Peer Review File

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Reviewer A

GENERAL

This is a case report of a patient with a gastrointestinal stromal tumor (GIST) associated with succinate dehydrogenase (SDH) deficiency. The patient suffered from mediastinal recurrence and underwent resection of the recurrent tumors. Because SDH-deficient GIST is a rare subtype of GIST, there are limited data on the management of this disease. In this regard, this reviewer thinks the manuscript is potentially useful and will contribute to treatment decision-making in GIST patient management. However, this manuscript fails to reach publication level because it has many drawbacks as a scientific paper. This reviewer recommends resubmission to case report-specific journals other than the Journal of Gastrointestinal Oncology after a thorough revision.

We deeply appreciate these observations and comments are addressed below.

SPECIFIC

1. **The critical point of this case is that the tumor was an SDH-deficient GIST. The authors should provide photographs of the immunohistochemical analysis of this tumor.**
   Reply: Photographic images of the histopathologic analysis from both the posterior mediastinal and diaphragmatic metastases have been included.
   Changes to text: Images have been included in the manuscript as Figure 3 - referenced in line 117.

2. **The final paragraph of "Case report" (lines 95-101) is littered with unscientific claims. This reviewer recommends deletion of this paragraph.**
   Reply: Thank you for this comment. The journal checklist for case reports requested 1-2 paragraphs on the patient's perspective of their care. Her perspective was included within the body of the manuscript "in quotes" as these were not scientific claims, but direct words from the patient on her disease the treatments she received. We can remove the patient statement from the manuscript; please provide editorial direction.
   Changes to text: Lines 95-101 have been deleted based on reviewer feedback and may be officially deleted from the document or moved to supplemental material upon directive of the editors.

3. **Figure 2 can be omitted, and a more concise explanation of the robotic surgery is required.**
   Reply: Thank you for this comment. The port placement figure has been removed from the body of the text and included as a supplemental figure. Description and

representation of port placement for this minimally invasive approach may be of value to the surgical audience who read this manuscript. The paragraph describing the operation has been edited to only highlight the important aspects of the case.

Changes to text:

Lines: Some details of the robotic surgery were deleted to allow for a more succinct explanation.

Line 106: Figure 2 has been replaced with Supplemental Figure 1.

4. **This reviewer could not understand the sentence "she had a strong family history of SDHA-deficiency in her mother, aunt, and children with no overt pathology identified." This sentence should be replaced with a more direct and clearer description**.

   Reply: Thank you for this comment, the sentence has been restructured for clarity.

   Changes to text:

   Line 81 – 82 modified: She had a history of confirmed germline *SDHA*-deletion in multiple family members including her mother, aunt and children.

5. **The patient age was inconsistent in the abstract and the text.**

   Reply: The abstract has been updated to reflect the age within the manuscript

   Changes to text: Age in abstract adjusted to 44 (Line 15)

6. **"Gleevec" should be changed to the generic name.**

   Reply: Thank you for this comment and manuscript has been updated.

   Changes to text:

   Line 86 – Gleevec changed to Imatinib.

Reviewer B

In the manuscript, the authors reported a case of succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors (GISTs) with recurrence to the paraesophageal region and diaphragm. This is a rare case of SDH-deficient GIST, and the report would be of interest for the journal's readers. However, there are several concerns to be addressed.

Comments,

1. **Some key photos of intraoperative findings should be shown rather than port placement in Figure 2.**

   Reply: Thank you for this comment. The port placement figure has been removed from the body of the text and included as a supplemental figure. Intraoperative pictures have been included as Figure 2a and Figure 2b.

   Changes to text:

   Line 110-113: Intra-operative photos referenced as Figure 2a and Figure 2b.

2. **Pathological findings of resected specimens should be shown. I wonder whether the metastatic lesions were lymph nodes or hematological metastases. Are there any differences such as Ki67 labeling index or mitotic index between the primary GIST previously resected and the metastatic lesions resected this time?**

   Reply: Thank you for this question. Histopathologic analysis of the posterior mediastinal mass and diaphragmatic mass are both consistent with metastatic GIST and not a lymph node. This patient was treated at our institution for a subsequent metastasectomy after her primary tumor had been removed. Unfortunately, we did not have access to tissue from her primary lesion for valuable comparison. Images from immunohistochemical staining on both masses have been included in the manuscript as Figure 3 (Line 117).

   Changes to text:

   Images from immunohistochemical staining have been included in the manuscript as Figure 3 (Line 117).

3. **The last paragraph in the "Case Report" section seems unnecessary.**

   Reply: Thank you for this comment. The journal checklist for case reports requested 1-2 paragraphs on the patient's perspective of their care. Her perspective was included within the body of the manuscript "in quotes" as these were not scientific claims, but direct words from the patient on her disease the treatments she received. We can remove the patient statement from the manuscript; please provide editorial direction.

   Changes to text: Lines 95-101 have been deleted based on reviewer feedback and may be officially deleted from the document or moved to supplemental material upon directive of the editors.

4. **Is this case a Carney-Stratakis syndrome? Any history of paragangliomas? Germline mutation tested?**

   Reply: Although this patient has a confirmed germline SDHA mutation (deletion) which could be associated with Carney-Stratakis syndrome, she has no history of paragangliomas, or pulmonary chondromas which have also been seen in the setting of Carney's triad (Line 67 – 68).

   Changes to text:

   This was clarified in Line 82-84 by adding, "neither the patient or her family members had a known history of associated of paragangliomas or pulmonary chondromas, suggestive of a syndromic process."

5. **It remained unclear what the authors would like to the best argue in this case report. Unusual pattern of metastases, surgical management of WT-GIST, or minimally-invasive approach for metastases?**

   Reply: Thank you for this observation, as we desire clarity regarding the aim of this manuscript. We aimed to showcase that the mediastinum and diaphragm are an extremely unusual pattern of metastases, confounded by limited chemotherapeutic options for management. Thus, for completion, we discussed surgery as the current standard of care for this histology and explored the utility of a minimally invasive

approach in this case given our patients extensive surgical history. It was our goal to provide a robust discussion clinical management the patient received, as well as give insight into other potential options.

Changes to text: N/A

Reviewer C

It would be also important to

1. **Provide further information on the response to prior everolimus therapy and the duration of response.**

   Reply: Thank you for this comment and the manuscript has been updated to include the duration of everolimus therapy and outcomes in this patient.

   Changes to text: Added lines 86-88: She was maintained on everolimus for close to 12 months until she developed evidence of disease progression in her liver.

2. **Further highlight other cases or situations where a minimally-invasive robotic-assisted approach would not be appropriate**

   Reply: We deeply appreciate this insightful inquiry. The main focus of this case report was to highlight the unusual location/presentation of metastatic disease of this histology. Surgical management must be tailored at a case-by-case basis at the discretion of the treating surgeon. Given the mediastinal location and history of multiple abdominal surgeries, a minimally invasive thoracic approach, while avoiding the abdomen, best suited a successful resection in this patient. A minimally invasive approach may not be appropriate based on the size (large), location, or in the presence of extensive adhesions which may obscure visualization.

   Changes to text: N/A

3. **Comment/discuss the neoadjuvant or adjuvant therapy potential with TKI to further decrease the risk of relapse/recurrence post-surgery**

   Reply: Thank you for this inquiry. There is a paucity of literature on the neoadjuvant/adjuvant use of TKI's in wild-type GISTs. Current data supports dose dependent neoadjuvant/adjuvant use of TKI's in *KIT* – mutated GIST, although this phenomenon is yet to be reproduced in resectable wild-type GIST. It must be noted that this case report strives to highlight the rarity of the location of metastatic disease for this histology, as well as discuss available treatment options. As such, for this manuscript neoadjuvant/adjuvant therapies are not discussed as our focus is within the metastatic setting of wild-type GISTs. However, TKI use after cytoreductive surgery in the metastatic setting for *KIT*/*PDGFR*-related GIST has also revealed relatively favorable outcomes. Ben-Ami and colleagues (2016) suggested efficacy of select TKI's (regorafenib) in the metastatic setting of WT GISTs and these promising findings potentially provide a unique area of exploration, especially in combination with a metastasectomy, however, this is beyond the scope of this case report.

Changes to text:
Added lines 146-148 - Multiple studies have shown the efficacy of metastesectomy in combination with first or second generation TKI's for *KIT*/*PDGFR*-related GISTs, however, these outcomes are yet to be extrapolated to WT GISTs.

4. **Provide any efficacy data on other TKI's (eg, sunitinib, etc) in the KIT/PDGFRA wild type or SDH deficient GIST**
   Reply: Thank you for this inquiry which provides an essential point of review. Lines 118 – 128 briefly discuss the use of 2nd and 3rd generation TKI's, as well as other agents (temozolomide and rogaratinib) currently in clinical trial. While a review of TKI efficacy in both *KIT*-mutated and wild-type GISTs may be appealing to the readership, this will require a more extensive retrospective review which is beyond the scope of this case report.
   Changes to text: N/A

5. **Further highlight the differences and similarities between KIT/PDGFRA wild type GIST (eg, SDH deficient GIST) in adults vs that in pediatric patients including the treatment options**
   Reply: Thank you for this insightful question, as the incidence of WT GIST can occur among all age groups. An observational study conducted by the Gastrointestinal Stromal Tumor Clinic at the National Institutes of Health, aimed at characterizing the molecular subtypes of WT GISTs. Their findings revealed that although WT GISTs had a higher incidence in children compared to adults (85% compared to 10-15% respectively), there were no mutational or clinical characteristics that were associated with a specific age group. Further studies with an expanded cohort may help delineate key differences among age groups, however, this is beyond the scope of this case report.
   Boikos SA, Pappo AS, Killian JK, et al. Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal Tumors: A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol. 2016;2(7):922-928. doi:10.1001/jamaoncol.2016.0256.

   Changes to text: N/A