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OPPONENT'S REVIEW OF DISSERTATION THESIS THE DIAGNOSTICS OF RARE SOFT TISSUE AND SKIN TUMORS USING HISTOLOGICAL, IMMUNOHISTOCHEMICAL, AND MOLECULAR BIOLOGICAL METHODS

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PhD. opponent: John M. Gross., M.D., Associate Professor at Johns Hopkins University

Overall Assessment

The Ph.D. thesis by Dr. Antonina Kalmykova presents an extensive and well-structured study on the diagnostic approach to rare soft tissue and skin tumors, utilizing histological, immunohistochemical, and molecular biological methodologies. It is written in the form of comments on the author's published articles, which are included in the dissertation The research is commendable in its depth, scientific rigor, and relevance to modern pathology. The work reflects a thorough understanding of tumor classification, molecular pathways, and diagnostic strategies, reinforcing its significance in the evolving landscape of soft tissue and skin pathology.

Content and Scientific Contribution

Dr. Kalmykova's work significantly contributes to the understanding of rare soft tissue and skin tumors. The research highlights:

- The morphological spectrum and molecular alterations of BAP1-inactivated melanocytic tumors.
- The discovery and characterization of *MITF::CREM*-rearranged tumors, further expanding the molecular classification of melanocytic neoplasms.

- Important findings regarding inflammatory leiomyosarcoma and its reclassification based on novel immunohistochemical findings.
- A large in depth clinicopathological, molecular and methylation study of an emerging class of soft tissue tumors with kinase gene alterations
- High-grade transformation of biphenotypic sinonasal sarcoma into rhabdomyosarcoma – a novel and important phenomenon in this rare sarcoma type
- A comprehensive update on changes made in the soft tissue tumor chapter in the novel WHO classification

The discussion aligns well with the most recent updates in the WHO classification of soft tissue and skin tumors, demonstrating the timeliness of this research. The thesis not only advances molecular diagnostics but also proposes refinements to tumor classification, a critical component in precision medicine.

Timeliness and Relevance

The study is highly relevant given the rapidly expanding field of molecular pathology. The integration of immunohistochemical, molecular and methylation profiling into routine diagnostics has become increasingly important, and this thesis provides valuable insights into their application in rare tumor subtypes. As a result, the study addresses an important niche in oncologic pathology, where diagnostic challenges remain especially in rare tumor types due to their rarity and complexity.

Final Remarks and Recommendation

Dr. Kalmykova's thesis is a very good scholarly work that demonstrates a high level of expertise in surgical pathology. It is methodologically sound, well-supported by published research, and makes a significant contribution to the classification and diagnosis of rare tumors. **I strongly endorse this dissertation as a valuable addition to surgical pathology and recommend its acceptance for the doctoral degree.**

Questions for Discussion

1) In the study of EWSR1::PATZ1-rearranged sarcomas, certain cases displayed a more indolent clinical course than previously reported. Do you believe any specific histological or molecular features might serve as reliable prognostic indicators to stratify these tumors further?

2) Given the consistent expression of skeletal muscle markers in *PATZ1* sarcomas, do you believe it should be classified among rhabdomyosarcomas?

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