Case Report: KIT mutation conferring Imatinib resistance in a GIST

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INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare, yet the most common mesenchymal tumour within the digestive tract .**Approximately 10% to 30% of GISTs have a malignant clinical course** [1].

Relatively recent advances have identified interstitial cells of Cajal as the precursor cell and gain of function **mutations in c-KIT and PDGRF-α** as the underlying driver. Approximately 75–80% of GISTs harbour a mutation in cKIT and 10% of GISTs have a mutation in PDGFRα[2].

These developments have allowed novel therapeutic options to emerge, primarily imatinib (Glivec). **Imatinib** mesylate inhibits activation of the KIT and platelet-derived growth factor receptor α proteins.

This has been considered a paradigm shift in medical oncology. Imatinib had not previously been used to treat a solid tumour yet was found to provide **clinical benefit in ~85%** of patient with advanced disease [3].

However some patients still have issues **with 40% to 50% developing resistance** within 2 years of beginning imatinib therapy [4]. This case discusses a patient who had a recurrent GIST associated with secondary mutations in KIT conferring resistance to imatinib.

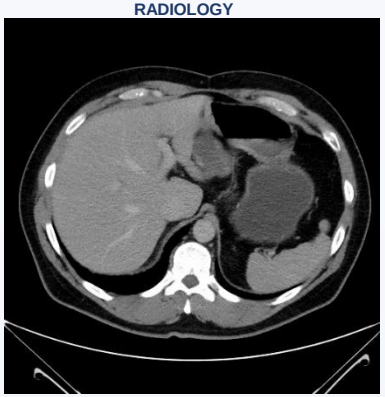
CASE HISTORY

This 54-year-old male was diagnosed with locally advanced gastric GIST in 2009 and treated with neoadjuvant imatinib from 2009- 2010. This was followed by partial gastric resection in 2010. Histology showed almost complete pathological response to imatinib, with only a **1.5mm focus of viable tumour remaining**. He did not receive adjuvant imatinib as this was not established practice at the time

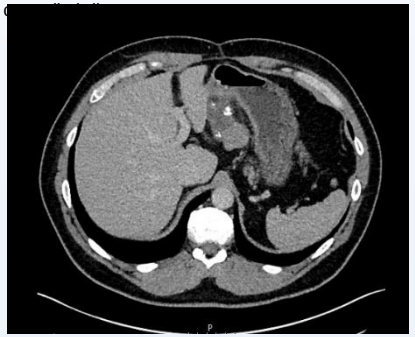
He was subsequently diagnosed with recurrent disease which was itself resected in 2011. Histopathology showed this had a high mitotic index. Molecular testing at this time showed **KIT exon 11 mutation**. Adjuvant imatinib was then prescribed until 2016.

A recurrent 10x9cm mass was identified in 2018 in the lesser omentum between the residual stomach and the liver. He then recommenced imatinib with a partial response. Maximal response was reached in 2020 and the patient underwent **partial gastrectomy and liver segmentectomy**. This was sent for histopathological and molecular analysis.

RADIOLOGY



December 2019 CT showing a predominantly cystic mass with a few areas of dystrophic rim calcification – cystic change is a common finding in Imatinib

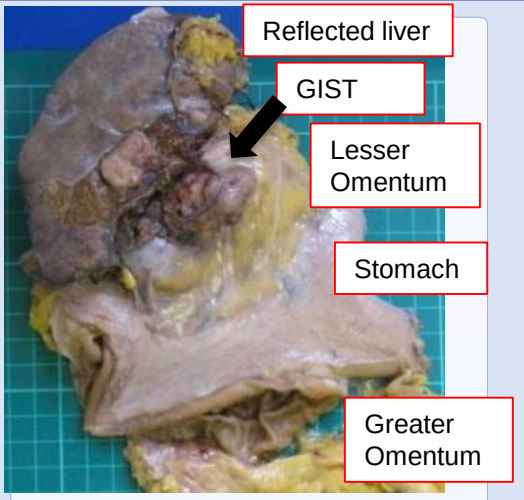


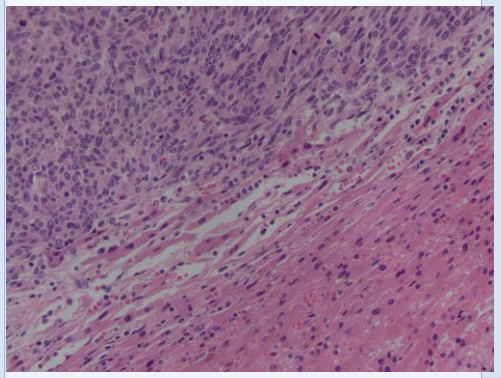
July 2020 CT shows the posterior and medial aspect of the cystic area now contains a 3cm enhancing soft tissue

HISTOLOGY

nodule - this suggests escape from Imatinib control GISTs can show spindle cell (70%), epithelioid(20%) or mixed (10%) morphology [7]. Staining for is positive in close to **95% of cases for both KIT (CD117) and DOG1** [1]. **Tumour size, site of origin and mitotic count** are the most important prognostic parameters. **Modified Fletcher's risk classification is widely used and incorporates these factors.**

Histological examination of the resection in 2020 showed that there were acellular areas of myxoid degeneration, indicating partial response to imatinib. However viable tumour with a high mitotic index remained. Direct invasion into the liver segment was identified.





Top- Gross specimen showing tumour in the lesser omentum. Bottom- Histology showing mitotically active tumour (top left) with adjacent liver (bottom right)

GENETICS

Genetic sequencing of KIT and PDGFR has been recommended for all GISTs to elucidate the underlying mutations.

Sequencing was performed of the tumour resected in 2011 and showed exon 11 mutation. These are common and associated with a response to imatinib.

Further sequencing, this time of the recurrent tumour resected in 2020, has identified the development of a mutation in **exon 13**. This has been shown to confer **resistance to imatinib** [3].

DISCUSSION

It has been nearly twenty years since gain of function mutations in KIT were identified as a driver in the oncogenesis of GISTs . The most common mutations arise in the juxtamembrane domain encoded by exon 11.

Primary mutations in exons 13 and 14 of KIT are uncommon and have been identified in only 1–2% of newly diagnosed GISTs. However, in the setting of **secondary imatinib resistance** these mutations appear more frequently and are of greater clinical significance [6]. It is likely that these mutations inhibit the binding of imatinib-KIT and re-activates the activating potential of the primary mutation.

It is postulated that this secondary mutation occurs due either to genomic instability on the allele containing the original mutation, and/or to selection by treatment of previously undetected imatinib resistant cells [3].

Use of Sunitinib (second-line tyrosin kinase inhibitor) and regorafenib (third-line multikinase inhibitor) can be considered in advanced GIST after treatment failure with imatinib [1].

CONCLUSIONS

This case helps illustrate the rising importance of personalised medicine and molecular pathology in helping manage patients. Further progress in molecular understanding of tumours, among other factors, can help clinicians when considering the optimal surgical and oncological therapies for their patients.

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