Y04 Succinate Dehydrogenase Deficient GISTs – a diagnostic and therapeutic dilemma? : A case report

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Introduction

- Gastrointestinal Stromal Tumours (GIST) are a rare type of malignancy arising from the gastrointestinal tract.
- Around 80% of these tumours harbour actionable mutations such as activating c-Kit proto-oncogene and platelet-derived growth factor receptor A (PDGFRA) mutations.
- The discovery and subsequent use of small molecule tyrosine kinase inhibitors, such as Imatinib and Sunitinib, to target these mutations has significantly improved the survival of those with GISTs.
- However, the remaining 20% with wild-type GISTs, do not respond well to standard treatment.
- One of the largest subgroups of wild-type GISTs are the Succinate dehydrogenase complex subunit B protein (SDHB) deficient type.
- This mutation phenotypically presents with unique clinical and pathological features which may be misinterpreted as standard GISTs.

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Case summary

- A 55 y/o male first presented in April 2020 with upper gastrointestinal (GI) bleeding.
- Gastric endoscopy found a mass in the antrum of the stomach which was confirmed to be GIST on histopathological examination.
- Immunohistochemistry (IHC) showed membranous staining for DOG-1, focal activity for smooth muscle actin (SMA) and negative for CD117 which overall features consistent with a GIST, epitheliod type.
- PET CT April 2020 showed a hypermetabolic region at the gastro hepatic region with liver metastases.
- May 2020 – November 2020 : started on Imatinib
- PET CT in October 2022 showed disease progression in the liver.
- December 2020 – April 2021 : Changed to Sunitinib
- PET CT in March 2021 showed worsening liver metastasis.
- In view of rapid progresion, a repeat biopsy from the gastric mass and liver lesion was sent for a broad panel next generation sequencing (NGS).
- IHC was positive for CD117 and negative for c-KIT and PDGFRA genes,and showed no expression of SDHB.
- He then received Temozolomide 85mg/m2 21 days on and 7 days off from June 2021 to January 2022.
- PET CT done in October 2021 showed partial response and the patient clinically improved.
- Unfortunately, he developed another episode of upper GI bleeding in January 2022 which led to a partial gastrectomy and was not on any treatment for 2 months until March 2022.
- PET CT March 2022 showed disease progression and oral Temozolomide was resumed.
- He was clinically improving initially however further imaging in June 2022 showed further progression of disease hence Temozolomide was discontinued.
- He was started with oral Regorafenib from August 2022 till date. The late commencement of each treatment is due to financial issues.

Serial Imaging

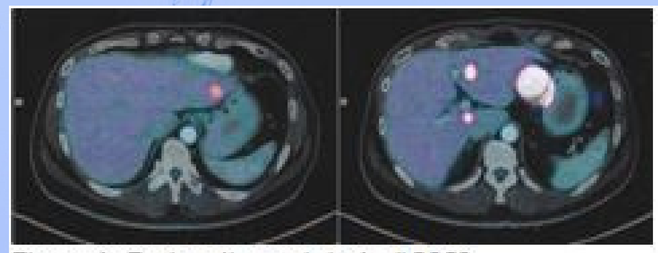

Figure A: During diagnosis in April 2020

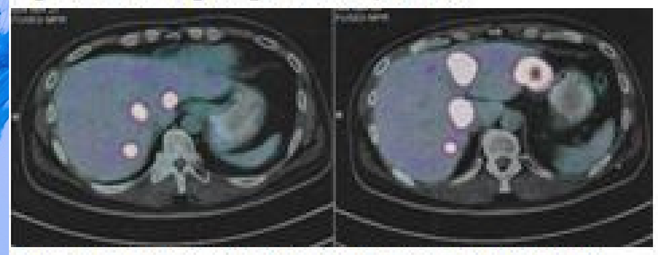

Figure B: Assessment on Imatinib in October 2020

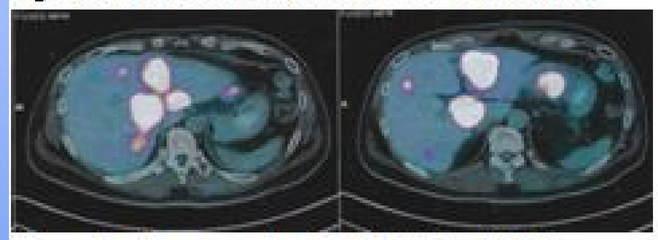

Figure C: Assessment on Sunitinib in April 2021

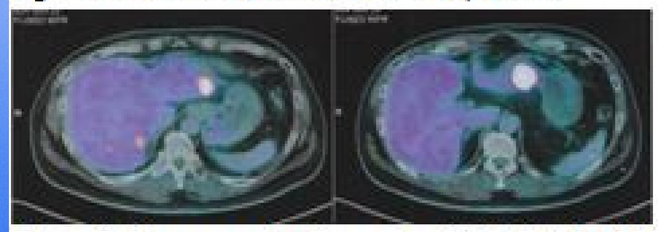

Figure D: Assessment on Temozolomide in October 2021

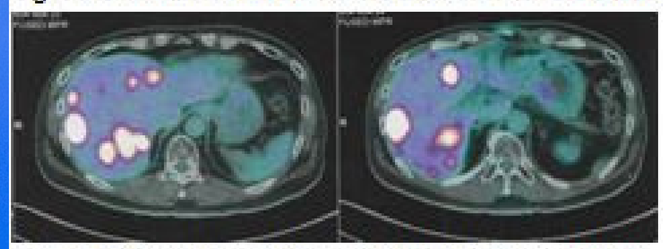

Figure E: Assessment on Temozolomide in June 2022

Discussion

- Despite GIST being a rare disease, we treat almost 200 cases a year.
- The majority of these patients have the classical variant of CD117/c-Kit mutated disease and respond very well to first line treatment with tyrosine kinase inhibitors.
- Approximately 80% of our patients have diseases that lie dormant for years on Imatinib.
- However, as reported in literature, 10-15% of them do not respond to standard treatments.
- Our routine practise does not call for routine NGS testing due to cost constraints.
- Patients are generally only subjected to repeat biopsies and further molecular testing if there is a high clinical suspicion.
- We would therefore, need a better tool to identify such patients at an early stage and ideally perform a small, select and more cost effective NGS panel for such patients.
- To date, there is no standard treatment available for GISTs with SDHB loss, in view of the rarity of the diagnosis.
- Temozolomide may be an option in this population as it has the longest progression free survival outcome compared to standard treatment, as seen in this case.

Declaration of conflict of interest : None

References

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