Surgical resection of intraorbital metastasis of a gastrointestinal stromal tumor resistant to chemotherapy

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**ABSTRACT**

**Purpose:** We present a case of a gastrointestinal stromal tumor (GIST) metastasis of the rectal primary resisting chemotherapy to the right orbit 15 years after excision of the primary lesion.

**Observations:** A 79-year-old man was diagnosed with rectal GIST at the age of 65 years and underwent rectal amputation. He underwent hepatectomy for GIST liver metastases at the age of 69 years and pericardiectomy for GIST pericardial metastases at 72 years of age. At the age of 79 years, positron emission tomography-computed tomography revealed the possibility of liver metastasis and metastasis to the right orbit of 10 mm in size. Magnetic resonance imaging revealed a well-circumscribed mass of 10 mm × 12 mm in the deep medial rectus muscle of the right orbit, which was referred to our department for ophthalmic examination. The latter revealed only mild abduction disorder in the right eye. Although chemotherapy was initiated, the tumor gradually increased, causing exophthalmos in the right eye, visual field impairment due to optic nerve exclusion, and decreased visual acuity. Due to repeated multiple metastases, the patient underwent right orbital exenteration and free flap reconstruction at the age of 83 years for radical cure. Pathological examination revealed c-Kit positive, CD34 positive, S100 protein minority positive, MIB-1 positive rate of 10% or more, and α-SMA negative, and the diagnosis was intraorbital metastasis of GIST.

**Conclusions and importance:** Orbital metastases in GISTs are extremely rare, and there is no established standard treatment. Therefore, a comprehensive decision must be made based on the final treatment goal and the patient’s background when selecting treatment.

1. **Introduction**

A gastrointestinal stromal tumor (GIST) is derived from Kahar’s intervening cells, which are pacemaker cells for gastrointestinal peristalsis.\(^1\) It is mainly found in the digestive tract, including the stomach (55.6%), small intestine (31.8%), colon, and rectum (6.0%). The incidence is reported to be 10–15 per million annually, with a male-female ratio of approximately 1:1.\(^1\) The main metastasis of GIST is the liver and peritoneal dissemination, and it rarely metastasizes to the lung, bone, brain, pleura, and lymph nodes.\(^3\) Only a few cases have been reported as intraorbital metastases. We report a rare case of rectal GIST metastasis to the right orbit 15 years after primary lesion resection.

2. **Case report**

A 79-year-old man was diagnosed with rectal GIST at the age of 65 years and underwent rectal amputation. At the age of 69 years, he underwent hepatectomy for GIST liver metastases and imatinib mesylate (Gleevec\(^®\)) 100 mg 3 cap/day was initiated. At the age of 72 years, he underwent pericardiectomy for GIST pericardial metastasis. Although no recurrence or metastasis was observed on computed tomography (CT) at 77 years of age, fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) at 79 years revealed a 10 mm-sized, well-circumscribed mass on the medial right orbit. The maximum standardized uptake value (SUVmax) on FDG-PET was 6.9 for
the same lesion. Additionally, a 25 mm-sized tumor (SUVTmax 13.2) was found in the lateral section of the left lobe of the liver, which was considered to be liver metastasis. Contrast-enhanced magnetic resonance imaging (MRI) revealed a well-circumscribed round nodule (10 mm × 12 mm) that was widely in contact with the medial rectus muscle inside the right orbit (Fig. 1a and b). The lesion showed a signal similar to that of muscle on T2-weighted images and a low signal on the apparent diffusion coefficient map, and a contrast effect similar to that of the extraocular muscle was observed (Fig. 1c and d). Additionally, a 30 mm round mass was found in the S3 region of the liver, with low signal on T1-weighted images, mild high signal on T2-weighted images, and marked high signal on diffusion-weighted images. This liver lesion showed no contrast effect and showed a low signal in the hepatocyte layer, and was considered to be a GIST liver metastasis from the course. Although he had no subjective symptoms at this time, he was referred to our department to evaluate visual function due to a tumor in the right orbit. There was nothing special regarding the history of ophthalmology. His best-corrected visual acuity at the first visit was 20/40 in the right eye and 20/32 in the left eye due to cataracts. The intraocular pressure was 12.0 mmHg in the right eye and 11.0 mmHg in the left eye. Slit-lamp microscopic findings showed good light reflex in both eyes without delay and no relative afferent pupillary defect. Fundus examination showed no abnormal findings in the optic nerve or retina. The Hess chart revealed a mild abduction disorder in the right eye. He was regularly examined by an ophthalmologist every 3 months, and the Hess screen test showed no exacerbation of ocular motility disorder. However, 1 year after the first visit, the visual acuity decreased to 20/50 in the right eye. The fundus findings showed optic disc swelling in the right eye, and the central flicker values were 35 Hz in the right eye and 42 Hz in the left eye, which were attenuated in the right eye than the left eye. These results suggested compression of the right optic nerve by an intraorbital tumor. Two years and 6 months after the first visit, the Hess chart became unmeasurable. CT performed at another department 2 years and 9 months after the first visit showed an increase in the tumor in the right orbit. Simultaneously, he became aware of exophthalmos in his right eye. Two years and 11 months after the first visit, his visual acuity in the right eye further declined to 20/80. The central flicker value was 20 Hz in the right eye and 44 Hz in the left eye, and further attenuation was observed in the right eye. The degree of exophthalmos was 12.0 mm for the right eye, 8.0 mm for the left eye (base 105.0 mm), and exophthalmos was observed in the right eye. Eye movements other than the downward rotation of the right eye were restricted. He was recommended to have a surgical resection by the gastrointestinal doctor, but he did not agree to the surgery and wanted to be treated with oral chemotherapy. However, 3 years and 2 months after the first visit, his visual acuity in the right eye further decreased to 20/300. Radiation therapy was also explained as he was old; however, the patient requested curative surgery. Three years and 4 months after the first examination, the co-operation of right orbital exenteration and free flap reconstruction was performed by the Department of Otolaryngology and Plastic Surgery of Yamaguchi University under general anesthesia (Fig. 2). First, a skin incision was made from the front along the Weber-Fergusson incision line just above the maxilla, and the infraorbital nerve was cauterized. The infraorbital wall, maxilla, and ethmoid bone were excised to secure the surgical field. Tissue in the orbit was peeled away along the peri-orbital membrane, and the supraorbital and supratrochlear nerves were cut at the upper edge of the orbit, and the anterior and posterior ethmoidal arteries were ablated. The optic nerve was amputated, and the orbital contents and associated tumors were removed. A 7 cm square free flap from the left forearm was used for eye suck reconstruction, and the facial artery, facial vein, radial artery, and cephalic vein were used for vascular reconstruction.

In the pathological examination of the right orbital tumor (Fig. 3), spindle-shaped cells with nuclear swelling proliferated in a bundle-like manner in hematoxylin-eosin staining (Fig. 3a). There were 10 or more fission images/50 high power fields (Fig. 3b). There was no necrosis or vascular invasion; however, infiltration into the surrounding striated muscle was observed. The stump was negative, and no infiltration into the optic nerve was observed. Immunological examination revealed diffusely positive c-Kit (Fig. 3c) and CD34 (Fig. 3d), markers for vascular endothelium and stem cells, diffusely positive. The nervous system marker S100 protein was minority-positive. The smooth muscle marker, αSMA was negative. The growth marker MIB-1 positivity rate (Fig. 3e) was 10% or more. Based on the immunohistochemical and histopathological findings, highly malignant GIST was diagnosed. After the operation, the transplanted flap survived and the wound course was

![Fig. 1. Magnetic resonance imaging (MRI) image of a tumor in the right orbit (upper) T1-weighted image (contrast), (Lower) T2-weighted image, (right column) Coronal section, (left column) Maxillary section. Inside the right orbit, a 10 mm × 12 mm-sized well-circumscribed circular nodule is observed in close contact with the medial rectus muscle. This tumor shows a contrast effect almost similar to that of the extraocular muscles (a, b), and at T2, it shows a signal similar to that of the muscle (c, d).](image-url)
good; however, aspiration pneumonia due to dysphagia was repeated from the early postoperative period. Since swallowing rehabilitation was necessary, the patient was transferred to another hospital 1 month after the operation. After the transfer, no recurrence of the orbital tumor was observed; however, CT showed a new tumor lesion suspected to be liver metastasis. During the course, the patient had repeated aspiration pneumonia and died 6 months after the operation.

3. Discussion

Here, we report a case of intraorbital metastasis of GIST, which is rare as a metastatic intraorbital tumor. According to a review of 2480 cases in Italy, 3% of malignant tumors, which account for approximately 30% of the total, are reported to be orbital metastases. The primary lesions were as follows: unknown (17%), renal cell carcinoma (11%), lung cancer (8%), nasopharyngeal cancer (4%), melanoma (3%), parotid adenocarcinoma (3%), squamous cell carcinoma (3%), neuroendocrine cancer (2%), prostate cancer, bladder cancer, gastric cancer, liver cancer, adrenal neuroblastoma, and penis cancer (1% each). Additionally, in a report of intraorbital tumors in 244 Japanese patients, 2% were metastatic tumors. The breakdown of the primary lesions of eight metastatic tumors was lung cancer in three cases, and breast cancer, prostate cancer, liposarcoma, leukemia, and leiomyosarcoma in one case each. However, GIST orbital metastasis is extremely rare, and to the best of our knowledge, only five cases have been reported to date. As a general rule, GIST is treated by surgical excision of the lesion; however, there are cases in which chemotherapy or radiation therapy is used. Since it is difficult to distinguish between benign and malignant GISTs even by using pathological diagnosis, many GISTs are indicated for surgery. Currently, there is little evidence-based literature on surgical treatment. An observational cohort study of 2560 patients with histologically diagnosed resectable GIST removed macroscopically completely at the surgery did not receive adjuvant or neoadjuvant therapy at 5, 10, and 15 years, estimated recurrence-free survival rates of 70.5%, 62.9%, and 59.9%, respectively. It was also suggested that the Fletcher, modified Fletcher, and Miettinen classifications can accurately predict the risk of recurrence after surgery. Regarding the effectiveness of adjuvant therapy, Joensuu et al. compared two groups of patients with GIST who received 400 mg of imatinib mesylate daily as adjuvant therapy, one group received for 1 year after surgery, and another for 3 years, and both recurrence-free and overall survival time extended in 3-year using imatinib mesylate group. Based on these results, 3-year oral imatinib mesylate is recommended as postoperative adjuvant therapy for medium-to high-risk patients according to the Miettinen classification. Chemotherapy using oral imatinib mesylate is also administered for unresectable, recurrent, and metastatic cases. For imatinib mesylate-resistant GIST, it is recommended to switch to sunitinib malate (Sutent®), and for sunitinib malate-resistant GIST, switch to regorafenib hydrate (Stiberga®) if the general condition is good. Radiation therapy is generally ineffective against GIST and is not considered to be a substitute for surgery. As a therapeutic effect, it is reported that the partial response/stable disease is approximately 80% at 3–6 months after 30–40 Gy of irradiation. Radiation therapy has been reported to be effective in alleviating the symptoms of metastatic GIST; however, its efficacy and safety have not been established.

Table 1 summarizes previous reports on intraorbital metastasis of
GISTs and our case. Akiyama et al. reported a metastatic case of primary GIST in the small intestine in a 60-year-old man. The patient was referred for a sudden, unilateral visual loss lasting a day, and an abnormal sensation around the left side of his head for a few days. CT showed a mass extending from the left optic canal to the left cavernous sinus. Surgical resection was not selected as the lesion was deep intracranial, and a total of 5400 cGy of radiation was administered over 6 weeks. No improvement in visual function was obtained, however, a partial relief of pain was obtained, no recurrence was observed for about 4 months until the patient died of liver dysfunction, and eye movements and eye position were maintained normally. 1 A 26-year-old man with primary duodenal GIST metastasis reported by Li et al. developed numbness and diplopia on the left face. Contrast-enhanced MRI revealed a 5 cm-sized lesion in the left orbit from the left temporal lobe, and CT showed erosion of the supraorbital wall and left skull. Partial surgical resection was performed, and decompression in the orbit improved visual acuity, exophthalmos, and diplopia. Pathological examination revealed a highly malignant GIST; therefore, extracorporeal irradiation therapy was performed to prevent a recurrence, and oral nilotinib hydrochloride hydrate was continued. According to a report by Yu et al. a 43-year-old woman was aware of left exophthalmos and decreased visual acuity, and MRI pointed out a lacrimal gland lesion. She had decreased vision due to increased intraorbital pressure, exophthalmos, omnidirectional ocular motility disorder, papilledema of the optic nerve, and retinal edema, which were improved by surgical resection. This case was confirmed as a primary GIST in the small intestine that metastasized to the orbit, as confirmed by immunohistochemical staining. She continued to take imatinib mesylate and no recurrence of the orbital tumor was reported, 6 months after surgery. A 66-year-old woman reported by Roelofs et al. developed blurred vision in the left eye and left orbital pain. CT showed a mass containing the superior rectus muscle that straddled the inside and outside of the muscle spindle in her left orbit. Biopsy and surgical resection were performed, and pathological examination revealed a highly malignant GIST. Oral administration of imatinib mesylate was continued; however, GIST metastasis to the right eye was observed 8 months after that to the left eye. The primary lesion was observed in the stomach. Woo et al. found a left anterior orbital mass in a 65-year-old woman that continued to grow for 3 weeks. CT revealed a tumor confined to the left anterior orbit. The tumor attached to the upper left rectus muscle was resected by surgery, and immunological examination confirmed that it was a highly malignant GIST. The primary lesion was observed in the stomach. Thus, there is no established treatment protocol for GIST intraorbital metastatic tumors. It should be decided comprehensively based on tumor size and site, age, ocular symptoms, ocular findings, general condition, reactivity to chemotherapy, malignancy, treatment goals, and patient wishes.

In our case, the GIST had metastasized to multiple locations before the orbit and was expected to be highly malignant. Even after chemotherapy with 300 mg daily of oral imatinib mesylate, the tumor continued to grow gradually, causing exophthalmos of the right eye, visual field impairment due to optic nerve compression, and decreased visual acuity. Additionally, a metastasized tumor in the right orbit was the only lesion that remained before surgery. Radiation therapy was also explained as the patient was old; however, he chose orbital exenteration as he wanted radical cure by surgical resection. GIST diagnosis and risk assessment were performed by pathological examination; c-Kit and CD34-positive spindle-shaped cells were found in the lesion, the MIB-1 positive rate was 10% or more, and GIST with high cell proliferation ability was diagnosed. In this case, although the lesion in the right orbit was completely removed, a lesion suspected as liver metastasis was confirmed after the operation. Even in previous reports, including this case, many cases of GIST with intraorbital metastasis have high cell proliferation ability in the pathological examination. In the case of Roelofs et al. the orbital GIST metastasized to the opposite orbit after surgical resection of one side. In summary, in cases of GIST intraorbital metastasis, attention should be paid to postoperative metastasis and recurrence even after total surgical resection.

4. Conclusions

We encountered a case in which GIST from the small intestine had metastasized in the right orbit 15 years after resection of the primary lesion and underwent right orbital exenteration. GIST orbital metastases are extremely rare, and no established standard treatment has been established. Therefore, a comprehensive decision must be made regarding treatment based on the final treatment goal and the patient's background.

Patient consent

Consent for publication of the case report was not obtained. This report does not contain any personal information that can lead to patient identification.

Funding

No funding or grant support was received for this case report.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

No conflict of interest exists.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.
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