatment including resection should be considered. However, in cases of

ABBREVIATIONS CT = computed tomography; FDG = fluorine-18 fluorodeoxyglucose; GIST = gastrointestinal stromal tumor; MRI = magnetic resonance imaging; PET = positron emission tomography; TKI = tyrosine kinase inhibitors.

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skull base metastases, treatment has been quite challenging because of the difficulty of complete resection due to surrounding vital structures such as the optic apparatus, cranial nerves, large vessels, and nasopharyngeal cavity. Therefore, standard treatment has not been established. A combination of surgery, radiotherapy, and TKIs has been used in individuals, however, its outcome has not always been favorable.³ So far, five cases of skull base metastasis of GIST have been reported, and the overall survival period from the diagnosis of metastasis is reported to be 4 to 22 months.⁵⁻⁹

We report a rare case of skull base metastasis of GIST treated with biopsy and only imatinib achieving more than 5 years of tumor control and survival.

Illustrative Case

A 52-year-old male with a history of GIST presented to our department with left facial swelling and numbness and was admitted for further investigation.

He was initially diagnosed with GIST on the posterior wall of the stomach by open biopsy 2 years before being referred to our department and received resection with cholecystectomy and partial duodenectomy after 8 months of neoadjuvant imatinib (standard TKI) treatment (Fig. 1A). The patient did not receive postoperative imatinib treatment at that time. He had a recurrence of the tumor in his liver and underwent resection 13 months after the first abdominal tumor resection. Tumors were histologically identical in both operations, showing features of GIST with spindle-shaped cells. The tumor cells were positive for KIT on the immunohistochemistry examination.

On admission to our department, there was left exophthalmos and bulging of the temporal region with sensory disturbance in the patient's left maxillary zone. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 70-mm lobed enhancing mass occupying the left middle cranial fossa, maxillary sinus, and the orbit with remarkable periosteal reaction. The tumor also invaded the temporal muscle and subcutaneous tissue (Fig. 1B and C). Positron emission tomography (PET) revealed an accumulation of fluorine-18 fluorodeoxyglucose (FDG) in the right ilium bone in addition to the middle cranial fossa and liver (Fig. 1D and E). Digital subtraction angiography showed significant tumor staining via the left maxillary artery, middle meningeal artery, and accessory meningeal artery (Fig. 1F).

After preoperative embolization of these feeders to reduce bleeding from the hypervascular tumor, we performed transnasal endoscopic tumor biopsy for a definitive diagnosis. We obtained a sample via the upper wall of the maxillary sinus that was adjacent to the tumor and found that the tumor was very hemorrhagic. Pathologically, the tumor sample demonstrated typical findings of GIST (Fig. 2A). Immunohistochemical staining with appropriate controls was positive for KIT and DOG-1 (Fig. 2B), proving the metastasis of GIST from the patient's peritoneal to the skull. We discussed the treatment strategy on our institutional cancer board and decided to reintroduce systemic imatinib treatment based on the following points: (1) the location of the tumor made total resection difficult without neurological and cosmetic deficits and (2) the GIST was metastasized not only to the skull base but to other parts of the body as well. We also planned resection of the tumor with the option of adjuvant radiation in case the efficacy of

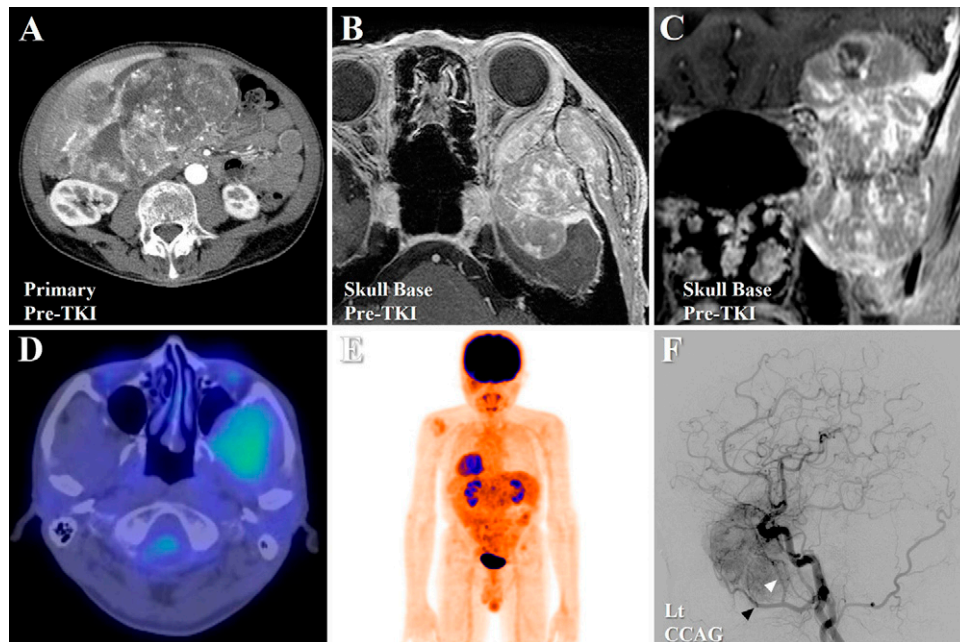


FIG. 1. A: CT at the primary examination revealed a well-contrasted 16-cm tumor behind the liver. **B and C:** Gadolinium-enhanced T1-weighted (Gd-T1) magnetic resonance image revealed a well-defined, lobe-shaped tumor (70 mm) located in the left middle cranial fossa invading the orbit, maxillary sinus, temporal muscle, and temporal bone. Periosteal reaction around the temporal bone suggested the metastasis of GIST. **D and E:** PET revealed an accumulation of FDG in the right ilium bone (SUVmax 1.9), the middle cranial fossa (SUVmax 2.8), and liver (SUVmax 3.3). **F:** Left common carotid artery angiography revealed significant tumor staining through the maxillary artery and middle meningeal artery. Prior to the biopsy, the second and third segments of the maxillary artery (*black arrowhead*) and deep temporal artery were embolized.

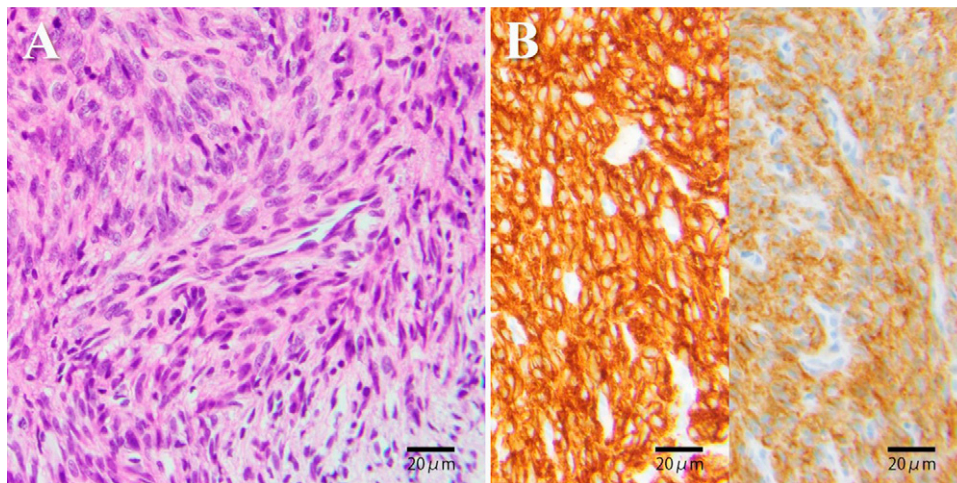


FIG. 2. A: Hematoxylin and eosin staining of the tumor collected from the maxillary sinus showed proliferating uniform spindle-shaped cells, which is a typical finding of GIST. **B:** Immunostaining for DOG-1 (*left*) and immunostaining for KIT (*right*). Both showed strong positivity.

imatinib treatment was insufficient. The course after the introduction of imatinib was uneventful, and the skull base lesion regressed soon after initiation of treatment. With the shrinking of the lesion, his exophthalmos progressively improved in 2 weeks and completely disappeared 3 months after the reintroduction of TKI. The primary peritoneal lesion kept shrinking and there were no additional metastatic lesions (Fig. 3A). The skull base lesion has not progressed radiologically for 63 months since the skull metastasis was revealed (Fig. 3B and C). Continuing to take imatinib orally, the patient is consistently being followed up on outpatient care without any additional deficit or side effects of imatinib.

The clinical course of this patient is summarized in Fig. 4.

Discussion

Observations

We report the longest well-controlled case of skull base metastasis of GIST treated only with reinduction of TKI, its pathology confirmed with endonasal endoscopic biopsy.

GISTs commonly metastasize to the intraperitoneal space. In one case series of malignant GISTs, metastases were generally seen in the liver (46%) and peritoneum (40%). A small number of

metastases (2%–3%) in other places such as retroperitoneum, lung, scar tissue, pleura, and bone is also reported in the article.¹⁰ Since the review of the literature revealed only a few case reports, intracranial metastasis of GIST is considered to be quite a rare condition. In intracranial metastases, the lesion varies from case to case, and the time from initial presentation to detection of metastasis was 0–12 years.^{9,11} In our case, 26 months had passed from the initial presentation in the duodenum.

Once intracranial metastases were revealed, the majority of the reported cases were treated using multidisciplinary treatment including surgery, chemotherapy, and radiotherapy. We initially started oral TKI treatment alone after the transnasal biopsy in our case. The tumor had not progressed for 63 months without resection. Reviewing the previous literature, only six cases had survived more than twelve months after diagnosis of intracranial metastases, and long-term survival was not obtained in any case without resection or radiological therapy.^{9,11} Therefore, this is the case with the longest progression-free survival, among those controlled by TKIs only.

We reviewed previous reports of five cases of skull base metastasis of GIST in detail and summarized them in Table 1, including

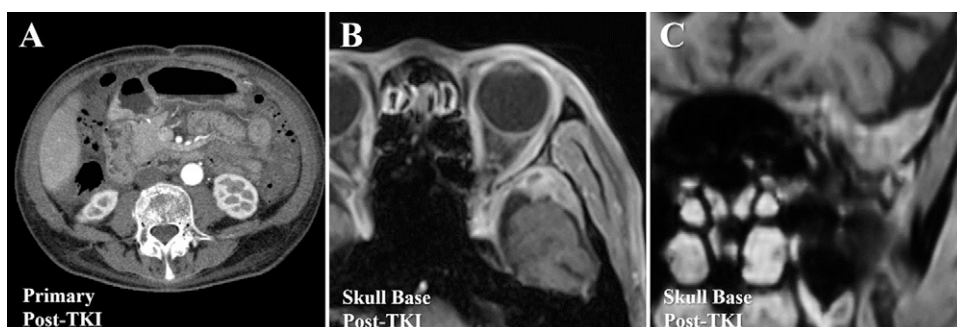


FIG. 3. A: CT obtained 56 months after the reintroduction of imatinib, revealing that the primary lesion remained shrunk and that there were no additional metastatic lesions in the intraperitoneal space. **B and C:** Gd-T1 MR images obtained 63 months after the reintroduction of imatinib, revealing that the tumor remained significantly shrunk and localized to the middle cranial base area.

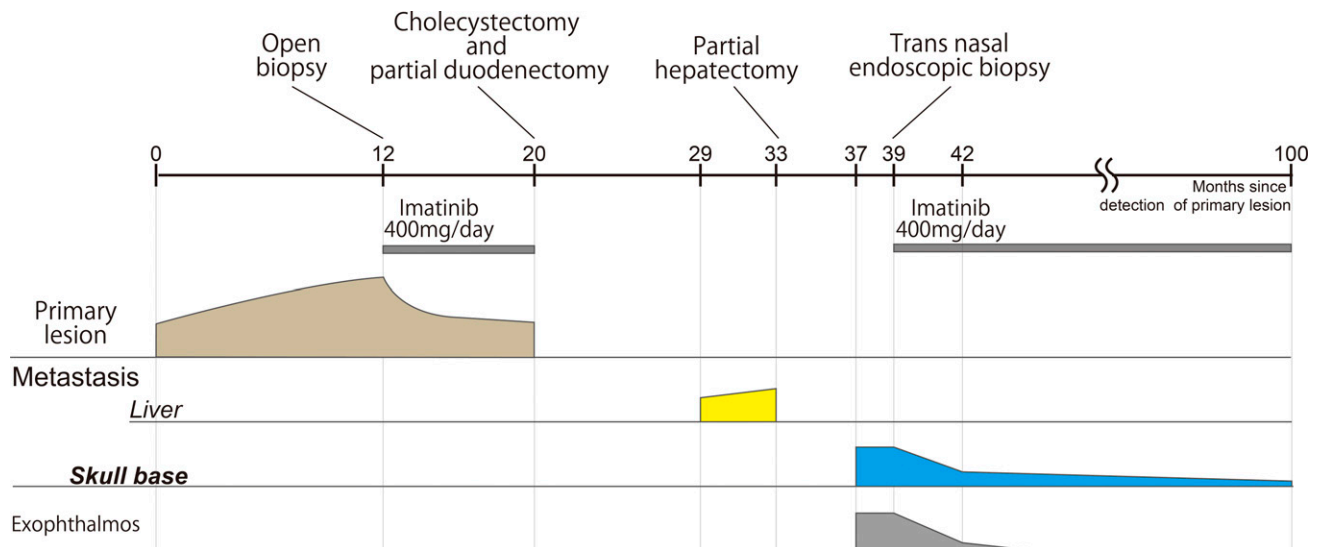


FIG. 4. The clinical time course of the patient since the detection of the primary peritoneal lesion. The vertical axis of the graph represents quantitative volume of the tumor.

our case.⁵⁻⁹ Among these six cases, the overall survival period after diagnosis of metastasis was 4 to 63 months. Only one case, in which TKI treatment was not able to be introduced, died of liver failure from liver metastasis of GIST, and other cases treated by TKI achieved progression-free survival without exception. This fact proves the efficacy of TKI for advanced or metastatic GIST.

Among the six cases, we revealed a tendency for GIST to metastasize to the floor of the middle cranial fossa; five cases (83%) experienced metastases in the middle cranial fossa invading surrounding vital structures such as optic apparatus, cavernous sinus, and internal auditory canal. We also found that all the cases with metastatic GISTs to the skull base had histories of GIST metastasis to the liver. This fact implies that skull base metastasis of GIST might be hematogenously disseminated via the portal system of the liver.

In four of the five previous cases, surgical treatment was performed for palliation of symptoms or cranial nerve salvage. This may be due to the characteristic of skull base metastasis that symptoms, including those of the cranial nerve, are likely to manifest. Among surgically treated cases, improvement of neurological deficits after the early postoperative period was obtained in only one case. In the present case, pretreatment exophthalmos due to the skull base lesion improved in 2 weeks and completely disappeared in 3 months after the reintroduction of TKI. If the symptoms are not severe or the mass effect is not life threatening, it is possible to achieve symptom relief with TKI alone without surgery.

Radiotherapy has been adapted for three out of five cases of skull base metastasis of GIST. Two cases were treated with postoperative adjuvant radiotherapy in addition to TKIs and achieved good disease control.^{6,7} The other was treated with palliative radiotherapy without TKI and died from uncontrolled tumor 8 months after radiotherapy.⁵ In addition, one case using gamma knife radiosurgery along with TKIs for recurrence of deep intracranial GIST metastasis had a good outcome.¹² In general, radiotherapy often plays a role in palliation and may stabilize single progressing liver or intra-abdominal metastatic lesions for several months.¹³ Although GIST

is considered to be sensitive to radiotherapy,¹⁴ there are no past reported cases of intracranial metastases of GIST treated by radiotherapy only. Considering these cases, radiotherapy as an additional therapy to TKIs may be useful for the control of intracranial metastasis of GIST.

Among the previously reported five cases of intracranial metastatic GIST with recurrence, four cases experienced local intracranial recurrence after the resection for the management of metastasis lesion, and all of the four recurrences were observed at the margin of the surgical site.^{5,11,12,15,16} Although resection is meaningful for tumor mass reduction, these results also suggest that surgery for intracranial GIST metastases may play a lesser role in long-term tumor control. Eventually, three of five patients who were introduced or switched to proper doses of TKIs showed no evidence of further recurrence or progression.^{11,12,16} Otherwise, the other two patients who did not receive TKI therapy died of tumor progression; one because TKIs were not yet developed and could not be used, and the other because he refused additional treatment.^{5,15} We suggest that TKIs can be effective not only for patients who are treated with them from the first instance of intracranial metastasis as in our case, but also for patients with recurrence after treatment of intracranial metastasis. Considering these cases, our case suggests the potential efficacy of TKIs as a primary treatment for cases of GIST with intracranial metastasis.

From a pathological point of view, most GISTs are immunohistochemically positive for KIT. DOG1 is also known to be specifically expressed in GISTs, detected by immunostaining. In our case, the sample taken from the upper maxillary sinus showed KIT positivity, which matched the pathological and immunohistochemical findings from the primary lesion. The primary lesion was initially treated by imatinib and responded well to the treatment. Therefore, imatinib treatment was reintroduced and long progression-free survival was achieved as a result.

As for genetic aspects, most GISTs (75%–80%) have *c-kit* genetic mutations. GISTs without *c-kit* mutations may have *PDGFRA* or *DOG-1* mutations. *PDGFRA* and *c-kit* mutations have predictive value

TABLE 1. Summary of previous cases of gastrointestinal stromal tumor metastases to the skull base

Authors & Year	Age (yrs)	Sex	Location of			Location of Metastases			Max Size (mm)	Tx for Primary Lesion	Tx for Metastasis	Immunohistochemical Staining	Overall Survival After Diagnosis of Skull Base Metastasis
			Primary Lesion	Skull Base	Systemic	Symptoms	Skull Base	Systemic					
Akiyama et al., 2004 ⁵	60	M	Small intestine	Cavernous sinus, optic canal, sphenoid wing	Liver	Visual loss, facial dysesthesia	NA	NA	Resection, RT, embolization	RT	C-KIT+	Death at 8 mos from liver failure	
Wong et al., 2011 ⁶	26	M	Duodenum	Mid fossa, orbit, temporal bone/muscle	Liver	Exophthalmos, facial numbness	61	61	TKIs	Resection, RT	C-KIT+	4 mos w/o progression	
Li et al., 2011 ⁷	26	M	Duodenum	Mid fossa, orbit, temporal bone/muscle	Liver	Facial numbness, diplopia	NA	NA	TKIs, RFA	Resection, RT	C-KIT+, CD34+	5 mos w/o progression	
Ishii et al., 2014 ⁸	54	M	Duodenum	Craniovertebral junction	Liver	Neck pain	45	45	Resection, TKIs	Resection, TKIs	C-KIT+	22 mos w/o progression	
Prablek et al., 2019 ⁹	57	F	Esophagus, stomach	Mid fossa, internal auditory canal	Liver	Facial palsy/numbness; hearing loss	34	34	TKI	Resection, TKI	C-KIT+	NA	
Present study, 2021	52	M	Duodenum	Mid fossa, orbit, temporal bone	Liver, costal bone	Exophthalmos, facial numbness	70	70	TKI	TKI	C-KIT+, DOG1+	63 mos w/o progression	

+ = positive; max = maximum; mid = middle; NA = not available; RFA = radiofrequency ablation; RT = radiotherapy; Tx = treatment.

for sensitivity molecular targeted therapy such as tyrosine kinase inhibitors. These genetic mutations also have diagnostic value. For example, *PDGFRA* can confirm the diagnosis in immunohistochemically KIT/DOG1-negative suspected GISTs.¹⁷

Long-term use of imatinib may provoke some adverse effects or resistance. The most frequent adverse effects include anemia, periorbital edema, fatigue, nausea, diarrhea, and muscle cramps, and severe adverse effects may lead to the discontinuation of imatinib treatment.² Although most GISTs respond to imatinib for a period of 12–36 months, over 80% of the patients treated with imatinib experience secondary resistance that leads to treatment failure.² This phenomenon is thought to be induced by additional genetic mutations in GIST-associated genes such as *c-KIT* and *PDGFRA*, which alters the molecular structure of tyrosine kinase proteins.¹⁸ Fortunately, the present case has not experienced any adverse effects or secondary resistance after the long-term use of imatinib.

In conclusion, certain cases of intracranial metastases of GISTs are difficult to treat and there are no reports on successful long-term multidisciplinary treatment including TKIs for skull base metastases. This report describes long-term survival in a case of skull base metastasis of GIST and suggests that TKIs may play an important role. The development of genetic studies in the future would facilitate further investigation of treatment for long-term survival.

Lessons

We report a case of skull base metastasis of GIST successfully treated with only systemic therapy with TKI, achieving significant tumor shrinkage for over 5 years. In the context of multidisciplinary treatment utilized for previous cases of skull base metastases of GIST, this case suggests that TKIs may play a pivotal role in favorable tumor control.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Miyawaki, Kawanishi, Umekawa, Shin. Acquisition of data: Miyawaki, Kawanishi, Umekawa, Fujitani, Ishizawa, Hongo, Shojima. Analysis and interpretation of data: Miyawaki, Kawanishi, Umekawa, Ishizawa. Drafting the article: Miyawaki, Kawanishi, Umekawa. Critically revising the article: Miyawaki, Umekawa, Fujitani, Hongo. Reviewed submitted version of manuscript: Miyawaki, Kawanishi, Umekawa, Fujitani, Ishizawa, Ushiku, Hongo, Teranishi, Shojima, Saito. Approved the final version of the manuscript on behalf of all authors: Miyawaki. Administrative/technical/material support: Miyawaki, Hongo, Teranishi. Study supervision: Miyawaki, Teranishi, Shin, Hasegawa. Pathological evaluation: Ushiku.

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