CASE REPORT

Killing two birds with one stone: a case of GIST and supervening CML

Vivek Rashmikanth Mehta,^{1,2} Uzma Khan,¹ Uyen Hoang,³ Michael Rachshut⁴¹Department of Internal Medicine, Mercy Catholic Medical Center, Darby, Pennsylvania, USA²Mercy Catholic Medical Center, Philadelphia, Pennsylvania, USA³Sinai Hospital of Baltimore, Baltimore, Maryland, USA⁴Department of Hematology Oncology, Mercy Catholic Medical Center, Philadelphia, Pennsylvania, USA**Correspondence to**

Dr Vivek Rashmikanth Mehta, vivekmehta@gmail.com

Accepted 25 September 2015

SUMMARY

A 50-year-old patient who presented with abdominal pain was found to have a suspicious 8×6×9 cm mass in the left upper abdomen on imaging. A complete surgical resection of the mass was performed subsequently and pathology revealed a gastrointestinal stromal tumour. The patient was started on adjuvant Imatinib following the resection. Four years later, reimaging demonstrated no evidence of disease and adjuvant therapy was discontinued. Nine months following discontinuation of Imatinib, routine blood work revealed marked leucocytosis. Further work up including peripheral smear and bone marrow biopsy showed findings consistent with chronic myelogenous leukaemia. Imatinib was restarted and the patient's white cell counts returned to normal range within a month.

BACKGROUND

Gastrointestinal stromal tumours (GIST) are rare neoplasms of the gastrointestinal tract, commonly affecting the stomach and proximal small intestine. Other structures in the abdomen, such as the retroperitoneum or the omentum, may also become tumour sites. Annual incidence of GIST in the USA is roughly 7–20 cases per million population per year, the middle aged and older age groups being the ones that are most commonly affected.

GISTs were first described by Gold and Stout in 1941 and were thought to derive from smooth muscles. A significant breakthrough in defining GISTs was achieved in 1998 when Japanese researchers Hirota and his colleagues found that most GISTs possessed CD117 (c-kit) mutations in contrast to leiomyomas, true leiomyosarcomas and other spindle-cell tumours of the GI tract.

The symptoms of GIST vary ranging from asymptomatic to non-specific symptoms such as abdominal pain, nausea and vomiting, to symptoms caused by tumour size and location, such as obstruction. CT imaging, endoscopy and endoscopic ultrasound may be used to further investigate suspicious lesions, but ultimately, resection and pathological diagnosis is required. KIT (CD117), platelet-derived growth factor receptor- α (PDGFR α) and DOG1 act as biomarkers of GIST tumours.

Imatinib is a tyrosine kinase inhibitor (TKI) that has been approved for treatment of KIT expressing GIST since it inhibits both c-KIT and PDGFR α mutations.¹ It is an oral medication that was initially marketed in 2001 for CML due to its ability to inhibit fusion protein bcr/abl found on Philadelphia chromosome positive chronic myelogenous leukaemia (CML), which is also a tyrosine

kinase mutation. Imatinib is first-line treatment for bcr/abl CML.

Coexistence of GIST with other specific cancers is rarely recognised. There have been reports of an association between GISTs and myeloid leukaemia, however, none of those patients were treated with TKIs. Furthermore, there have been no documented case reports of CML having been discovered after treatment of GIST (also a tyrosine kinase mutation) with a TKI.

CASE PRESENTATION

A 50-year-old man who presented with 3 months of intermittent, epigastric and left upper quadrant abdominal pain, was found to have a suspicious mass on abdominal CT (figures 1 and 2).

The patient subsequently underwent an exploratory laparotomy with complete surgical resection of a 12×6×6 cm mass arising from the lateral border of the greater curvature of the stomach. Histopathology with H&E stained sections showed solid growth of spindle cells and extensive stromal hyalinisation (figures 3 and 4).

This was consistent with high-grade stage IIIB, T4N0M0/G2 GIST. It was also found to be c-kit positive (CD117). The patient was started on adjuvant therapy with Imatinib following the resection.

Owing to unremitting abdominal pain, he had a positron emission tomography (PET CT) performed 7 months after his initial resection, which revealed an area of increased fluorodeoxyglucose uptake. The patient underwent an exploratory laparotomy with subtotal gastric resection. The

Figure 1 Sagittal view of abdominal CT revealing a soft tissue mass within the left superior aspect of the abdomen.

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To cite: Mehta VR, Khan U, Hoang U, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211698

Figure 2 Coronal view of abdominal CT revealing a soft tissue mass within the left superior aspect of the abdomen.

patient also had a mass in his right axilla, which was excised. Pathology did not show any evidence of recurrent disease. He was continued on adjuvant therapy with Imatinib 600 mg/day due to his high risk of recurrence/metastasis.

Four years later he presented for follow-up with a different oncologist due to retirement of his previous oncologist. At that time he was still taking Imatinib. Current recommendation for adjuvant therapy in patients after complete resection of a GIST is Imatinib 400 mg/day for 3 years.² Since our patient had been on adjuvant Imatinib for over 3 years, reimaging was performed to evaluate the status of his GIST. Imatinib was discontinued after reimaging demonstrated no evidence of disease on PET CT.

Nine months later, on routine blood work, the patient was noted to have a marked leucocytosis. Further work up was performed with peripheral smear showing maturing white cell count in all stages of development and bone marrow biopsy demonstrated hypercellular marrow (figures 5 and 6). Fluorescence in situ hybridisation was positive for bcr/abl t(9;22).

OUTCOME AND FOLLOW-UP

The patient was diagnosed with CML and Imatinib 400 mg/day was restarted. The patient's white cell counts returned to

Figure 3 (H&E, LP ×4) slide. Well-circumscribed mass showing solid growth of mesenchymal (spindle) cells, a feature of gastrointestinal stromal tumours.

Figure 4 (H&E, HP ×40) slide. Cellular proliferation of bland spindle cells with pale to eosinophilic fibrillar cytoplasm, increased nuclear size with hyperchromasia and some nuclear pleomorphism. A mitotic figure is seen in the upper corner. Extensive stromal hyalinisation is present.

normal range within a month. He continues to be in remission for both GIST and CML.

DISCUSSION

GISTs have mutational activation of either of the two proto-oncogenes, c-Kit or PDGFRA, which stimulates the growth of malignant cells. Recognising these tyrosine kinase mutations has enabled targeted therapy of GISTs with TKIs.

TKIs interrupt signalling through c-Kit and PDGFRA, which decreases proliferation and boosts apoptosis of malignant cells. Since the introduction of Imatinib, survival of patients with GIST has increased to more than 5 years.³ With concurrent use of Imatinib, there has been an improvement in the survival of patients compared to use of surgery alone.⁴ Based on these findings, Imatinib was approved in 2008, in USA, for adjuvant treatment of completely resected GISTs ≥3 cm in size. TKIs are also well known for their use in CML, for which imatinib is a first-line treatment. CML is almost invariably positive for the Philadelphia chromosome t(9;22)(q34;q11), resulting in a bcr-abl fusion gene, a tyrosine kinase.

This particular patient was on Imatinib for more than 4 years for treating a GIST. Other cancers have been associated with GISTs and there has also been an association between GIST and

Figure 5 (H&E, LP ×10) slide. Hypercellular bone marrow is demonstrated (95% cellularity).

Figure 6 (H&E, HP ×40) slide. Cells of the myeloid lineage are markedly predominant and show all stages of maturation. Rare erythroid and lymphoid precursors seen. Findings consistent with chronic myeloid leukaemia.

myeloid leukaemia.^{5–7} However, to the best of our knowledge, there have been no case reports, to date, documenting the emergence of CML with cessation of Imatinib after completion of at least 3 years of adjuvant therapy for GIST.

Extending adjuvant therapy with a TKI beyond 3 years is fraught with the possibility of developing Imatinib-resistant mutations and secondary malignancies. Secondary myeloid malignancies have been reported in patients with CML who received Imatinib as treatment. These patients developed chromosomal abnormalities, and a small percentage developed acute myelogenous leukaemia.⁸

Most of the side effects have been observed early in the treatment and association with favourable outcome has also been suggested for patients who had side effects. Most of the side effects can be controlled by reducing the dose.^{9–11} More information regarding teratogenicity of the Imatinib is becoming available as well.¹²

Learning points

- ▶ Imatinib is often used in the treatment of gastrointestinal stromal tumours and chronic myelogenous leukaemia.
- ▶ Further studies are needed to assess risk versus benefit of longer duration of treatment with Imatinib.
- ▶ High suspicion is warranted for emergence of second malignancy while on Imatinib.

The possibility arises that CML could have surfaced in this patient as a secondary malignancy acquired due to Imatinib adjuvant therapy for the patient's GIST. The current recommended duration for adjuvant therapy with Imatinib is 3 years; further studies are not yet available to suggest if a longer course would be beneficial or harmful.

There is also a possibility that CML could have been a separate malignancy that had developed but was masked by Imatinib and surfaced when Imatinib was discontinued. Further studies regarding longer duration of treatment with Imatinib for GIST and outcomes could provide us with better answers in the future.

Acknowledgements Department of Pathology, Mercy Catholic Medical Center.

Contributors UK and UH were involved in the drafting the manuscript and obtaining images. MR identified and has been managing the case and was involved in final revision of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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