Journal of Clinical and Translational Pathology **2023** vol. 3(4) | 149–150
DOI: 10.14218/JCTP.2023.00065

Editorial

Helping to Correct the Frequent Invisibility of Pediatric Pathology: A Rare and Much Needed Collection of Papers Highlighting Topics in a Dismissed Specialty

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Received: December 4, 2023 | **Revised:** December 20, 2023 | **Accepted:** December 20, 2023 | **Published online:** December 30, 2023

Citation of this article: Reyes-Múgica M. Helping to Correct the Frequent Invisibility of Pediatric Pathology: A Rare and Much Needed Collection of Papers Highlighting Topics in a Dismissed Specialty. J Clin Transl Pathol 2023;3(4):149–150. doi: 10.14218/JCTP.2023.00065.

Pediatric pathology (PP) is considered a "relatively invisible" specialty for several reasons. First, most pathologists are quite capable of confronting diagnostic issues in PP without much difficulty. Second, using GI pediatric biopsies as an example, most biopsies from children reveal mild abnormalities or apparently normal histological findings. Based on these premises, most pathology laboratories have little or no need to hire pathologists with a subspecialty in PP. Of course, pediatric diseases are relatively rare compared to diseases in adults. Therefore, diseases in children, particularly those requiring a more in-depth medical study, including pathology, mostly fall into the rare disease category. Consequently, it is understandable that PP is a relatively remote field, infrequently visited by most pathologists. However, when pediatric cases are challenging, things can become very complicated, requiring a strong foundation in PP, extensive experience and a tailored approach for their study.

The above-mentioned ideas are illustrated in the current issue of the *Journal of Clinical and Translational Pathology* (JCTP), which includes five excellent manuscripts addressing complex issues in PP. These not only deserve attention for the specific topics analyzed, but also draw our attention to the relative frequency with which PP is incorrectly dismissed. One piece of evidence to support the last point is that the WHO Blue Books series did not publish a volume dedicated to the "Classification of Pediatric Tumors" for more than six decades. Instead, the pathology of neoplasms in children was scattered throughout the other Blue Books, and their descriptions were relatively limited. Fortunately, this situation was rectified when, in February of 2022, the first ever WHO Blue Book dedicated to pediatric tumors was published online,[1] and the corresponding printed version became available in August of 2023.This also marks the first time that the WHO Blue Book series requires two volumes to publish one of its books.

The five articles published in this issue of the JCTP shed light on the following topics: Spitzoid melanoma, embryonal rhabdomyosarcoma, pediatric histiocytic disorders, rhabdoid tumors and cytology of pediatric soft tissue tumors. These represent a relatively wide spectrum of disorders occurring with high frequency in pediatric hospitals.

Asadbeigi *et al*. discuss the diagnostic approach and terminology used in Spitzoid melanocytic lesions in children.[2] They emphasize that, based on the current understanding, a sentinel node biopsy is not recommended in patients with Spitzoid neoplasms. It is preferable to follow up on patients with Spitzoid melanoma using serial ultrasound. They also mention that at the moment, there is not a single marker or test capable of establishing a definitive diagnosis in this group of lesions. The usual criteria recommended for the assessment of conventional melanoma do not apply to these lesions, because benign Spitz lesions can feature nuclear atypia, consumption of the epidermis, lymphocytic aggregates and mitoses in the deep dermis. Among the recommended tools for the assessment of these lesions, they include PRAME immunohistochemistry, FISH for p16 and Ki-67 assessment of the proliferative index. They also recommend FISH analysis for chromosome 6 & 11 and CGH. Among the conclusions, it should be emphasized that Spitz melanoma in children frequently has a favorable behavior and this needs to be highlighted in the pathology report. Many of these points can also be found in the corresponding chapter of the PED5 Blue Book.[1]

Wang D and Wang HY[3] present an unusual case involving a 22-year-old patient with a mediastinal mass, wherein the diagnosis of embryonal rhabdomyosarcoma was established after an extensive and complicated pathological analysis. This case exemplifies what has sometimes been referred to as "leukemic rhabdomyosarcoma",[4] an exceptionally rare clinicopathological presentation of this predominantly pediatric type of tumor. The extensive analysis required for diagnostic confirmation in this case is an example of how certain cases of classic PP can be so complicated. The authors provide updated information regarding the immunohistochemical and genetic analyses necessary for assessing these tumors. Among the distinctive features shown by this case, it

Abbreviations: ALK-H., ALK-histiocytosis; HLH, hemophagocytic lymphohistiocytosis; HS, histiocytic sarcoma; JCTP, Journal of Clinical and Translational Pathology; JXG, juvenile xanthogranuloma; LCH, Langerhans cell histiocytosis; MKI, mitosis/karyorrhexis index; MRT, malignant rhabdoid tumor; PP, Pediatric Pathology; RDD, Rosai-Dorfman-Destombes disease.

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is mentioned that the tumor expressed PAX5, which has not been previously documented in rhabdomyosarcoma and was a major confounding element in the workup of the case, emphasizing the possibility of a hematological disorder.

Cheng JJ, *et al* provide a comprehensive analysis of the histological, immunophenotypical and genetic characteristics of the major forms of histiocytic disorders in children, including Langerhans cell histiocytosis (LCH), juvenile xanthogranuloma (JXG), Rosai-Dorfman-Destombes disease (RDD), hemophagocytic lymphohistiocytosis (HLH), histiocytic sarcoma (HS) and ALK-histiocytosis (ALK-H).[5] Histiocytic disorders are relatively common in children, and this review provides updates on the appropriate and current classification systems, immunohistochemical approach and genetic analysis. The paper covers hematopathology, dermatopathology and genetic/molecular pathology issues, outlining the most effective diagnostic approaches. Specific morphological features, such as the famous *emperipolesis* and characteristic of RDD, are nicely described and illustrated. The table presented in this paper is a valuable resource for keeping handy at your sign-out table and provides a concise listing of clinical, pathological and genetic points that are essential when dealing with these histiocytic disorders.

He M, *et al* present five examples of malignant rhabdoid tumor (MRT) studied with whole-exome sequencing.[6] Diagnostic germline gene mutations of *SMARCB1/INI1* in all of them confirmed the pathological diagnosis. In addition, somatic copy number alterations in pre- and post-treatment showed interesting multiple somatic copy number alterations involving genes important in tumorigenesis, some of which may represent actionable targets. Some somatic copy number alterations were specific for post-treatment tumors. This study shows that not only driver mutations, but also recurrent somatic copy number alterations are present in MRT. These alterations are associated with malignancy-related genes, including *SMARB1, SMARCCA4, PD1, TWIST2, TRIAP1, MTA1* and *X1AP*. MRTs post-treatment show alterations in *LMO1, MMP26, TRIAP1, TRAF3* and *SLC9A3R1*. In two metastatic cases, only 11p15.4 was found as a recurrent somatic copy number alteration, suggesting that the gain of 11p15.4 may indicate the possibility of metastasis.

Finally, Sun J and Fan F present the case of a three-year-old boy with an intraabdominal retroperitoneal mass from which cytological analysis of a fine-needle aspiration featured striking multinucleated cells.[7] Several possible diagnoses were entertained, such as a giant cell tumor, hemopoietic tumor, Hodgkin lymphoma and non-Hodgkin lymphoma. Neuroblastic tumors, such as neuroblastoma and ganglioneuroblastoma/ganglioneuroma, were also considered. Histological examination confirmed a neuroblastoma of unfavorable histology, characterized by one area with abundant Schwannian stroma intermixed with immature neuroblasts and ganglion cells, and another area with limited Schwannian stroma, containing a poorly differentiated neuroblastoma component with an intermediate mitosis/karyorrhexis index (MKI), which was interpreted as unfavorable histology. Putting all elements together, the case was classified as a composite ganglioneuroblastoma, also known as nodular ganglioneuroblastoma. The multinucleated cells were interpreted as neuroblasts and ganglion cells in variable stages of maturation. The authors discuss the difficulties related to cytological analysis of the spectrum of neuroblastic tumors in children, and emphasize the lack of appropriate literature describing this topic.

Overall, these five papers deal with relatively well-known areas in PP, providing a unique perspective rarely explored in general pathology. I am confident that readers will benefit from discovering numerous interesting and less commonly known aspects within the field of PP.

Acknowledgments

None.

Funding

None.

Conflict of interest

The author has no conflict of interests to declare.

Author contributions

Reyes-Múgica M is the sole author of the manuscript.

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