Peer Review File

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Reviewer A

In this manuscript, the authors provide a nice summary of pathological and clinical data from 12 pediatric cases of epithelioid inflammatory myofibroblastic sarcoma, a rare and highly aggressive subtype of inflammatory myofibroblastic tumors with few published series. As such, I believe this manuscript adds to the literature and provides clinicians with additional information that could inform treatment and follow-up regimes. This retrospective study was conducted ethically with IRB approval and has sound methodology. However, I believe that further revision is necessary to prepare this manuscript for publication.

This study aimed to describe the clinical experience from these cases and to discuss treatment through the lens of precision medicine. I believe that the authors did not fully achieve this aim with the data provided in their manuscript. For instance, the authors defined precision medicine in the introduction to include applying molecular and genetic information along with the patient's living environment to develop individualized treatment plans. However, the authors did not include many of these factors in their results section, including the targeted therapies used for patients and variables related to their comorbid conditions, family history, and social conditions/risk factors. The authors could better achieve their aim with the inclusion of these variables in the authors' analysis.

Comment1: Thank you for your comments. We have incorporated the family history and the patients' co-morbidities into the results section. However, regrettably, we did not identify any pertinent positive factors in these children. We attribute this lack of findings to the possibility that the mutation in EIMS originates from a somatic cell line rather than an embryonic line.

Reply1: Add "All 12 children had no family history of tumor-related genetic diseases or other tumors." to the result.

Changes in the text1: On line 184 of page 6.

Critiques:

- Line 132: Vague definition for disease progression: "tumor size." Please consider defining how this variable relates to disease progression more clearly. How was the occurrence of distant metastasis and recurrence determined?

Comment2: Thank you for your suggestion. Following your reminder, we recognized that the term 'tumor size' might be ambiguous. Consequently, we have meticulously refined the definition based on RECIST 1.1 to denote an increase of at least 20% from the nadir of the summed measurements. The revised definition now reads, "the sum of the largest diameters

of the target lesions increased by at least ≥20%". We clarified the occurrence of distant metastasis and recurrence by imaging and postoperative pathology in children who were eligible for surgery.
Reply2: Add "increase by at least 20% from the nadir of the summed measurements".
Changes in the text2: on line 134 of page 5.

- How patients lost to follow-up were accounted for was not discussed in the methods.
Comment3: Thank you for your feedback. We have incorporated additional information on the reasons for patient attrition into the results. Specifically, cases 6 and 9 were lost to follow-up. In case 6, after undergoing biopsy, treatment was discontinued, and subsequent attempts to establish contact with the family proved unsuccessful, leading us to hold a pessimistic view regarding the patient's survival. In the case of patient 9, loss occurred due to the absence of outpatient review records and an inability to establish phone contact with the family, leaving the patient's survival status unknown. As these instances of lost follow-up are attributed to socio-family factors, we have refrained from further elaboration in the discussion section, and we appreciate your understanding on this matter.
Reply3: Add "because the patient withdrew from the treatment and there was no outpatient record or telephone contact."
Changes in the text3: On line 233 of page 8.

- Line 193: The information discussed in this sentence appears to relate to figure 2, not figure 1.
Comment4: Thank you. We have made a modification according to your suggestion.
Reply4: Exchange the locations of Fig1 and Fig2.
Changes in the text4: Fig1 and Fig2.

- Line 212: The information in this sentence appears to relate to figure 1, not figure 2.
Comment5: Thank you. We have made a modification according to your suggestion.
Reply5: Exchange the locations of Fig1 and Fig2.
Changes in the text5: Fig1 and Fig2.

- Lines 224/232: Which targeted therapies were used? I believe the treatments used and their relationship to tumor histology are crucial to this analysis.
Comment6: Thank you for your comments. In our study, three children received targeted therapy, with two undergoing oral ALK inhibitors and one receiving an oral ROS1 inhibitor. As you rightly suggest, discussing the treatment and its correlation with tumor histology is valuable. However, determining an appropriate treatment is challenging until the pathology is definitively identified.For the children in this study, at the initial diagnosis, we preferred surgical treatment if there was a chance of surgery; if there was no chance of surgery at the

initial diagnosis, we performed biopsy and further sought the help of neoadjuvant chemotherapy or targeted therapy, and if there was a chance of surgery after neoadjuvant therapy, the children would undergo surgical treatment, and if there was still no surgical condition, they would continue to receive radiotherapy.For children who are initially diagnosed with surgery, according to the tumor invasion situation and the family's wishes, a one-step consolidation therapy will be chosen, including postoperative chemotherapy, radiotherapy and targeted therapy, to reduce the possibility of tumor recurrence. Since EIMS is extremely rare, the optimal treatment modality still needs to be further explored.
Reply6: Add “ALK inhibitors” or “ROS1 inhibitors”
Changes in the text6: on line 222， line 226 and line 239 of page7.

- Line 334: The claims made in this sentence regarding the reasons for improved survival are not supported by results in this manuscript. Please consider adding supporting evidence, rewording, or omitting.
Comment7: Thank you. We have made a modification according to your suggestion.
Reply7: Deleted “The long-term survival and recurrence rates achieved……and the increased frequency and intensity of follow-up.”
Changes in the text7: On line 341 of page 11.

Reviewer B

Authors describe a retrospective observational series of epithelioid IMT which include 12 children, all of which were treated by various modalities in addition to surgery. The manuscript is well written, and authors have advocated for multimodality approach to manage this rare malignancy.
I have few suggestions for authors:
1. Fig 1c may be replaced by 400x image as perinuclear ALK positivity is no visible at 200x
Comment8: Thank you. We have made a modification according to your suggestion.
Reply8: Replace Fig 2c.
Changes in the text8: Fig 2c.

2. A paragraph of radiological and histological differentials with pitfalls will add further value to this manuscript.
Comment9: Thank you for your comment, at the beginning of the study, we were looking forward to radiology to help us in diagnosis, unfortunately, since tumors can originate from soft tissues all over the body, we were unable to identify characteristic radiological evidence to differentiate EIMS from other malignant tumors as reported by our study results and previous literature.

For histologic identification, we can identify EIMS by the WHO definition of EIMS, which includes "plump epithelioid or histiocytoid tumor cells with vesicular chromatin, prominent nucleoli, and amphophilic or eosinophilic tumors. amphophilic or eosinophilic cytoplasm, often admixed with neutrophils in an abundant myxoid stroma".

While this rare tumor was familiarized with It is possible to make an accurate diagnosis based on his histologic and immunohistochemical findings.

Reply9: no modification.

Changes in the text9: no modification.