Clinical Oncology: Case Reports

Case Report

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Rare Intracranial Relapse of a Resected Gastrointestinal Stromal Tumour: A Case Report

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Abstract

Background: Gastrointestinal Stromal Tumours (GIST) are c-kit positive mesenchymal tumours that constitute the most common nonepithelial neoplasms of the gastrointestinal tract, commonly metastasizing to the liver and peritoneum. Intracranial metastasis of GIST is extremely rare, with only 19 cases previously reported worldwide, thus presenting a diagnostic challenge and unique treatment considerations.

Case presentation: A 49-year-old gentleman presented with an acute onset of left-sided weakness and an unsteady gait. His past medical history is significant for pulmonary cryptococcosis and localised high-risk gastric GIST harbouring KIT exon 11 deletions. He had undergone a R0 gastric wedge resection six years ago, completed three years of adjuvant imatinib, and had been on routine surveillance for the past three years.

A computed tomography and magnetic resonance imaging scan of the brain revealed a large intra-axial lesion in the right parietal lobe and two smaller brain lesions. Further imaging studies of the chest, abdomen and pelvis found no evidence of local recurrence of GIST, and no evidence of distant metastases. A right craniotomy and excision of the right parietal lobe lesion were performed. Immunohistochemical examination demonstrated malignant spindled to epithelioid cells that were strongly positive for CD34, CD117 and DOG1, establishing the diagnosis of GIST. Further mutational analysis revealed a 24-nucleotide deletion in exon 11 consistent with the mutation seen in the primary gastric GIST resected six years ago. The patient was subsequently treated with palliative systemic imatinib with a good response.

Conclusions: Isolated intracranial metastasis of GIST is exceedingly rare. We describe a treatment strategy that appears effective for patients with intracranial GIST metastasis, which includes surgical resection and palliative systemic treatment with imatinib. Further work is needed to determine the disease and patient factors that predispose to the development of brain metastases in GIST and whether specific mutations are associated with distinct patterns of metastasis.d.

Keywords

Gastrointestinal stromal tumour; Metastatic GIST; Gastric GIST; High-risk GIST; Mutation analysis; Imatinib; Tyrosine kinase inhibitors; KIT-mutated GIST; Brain metastasis

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Introduction

Gastrointestinal Stromal Tumours (GIST) are c-KIT positive mesenchymal tumours arising from the Interstitial Cells of Cajal that constitute the most common nonepithelial neoplasm of the gastrointestinal tract [1,2]. The stomach is the most common primary site of GIST (60%), followed by jejunum and ileum (30%), duodenum (5%) and colon and rectum (5%), with a minority of cases occurring in the oesophagus, omentum and mesentery [3]. Common sites for GIST metastasis include the lungs and liver *via* the haematogenous spread and the peritoneum *via* peritoneal seeding [4]. Intracranial metastasis of GIST is exceedingly rare, and with the inclusion of this case, there have been just 20 cases worldwide reported to date [5].

Imatinib, a Tyrosine Kinase Inhibitor (TKI), is considered the standard of care for KIT-mutated metastatic or unresectable GIST and has been found to be highly effective in the treatment of GISTs harbouring KIT exon 11 mutations [6]. Imatinib has limited ability in crossing the blood-brain barrier [7], although its role in the setting of a disrupted blood-brain barrier has not been well explored.

This report describes a patient with a high-risk gastric GIST that was surgically resected and treated with adjuvant imatinib with success, but that later relapsed several years later with isolated brain metastasis.

Case Presentation

A 49-year-old gentleman presented to the emergency department with an acute onset of left-sided weakness associated with an unsteady gait. Fine motor deficits noted in his left hand also particularly affected his function given his left-handedness. There was no acute blurring of vision, vomiting, or sensory deficits. His past medical history is significant for Barrett oesophagus and pulmonary cryptococcosis which was successfully treated 3 years ago. He was diagnosed 6 years ago with a localised high-risk gastric GIST harbouring KIT exon 11 deletion and had undergone a microscopically margin-negative (R0) gastric wedge resection. He has since completed 3 years of adjuvant Imatinib 400 mg per day and has been on routine surveillance for the past 3 years. Blood tests on admission showed: haemoglobin 13.9 g/dL, white cell count 5.5×10^9/L, platelet count 257×10^9/L, creatinine 82 µmol/L, urea 3.9 mmol/L, sodium 141 mmol/L, and potassium 4.2 mmol/L.

A non-contrasted Computed Tomography (CT) scan of the brain revealed a large intra-axial lesion in the right parietal lobe measuring 4.1 cm × 3.2 cm and a smaller 0.8 cm lesion near the splenium of the left corpus callosum (Figure 1a-1d). Extensive oedema in the right cerebral hemisphere with mass effect effacing the right lateral ventricle and mild midline shift to the left was also evident (Figure 1a, Figure 1c). Neurosurgical opinion was sought and immediate surgical decompression and/or intravenous mannitol were not deemed necessary, since there were no clinical manifestations of raised intracranial pressure. Dexamethasone was commenced for tumour-related vasogenic oedema, which improved his symptoms. A CT scan of the chest, abdomen and pelvis with contrast found no evidence of local recurrence of GIST, and no evidence of distant metastasis (not shown).

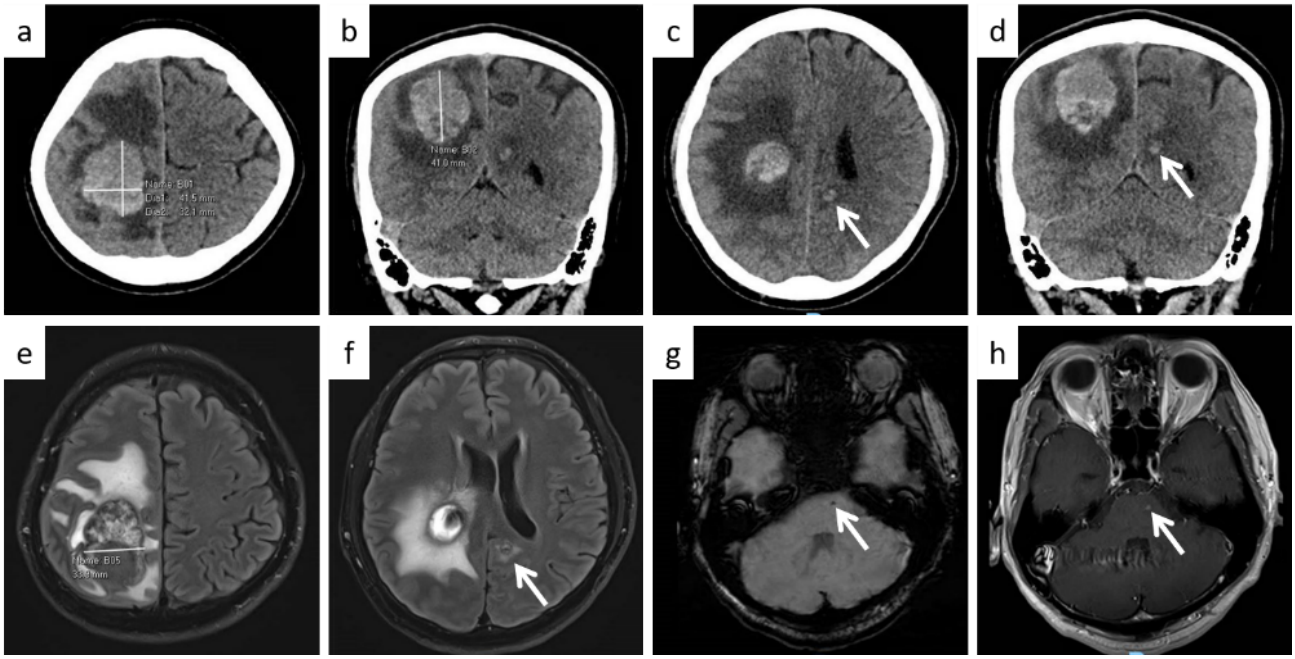

Figure 1: Brain imaging showing the dominant lesion in the right parietal lobe, with two smaller lesions. One just superior to the splenium of the left corpus callosum and another in the left hemipons. The latter was only visible on MRI imaging; a) Non-contrast CT imaging of the dominant right parietal lobe lesion measuring 4.1 cm × 3.2 cm in axial view and; b) coronal view; c,d) A smaller lesion superior to the left corpus callosum shown in axial and coronal views on non-contrast CT imaging, marked with arrows; e) MRI with gadolinium contrast showing a 6.2 cm × 3.1 cm × 3.3 cm well-defined heterogeneously enhancing mass in the right superior parietal lobe; f) a smaller lesion superior to the splenium of the left corpus callosum, and; g,h) a small punctate lesion in the left hemipons, marked with arrows.

Further investigation with Magnetic Resonance Imaging (MRI) of the brain with contrast was obtained. This revealed a 6.2 cm × 3.1 cm × 3.3 cm well-defined heterogeneously enhancing mass lesion of mixed-signal intensity on both T1-weighted (not shown) and T2-FLAIR sequences in the right superior parietal lobe, with associated internal haemorrhage, restricted diffusion and significant perifocal oedema (Figure 1e, Figure 1f). Two more sub-centimetre lesions were also noted, one in the posterior aspect of the left cingulate gyrus just superior to the splenium of the left corpus callosum (Figure 1f), and another in the left hemi-pons (Figure 1g, Figure 1h).

A right craniotomy and excision of the right parietal lobe tumour was performed, and histological examination revealed infiltration of glial tissue by malignant spindled to epithelioid cells, with moderate nuclear pleomorphism, occasional intranuclear pseudo inclusions and rhabdoid morphology (Figure 2a, Figure 2b). Focal necrosis was seen (Figure 2a, Figure 2b) as well as increased mitotic activity of up to 9 mitoses per 10 high powered fields, or 14 mitoses per 5 mm^2 (not shown). Further immunohistochemical studies show that the malignant cells were strongly positive for CD34 (not shown), CD117 (Figure 2c) and DOG1 (Figure 2d) with weak focal positivity for EMA (Figure 2e, Figure 2f) and GFAP (not shown), which is highly compatible with the diagnosis of metastatic GIST. This was also corroborated with similar pathological features in the previous gastric wedge resection six years ago (Figure 3). The Ki67 proliferative index was approximated to be 10%-20%. These cells were also negative for SSTR2, which has been described to be an independent factor for poor prognosis of GIST [8]. This is likely because with high positive expression of SSTR2, agitating SSTR 2 can transduce its antiproliferative functions that can have inhibitory effects on the mitogenic MAPK and survival PI3K pathways [9].

Further mutation analysis and molecular profiling of the resected metastatic tumour revealed a 24-nucleotide deletion at exon 11, from position c. 1668 to position c. 1691, resulting in a small deletion-insertion involving the amino acids at codons 556-564. This finding was the same mutation seen in the patient's previously resected primary gastric GIST, confirming the diagnosis of intracranial GIST metastasis.

The patient recovered remarkably well post-operatively, with alleviation of most of his neurological symptoms. MRI imaging at five days after surgery showed no early complications (Figure 4a) and the residual smaller lesions remained unchanged in size (Figures 4b and 4c). Palliative imatinib 400 mg OM was commenced. Interval MRI brain after six weeks of imatinib showed a significant reduction in size of residual brain lesions with almost complete disappearance (Figures 4e and 4f). At the time of writing, the patient has regained his functional ability and has been on Imatinib for close to four months.

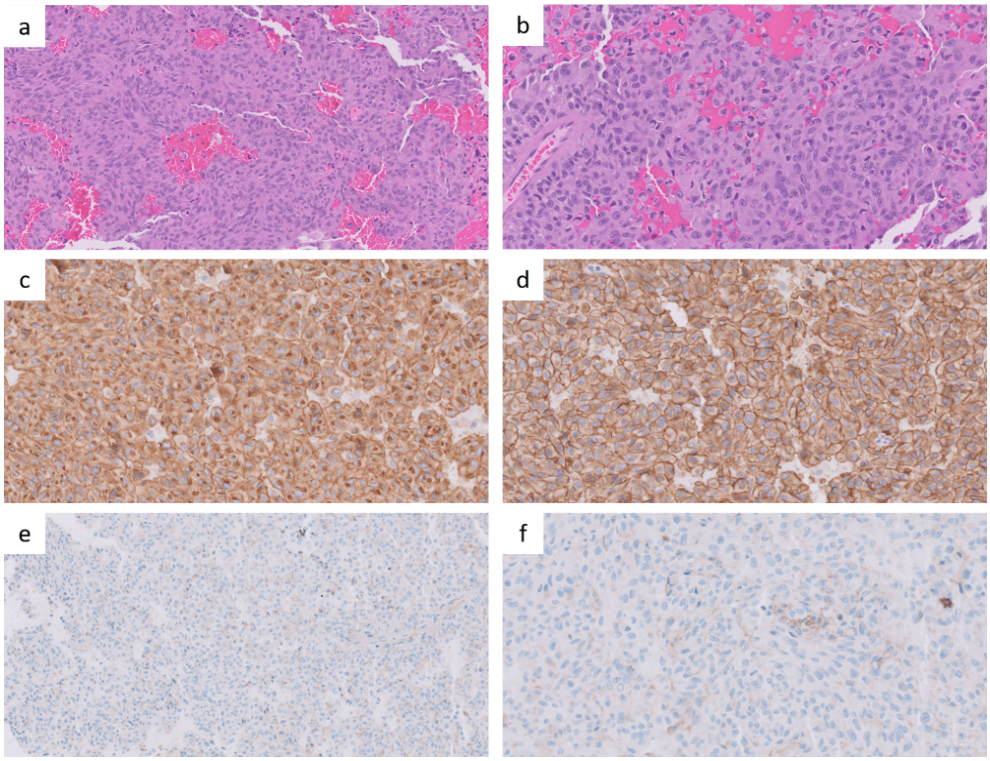

Figure 2: Histology of the resected right parietal lobe tumour; a) Malignant spindled to epithelioid cells, haematoxylin-eosin [H&E], original magnification x100 and; b) original magnification x200; c) The tumour cells are strongly positive for CD117; d) and DOG1 original magnification x200; e) Tumour cells show weak focal positivity for EMA, original magnification x100; f) original magnification x200.

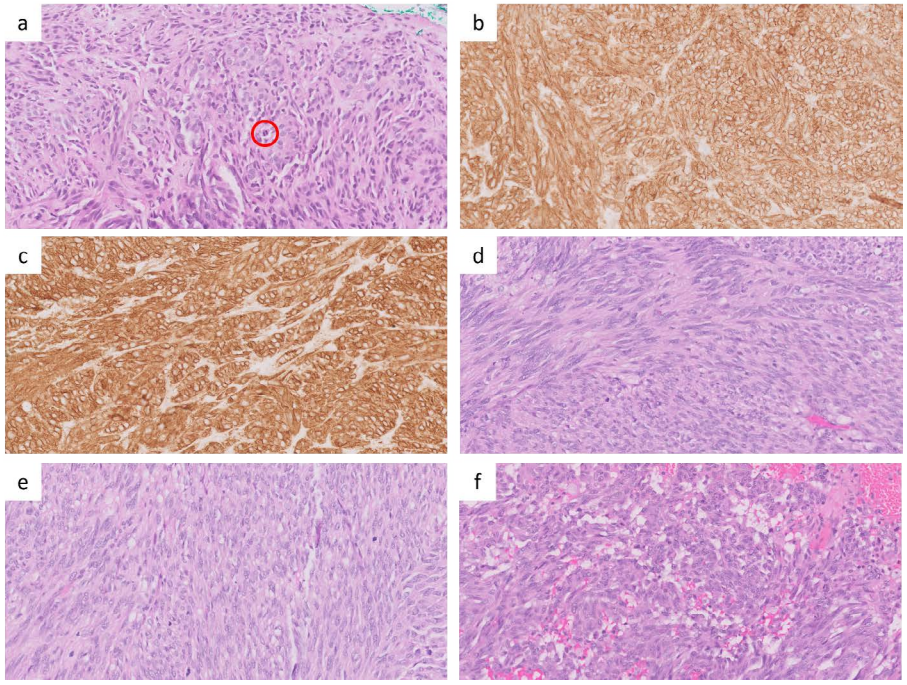

Figure 3: Histology of the primary gastric GIST from 6 years prior; a): Initial biopsy showing interlacing fascicles of spindle cells, haematoxylin-eosin (H&E), original magnification x200. A mitotic figure is highlighted (circled in red). These cells are strongly positive for CD117; b): DOG1; c): original magnification x200. Subsequent gastric wedge resection showed spindled cells with a high mitotic count, H&E; d): original magnification x100; e): original magnification x200; f): Spindled to epithelioid cells in the gastric wedge resection that in areas look similar to the metastatic brain lesion, H&E, original magnification x200.

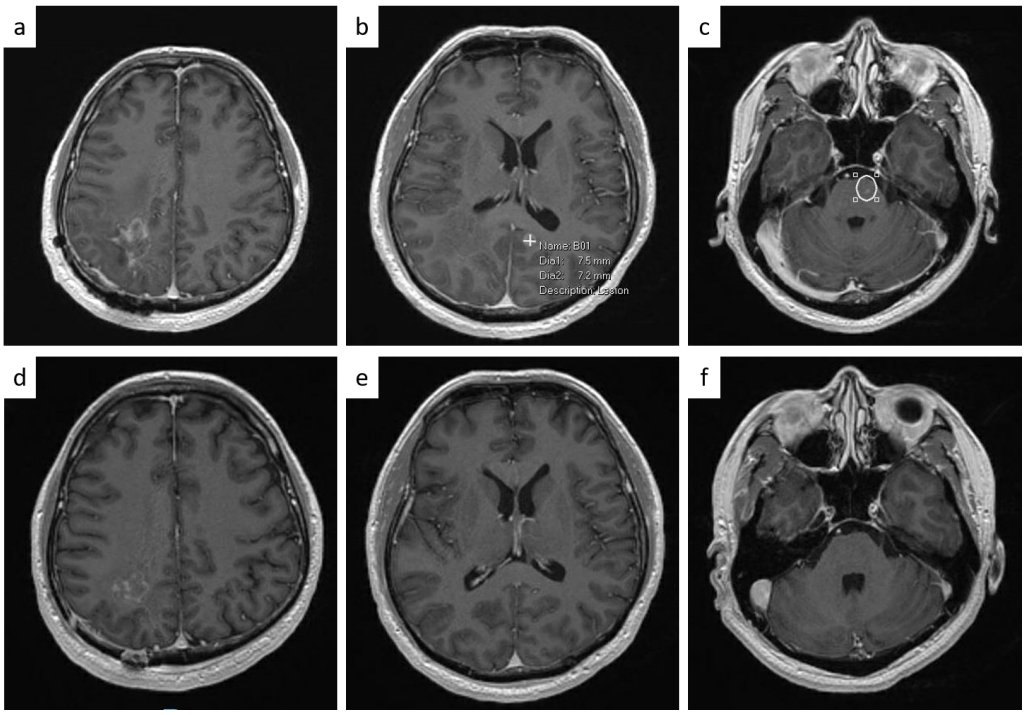

Figure 4: MRI brain imaging taken five days after right craniotomy and excision of right parietal lobe tumour; (a-c): at six weeks post-operatively; (d-f); a) Post-surgical changes at the resection site, resolving at six weeks (d); b) The residual small lesion superior to the splenium of the left corpus callosum appears largely unchanged in size at five days post-operatively. This has disappeared after six weeks of imatinib (e); c) The punctate lesion in the left hemipons is largely unchanged in size at five days post-operatively. This is no longer visible after six weeks of imatinib (f).

Discussion

Differential diagnoses

While the patient had a previous diagnosis of GIST, the extreme rarity of intracranial metastasis of GIST prompted careful consideration of various differential diagnoses at presentation, as these would affect subsequent investigations and management.

Infective aetiologies that were considered for this case included meningoencephalitis due to disseminated haematogenous cryptococcosis from previously treated pulmonary cryptococcosis [10]. The patient had been treated with Fluconazole 400 mg/day for 8 months, and a resolution of his symptoms, signs and initial pulmonary radiological abnormalities was observed. Classical radiological features of cryptococcal meningoencephalitis such as dilated Virchow-Robin spaces, pseudocysts, cryptococcomas and leptomeningeal enhancement were also absent [11], making this less likely an aetiology. The patient also did not manifest any clinical symptoms consistent with meningoencephalitis, such as fever, neck stiffness or photophobia. His symptoms of left-sided weakness and unsteady gait resolved within a week of dexamethasone treatment without any antimicrobial cover, and he remained clinically well.

Malignant aetiologies such as brain metastasis from a primary tumour, and primary tumours of the central nervous system such meningiomas and gliomas were also considered. Possible sources of a primary malignancy that had metastasised to the brain were not immediately evident on contrasted CT scans. A thorough skin examination deemed brain metastasis from cutaneous melanoma less likely, but this would nevertheless need to be excluded.

Meningiomas are often slow growing, with rates reported at around 2.4 mm/year [12], and comparison with a previous CT brain study 2 years ago showed no intracranial lesions, making it less likely a diagnosis. Glioblastomas are usually large masses at diagnosis often associated with a necrotic core [13], and highly prevalent symptoms that are associated with glioblastomas such as seizures, drowsiness and dysphagia were also absent in the patient [14]. Radiological findings were also less consistent with low-grade gliomas which typically have no contrast enhancement following contrast gadolinium injection [15].

A Primary Central Nervous System Lymphoma (PCNSL) was unlikely, given the lack of typical radiological features, including its characteristic appearance on MRI as a solitary parenchymal lesion with diffuse homogeneous contrast enhancement and no associated internal haemorrhage [16]. This was still an important consideration as the treatment for PCNSL would involve multiagent systemic chemotherapy and steroids, without the need for resection, given the high likelihood of excellent response [17]. Furthermore, unlike the situation in metastatic brain tumours, the intent of treatment for PCNSL would be for cure [18,19].

Although radiologically indeterminate, the intracranial lesions detected on CT and MRI, in this case, were suspicious for haemorrhagic cerebral metastasis, and the multidisciplinary tumour board recommendations were in agreement with our decision to proceed with surgical resection of the dominant tumour in the right parietal lobe for histological confirmation. Neurosurgery was confident of maximal safe resection of the dominant brain lesion with good functional recovery. Importantly, should the diagnosis be confirmed as metastatic melanoma, this would also be a reasonable

approach since metastatectomy in melanomas with oligometastatic disease has been associated with improved overall survival [20]. Equally, metastatectomy of oligometastatic GIST is also acceptable [21], if the brain lesion was confirmed as GIST.

Treatment strategy

The challenges, in this case, included the diagnostic evaluation of the intracranial lesion and the decision of the best management plan for the patient. This is an extremely rare occurrence of metastatic GIST to the brain and evidence for optimal management in such cases is scant, requiring unique considerations for treatment. The currently reported case would only be the twentieth reported case, to date. Prablek et al. also found substantial variation between studies in treatment regime [5]. There are no evidence-based guidelines for the treatment of GIST with intracranial metastasis.

Maximal safe surgical resection of the dominant lesion was the first step in both the determination of the underlying histology and the treatment of this patient, with consideration of radiation therapy and systemic tyrosine kinase inhibitor treatment postoperatively. Metastatectomy of oligometastatic GIST is also an accepted management option [21]. The aim of surgical resection would be for cytoreduction, in addition to confirming the histological diagnosis. In this case, it also provided symptomatic control. The two smaller sub-centimetre lesions at the left cingulate gyrus and left hemi-pons were asymptomatic; surgical removal would likely cause significant functional damage with minimal benefit, and hence the decision was made for these to be treated non-surgically.

Targeted therapy options for GIST include imatinib, which is a small-molecule tyrosine kinase inhibitor with potent inhibitory activity against KIT, which is largely considered the standard first-line therapy for advanced and metastatic GIST [22-24]. Notably, KIT exon 11 mutant GISTs have an increased sensitivity to imatinib treatment compared to GISTs with other genomic alterations [25]. KIT exon 11 mutant GIST patients also have a progression-free and overall survival advantage when compared to patients with non-KIT exon 11 mutant GISTs [6]. Although imatinib has been found to have a limited ability in penetrating an intact blood-brain barrier [26], there is some evidence suggesting that it can reach therapeutic levels intracranially in the setting of a compromised blood-brain barrier [27]. In this case, the presence of the tumour itself in addition to the interval craniotomy and surgical resection performed may have disrupted the blood-brain barrier, and it is therefore theoretically possible for imatinib to be able to penetrate the brain. Given the KIT exon 11 mutational status of his resected brain tumour, his remaining brain metastases were predicted to be sensitive to treatment with palliative imatinib of 400 mg per day. The good responses seen on interval MRI scans are in support of our hypotheses.

Although GISTs have traditionally been known to be minimally responsive to radiotherapy [28], recent studies have shown that GISTs may not be uniformly radioresistant and may benefit from radiotherapy, frequently stabilizing for several months post-treatment [29,30]. Short courses of radiotherapy have also been shown to be an effective palliative treatment option for locally advanced and metastatic GISTs [31]. In a series of 18 symptomatic tumours, partial palliation was achieved with radiotherapy in 17 (94.4%) and symptoms were completely alleviated in 8 (44.4%). Given that treatment with radiotherapy was well tolerated and not associated with additional toxicity with concurrent treatment with tyrosine kinase inhibitor therapy, it should be considered in the multidisciplinary care of patients with progressive or metastatic GIST. In this case, stereotactic radiosurgery to the resected cavity as well as to the two remaining sub-centimetre lesions in the left cingulate gyrus and left hemi-pons was discussed as a treatment option in addition to palliative imatinib. However, it was collectively decided to avoid stereotactic radiosurgery in view of possible long-term sequelae, such as radiation necrosis. Furthermore, he has responded clinicoradiologically to palliative imatinib.

Areas for further research

Malignant GISTs have been reported to have tropism to specific organs including the liver and peritoneum, tending to remain in the abdominal cavity even at a very advanced stage [32]. A systematic review of the literature found only 19 instances of GIST with brain metastases [5]; (Table 1). Remarkably, in four of these cases, brain metastases were identified prior to the discovery of the primary GIST site. The majority of cases had other sites of metastases in addition to the brain, suggesting a heavier burden of disease that may make brain metastases in these cases more plausible. This is in contrast with our patient, who had no evidence of disease after undergoing a total resection of the primary gastric GIST, with relapse of isolated intracranial disease only six years later. This calls into question whether the particular tumour described in this case had harboured a propensity for tropism to the brain.

Whether an immunocompromised state predisposes an individual to intracranial brain metastases also remains unanswered. Although our patient had tested negative for Human Immunodeficiency Virus (HIV) infection, his history of pulmonary cryptococcosis, an invasive fungal infection that predominantly affects immunocompromised hosts, suggests that he may have had a weakened immune system [33,34]. Local and systemic immunosuppression in patients with malignancies may render them more prone to developing primary brain tumours and systemic metastases [35,36].

Notably, of the 19 cases reported to date (Table 1), the mutational status had only been described in six of these cases, of which three had no genomic alteration in c-kit, one had a six-amino acid residue insertion between codon 579 and 580 in exon 11, and another had an in-frame GCCTAT insertion/duplication in exon 9. KIT mutations have been shown to be a useful prognostic biomarker in GIST, where exon 11 deletions, in particular, portend a more aggressively metastasising phenotype associated with poorer clinical outcomes [6]. Braconi et al. found that in 104 patients, 74% of GISTs with exon 11 mutations were associated with metastases, in contrast to only 5% of wild-type GIST that were found associated with metastases [37,38]. However, little is known about the location and pattern of GIST metastases in relation to its mutational status. It could be useful to investigate whether the site of metastasis may be associated with the mutational status of the tumour, which could potentially guide the choice and type of surveillance imaging.

Conclusion

Isolated intracranial metastasis of GIST is exceedingly rare. We report the twentieth case worldwide, to date, and describe a treatment strategy that appears safe and effective for our patient, which includes surgical resection and palliative systemic treatment with imatinib. Stereotactic radiosurgery can be considered subsequently for lesions refractory to systemic treatment. Further work is needed to determine the disease and patient factors that predispose to the development of brain metastases in GIST and whether specific mutations in GIST are

Table 1: Summary of reported cases of intracranial GIST, modified from Prablek et al. [5] with the addition of primary tumour treatment details and Modified NIH risk stratification, as well as inclusion of the present case (case 20). NIH: National Institutes of Health; CNS: Central Nervous System; Mets: Metastases; NR: Not Reported; PDGFR: Platelet-Derived Growth Factor Receptor.

Case	Age	Sex	Primary Site	Treatment of primary tumour	Modified NIH Risk Stratification	CNS site	Size of CNS lesion	Other sites of mets	Interval between diagnosis and CNS mets	Treatment of CNS tumour	Mutation status	Outcome (from time of CNS diagnosis)
1	60	M	Small bowel	Local resection	NR	Left cavernous sinus	NR	L5-S1 vertebra	7 years	Radiation (54 Gy), not further described	NR	Death at 8 months
2	66	M	Small bowel	Local resection and adjuvant chemotherapy (no further details given)	NR	Right cerebellar hemisphere	4 cm	NR	CNS lesion found first	Total resection of cerebellar tumor with adjuvant radiation and chemotherapy (no further details given)	NR	Remission at 12 months
3	75	M	Mesentery	Imatinib 400 mg twice a day	NR	Both hemispheres, (dural based)	Infiltrative	Liver	14 months	Imatinib 400 mg twice daily	NR	Remission at 4 months
4	57	M	Stomach	Partial gastrectomy	NR	Left cerebellar, left frontal	3 cm for cerebellar lesion, size of frontal lesion not provided	NR	13 months	Total resection for cerebellar lesions, SRS (18 Gy) to frontal lesion	NR	Remission at 15 months
5	45	M	Small bowel	Local resection	NR	Pontomedullary junction, cerebellum, leptomeninges	2 cm for primary lesion, others very small	NR	5 years	Imatinib 800 mg daily	NR	Death at "a few weeks"
6	54	F	Oesophagus	Oesophagectomy, systemic imatinib 400 mg per day	High risk	Left frontal lobe	5 cm	Liver	6 years	Neoadjuvant imatinib 400 mg daily, then total resection, SRS (dose not reported)	KIT (exon 11)	Remission at 6 months
7	47	M	Jejunum	Local resection, 4 cycles of doxorubicin and dacarbazine	NR	Left parasagittal (dural based)	NR	Liver	25 Months	Total resection, Imatinib 800 mg daily	KIT (exon 9)	Death at 35 months
8	70	M	Stomach	Local resection	NR	Left occipital, (dural based)	5.5 cm	Lung	10 years	Total resection and radiation, not further described	NR	Death at 8 months
9	15	M	Stomach	Local resection	Intermediate risk	Right Frontoparietal, (dural based)	4.2 cm × 3.3 cm × 3.1 cm	Liver	12 years	Many TK inhibitors prior to discovery of CNS lesion, Total resection	No mutation in KIT or PDGFR-α	Remission at 6 months
10	56	F	Stomach	Imatinib 400 mg daily	High risk	Many small lesions	NR	Lung, Liver, Pelvis	3 weeks	Imatinib 400 mg daily, then 600 mg daily	NR	NR
11	76	M	Jejunum and Duodenum	Local resection	NR	Right parietal, Right cerebellar hemisphere	2 cm	NR	4 months	Imatinib 400 mg daily, radiation (WBRT 40 Gy)	No mutation in KIT	Death at 4 months
12	68	F	Perisacral	Local resection and radiotherapy	NR	Right parietal lobe, (dural based)	3 cm	NR	2 years	Total resection, imatinib 800 mg daily	NR	Remission
13	77	M	Jejunum	Local resection, imatinib 400 mg once daily	NR	Right cerebral peduncle, left occipital lobe	2.4 cm, 2.2 cm	NR	CNS lesion found first	Total resection, WBRT (39 Gy), imatinib 400 mg daily	No mutation in KIT or PDGFR-α	Death at 4 months

14	61	M	Stomach	Partial gastrectomy and adjuvant imatinib	NR	Pituitary	1.5 cm ×3.5 cm ×2 cm	NR	NR	Total resection, SRS and imatinib not further described	NR	NR
15	42	M	Mesentery	Imatinib 600 mg daily, multiple cytotoxic chemotherapy regimens	High risk	Right Parietal lobe	3.5 cm	NR	CNS lesion found first	Total resection, WBRT (60 Gy), imatinib 600 mg daily, multiple cytotoxic chemotherapy regimens	NR	Death at 10 months
16	80	M	Small bowel	Local resection	NR	Cerebellar vermis, Right frontal lobe	4 cm	Cardiac apex, subclavian vessels	CNS lesion found first	Total resection, radiotherapy (22 Gy) not further described	NR	Death at 4 months
17	74	M	Jejunum	Local resection, imatinib 400 mg once daily	NR	Right prefrontal gyrus	1.4 cm ×1.5 cm	Liver	6 years	Sunitinib 50 mg daily, SRS not further described	NR	Remission at 9 months
18	26	M	Duodenum	Imatinib 800 mg	NR	Left frontotemporal	6.1 cm ×4.1 cm	Liver	6 years	Total resection, radiation not further described	NR	Remission at 4 months
19	57	F	Oesophagus and stomach	Imatinib 400 mg	NR	Left temporal, (dural based)	2.9 cm ×3.1 cm ×3.4 cm	Liver		Total resection, imatinib 400 mg daily	NR	Follow-up in progress
20	49	M	Stomach	Gastric wedge resection, systemic imatinib 400 mg daily	High risk	Right parietal lobe, left cingulate gyrus, left hemi-pons	6.2 cm × 3.1 cm × 3.3 cm for parietal lobe tumour, and two < 1cm lesions	None	6 years	Resection of dominant lesion, palliative imatinib 400 mg daily	KIT (exon 11)	Follow-up in progress

associated with distinct patterns of metastasis.

Declarations

Ethics approval and consent to participate

Patient information was de-identified and informed consent has been obtained from the patient.

Consent for publication

Written, informed consent for publication of this report has been obtained from the patient. All identifying information has been removed to preserve confidentiality. We would like to thank the patient for his contribution to this article.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study conception and design: VSY, MWC, TTB, EKC, MFHR; data collection: LLHS, VSY, LB, SCPY, PYT; analysis and interpretation of results: VSY, LLHS, PYT; draft manuscript preparation: LLHS, VSY, PYT. All authors reviewed the results and approved the final version of the manuscript.

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