The Application of Current Classification Systems in Pediatric Cytopathology: Perspectives from the Pediatric Cytopathology Symposium at the 20th International Congress of Cytology 2019

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A pediatric cytopathology symposium was held at the recent 20th International Congress of Cytology, which convened in Sydney, Australia, in May 2019. This educational event brought together cytopathologists from different countries and different institutions to discuss some of the practical considerations when applying current diagnostic classification systems to cytopathology specimens from young (pediatric and adolescent) patients. Within the past decade, various classification systems have been developed to create more standardized terminology for cytopathology specimen reporting among institutions, which can lead to improved management guidelines based on evidence-based medicine. It is well known that a majority of the peer-reviewed publications in cytopathology discussing the usefulness of these classification schemes predominantly contain case cohorts of adult patients. Although pediatric cases are not excluded from following these diagnostic guidelines, there is less of an emphasis on this age group with respect to unique findings and management differences. Thus, discussing the role of these guidelines and their applications in pediatric cases at an international educational gathering can not only be beneficial in educating the cytopathology community about the value of applying these classification systems to pediatric populations, but also can raise awareness of unique entities in cytologic specimens obtained from young patients. ***Cancer Cytopathol* 2019;127:625-631**. *© 2019 American Cancer Society*.

KEY WORDS: classification; cytology; cytopathology; pediatric; terminology.

INTRODUCTION

On May 6, 2019, a pediatric cytopathology symposium was held at the 20th International Congress of Cytology 2019, which convened in Sydney, New South Wales, Australia. This educational event brought together cytopathologists from different countries and different institutions to discuss some of the practical considerations when applying current diagnostic classification systems to cytopathology specimens obtained from young (pediatric and adolescent) patients (Fig. 1).

Within the past decade, various classification systems have been created to promote more standardized terminology for cytopathology specimen reporting among institutions, which can lead to improved management guidelines based on evidence-based medicine. It is well known that a majority of the peer-reviewed

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Figure 1. Pediatric cytopathology symposium at the 20th International Congress of Cytology 2019, which convened in Sydney, New South Wales, Australia, from May 5 to May 9, 2019. Faculty included (from left to right): Colleen Wright, MD, MMed, PhD; Esther Diana Rossi, MD, PhD; Sara E. Monaco, MD; Zubair W. Baloch, MD, PhD; and Lisa A. Teot, MD.

publications in cytopathology discussing the usefulness of these classification schemes predominantly contain case cohorts of adult patients. Although pediatric cases are not excluded from following these diagnostic guidelines, there appears to be less of an emphasis on this age group with respect to unique findings and differences in management. Thus, discussing the role of these guidelines and their application in pediatric cases at an international educational gathering can not only be beneficial in that it educates the cytopathology community about the value of applying these classification systems to pediatric populations, but it also can create awareness of unique entities in cytologic specimens from young patients (Fig. 2).

Thyroid Fine-Needle Aspiration Biopsy Reporting and Management Guidelines in Children (Dr. Zubair W. Baloch)

The Bethesda System for Reporting Thyroid Cytopathology, initially created in 2008 and revised in 2017,[1] has been successful in standardizing thyroid reporting for thyroid fine-needle aspiration (FNA) specimens, including those obtained from young patients,[2,3] and even has been applied to intraoperative consultation specimens of pediatric thyroid lesions.[4] In children, thyroid nodules are less common than in adults, but when present, they have a greater tendency to be malignant, multifocal, and to present with more advanced disease, despite these patients having a good overall prognosis.[5,6] Some of the many causes of diagnostic challenges in the cytologic interpretation of pediatric thyroid FNA specimens include a higher frequency of cystic nodules compared with adults,[7,8] and focal nuclear and architectural atypia mimicking malignancy observed in autonomous functioning nodules, dyshormonogenetic goiter, and other benign conditions (Figs. 2A and 2B).[9,10] In the spectrum of malignant lesions, cytopathologists should be aware of the increased incidence of the diffuse sclerosing variant of papillary thyroid carcinoma, which typically demonstrates numerous microcalcifications and may prompt an FNA biopsy in a child with diffuse thyroid enlargement or a goiter in the absence of a discrete nodule. There also are numerous genetic syndromes that predispose children to an increased risk of thyroid cancer and thus require close monitoring, a fact that highlights the importance of obtaining a thorough clinical and family history in these patients (Table 1).

The American Thyroid Association (ATA) has published management guidelines for children (defined as individuals aged ≤18 years, but these guidelines could apply to the management of patients up to age 21 years)

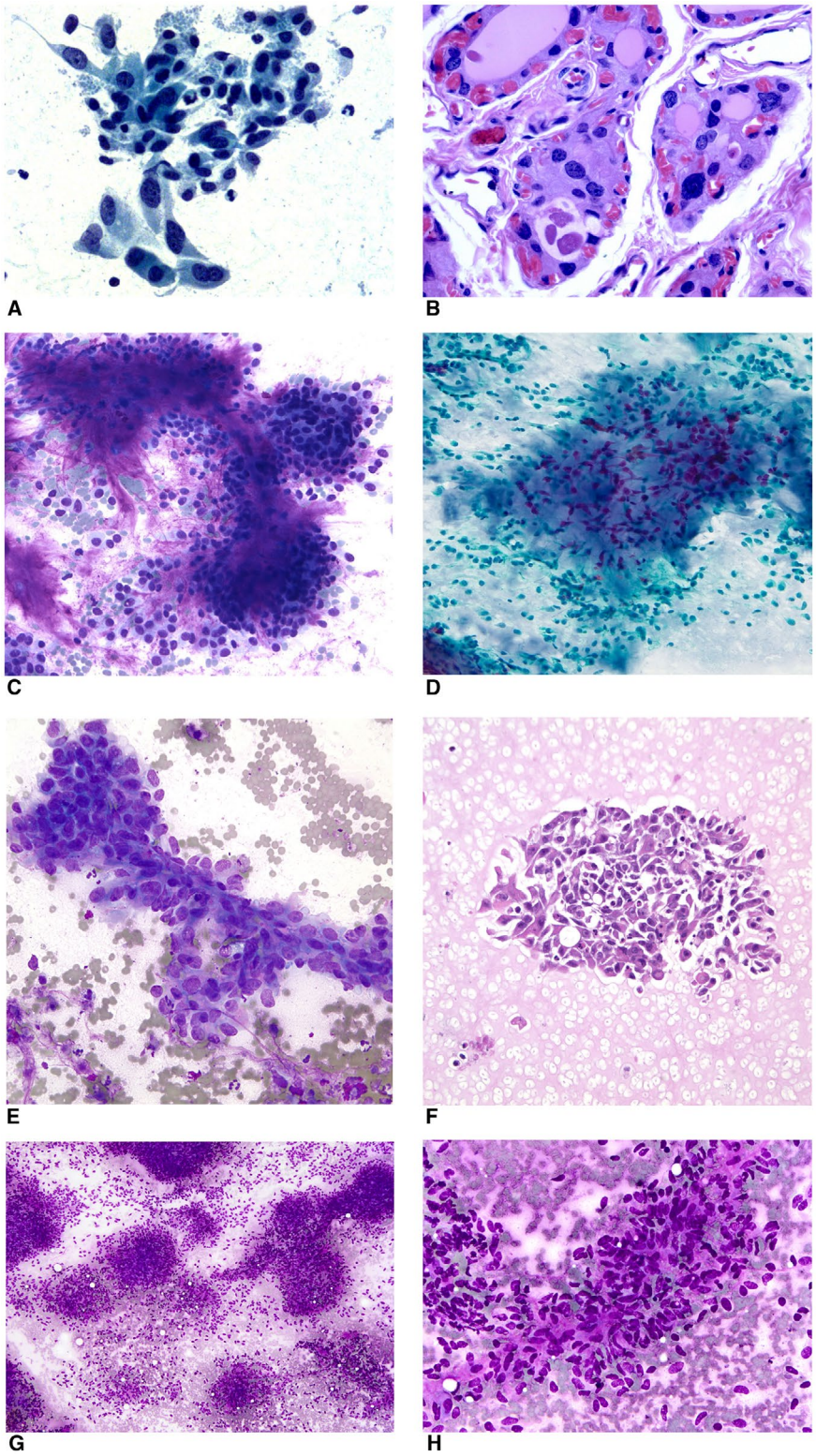

Figure 2. Examples of rare entities to consider in pediatric cytopathology. (A and B) Focal nuclear atypia in dyshormonogenetic goiter (A: Papanicolaou stain at high power; B: H & E stain at high power). (C and D) Cellular pleomorphic adenoma in the parotid gland of a young patient (C: Diff-Quik stain at medium power; D: Papanicolaou stain at medium power). (E and F) INI1-deficient pancreatic undifferentiated carcinoma with rhabdoid features in a young adult presenting with a malignant pancreatic lesion (E: Diff-Quik stain at high power; F: H & E stain at medium power). (G and H) Poorly differentiated synovial sarcoma mimicking a Ewing sarcoma or spindle cell tumor (G: Diff-Quik stain at low power; H: Diff-Quik stain at high power).

TABLE 1. Comparison of Key Findings in Children When Compared With Adults With Regard to Thyroid, Salivary Gland, Pancreatobiliary, and Soft-Tissue Lesions

Organ System	Key Findings in Children Compared With Adult Populations
Thyroid	• Nodules are more likely to be malignant, multifocal, and associated with advanced disease, but have a good prognosis • Cystic lesions are more common • Focal atypia mimicking malignancy can be noted in autonomous functioning nodules and dyshormonogenetic goiter • Higher risk of malignancy for indeterminate nodules • Tumors associated with genetic syndromes can manifest • Certain subtypes of papillary thyroid carcinoma are observed more commonly (eg, diffuse sclerosing variant)
Salivary gland	• Pleomorphic adenomas are the most common benign neoplasms, but can have greater cellularity and less stromal material • Mucoepidermoid carcinomas are the most common primary salivary gland malignancies, but typically have a good clinical outcome
Pancreatobiliary	• Neoplastic mucinous cysts are rare • Benign lesions tend to be more likely developmental or inflammatory in origin • Pancreatoblastoma, pancreatic endocrine neoplasms, and solid pseudopapillary neoplasms are the common primary pancreatic tumors, and adenocarcinoma is exceedingly rare • Pancreatic undifferentiated rhabdoid carcinoma with SMARCB1 (INI1) loss is a malignant tumor that should be considered in young patients • Embryonal rhabdomyosarcoma should be a consideration for any small, round, blue cell lesion detected in the biliary tract in children
Soft tissue	• Rhabdomyosarcoma is more often of the embryonal or alveolar subtype in children, but is high grade/pleomorphic and more difficult to treat (less chemosensitivity) in adults • Bone tumors are more often primary tumors, and rarely metastases, whereas adults more often have metastases • In general, the outcome for soft-tissue tumors in adults and children can vary, and these malignancies usually necessitate an experienced multidisciplinary team with experience in the specific age group

with thyroid cancer. These guidelines and recommendations are helpful to be aware of when interpreting thyroid FNA specimens in young patients.[5] The ATA guidelines highlight the unique aspects of the management of pediatric thyroid nodules, including the recommendation for surgical resection (typically lobectomy with isthmusectomy) for patients with hyperfunctioning nodules and those with indeterminate FNA cytology given the higher risk of malignancy compared with that in adults.[2,5] In the setting of indeterminate results, the ATA guidelines also state that molecular testing may be of benefit, and in some practices, this is helpful for surgical planning to minimize staged thyroidectomies and multiple surgeries.[11] When adjunct molecular testing has been performed in pediatric thyroid FNA cases, the incidence of genetic abnormalities tends to be higher, with a greater prevalence of *RET-PTC* and *NTRK* rearrangements and a lower incidence of *BRAF* mutations, compared with that reported in adults in most studies.[2,6,12-14] Future developments that could be considered in pediatric thyroid FNA cases are the reportingof a modified risk of malignancy based on published data in this age group, and stratifying the risk of malignancy into subgroups to separate younger children (those aged <10 years) from older children and adolescents (those aged >10 years), given that the results from young adults more closely align with the findings in adult populations.

Salivary Gland FNA Biopsy Reporting in Children (Dr. Esther Diana Rossi)

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was published in 2018,[15] and has been shown to be helpful in young patients in rare studies.[16] In general, salivary gland malignancies are rare in children, but when these tumors do occur in the major salivary glands, they are more likely to be malignant compared with tumors detected in adults. Of the malignant lesions, mucoepidermoid carcinoma is more common, and tends to present at a less advanced stage and rarely with metastases, and demonstrates a better clinical outcome compared with in adults.[17] Of the nonmalignant lesions, pleomorphic adenomas are the most common benign neoplasms, whereas congenital lesions (first branchial arch abnormalities, hemangiomas, and lymphangiomas) and infectious or inflammatory etiologies are common nonneoplastic lesions to consider.[18] Although pleomorphic adenomas also are common in adults, those occurring in children tend to be more cellular and lack the classic stroma-rich aspirates encountered in adults (Figs. 2C and 2D)(Table 1).[19] Cellular pleomorphic adenomas could be challenging on FNA, and some cases will be classified in the MSRSGC category IVB as "neoplasm: salivary gland neoplasm of uncertain malignant potential." It is interesting to note that neurogenic tumors, such as schwannomas, also can occur within or within the vicinity of the

pediatric salivary gland, and most likely will be reported as MSRSGC category IVA: "neoplasm: benign."

The list of ancillary markers (immunostains and fluorescence in situ hybridization) that are helpful for providing a specific salivary gland FNA interpretation is expanding at a quick pace. These tests can aid in subtyping salivary gland neoplasms as well as other malignancies observed in young patients (eg, lymphoma, rhabdomyosarcoma, and synovial sarcoma), and have been used with success in preoperative FNA specimens with ancillary studies to help plan surgical treatment. The efficacy of the MSRSGC in stratifying salivary gland lesions in larger case cohorts of pediatric FNA patients with clinical and surgical follow-up will be something to examine in future studies.

Pancreatobiliary Cytology Specimen Reporting in Children (Dr. Sara E. Monaco)

The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology (PSC-RPBC) initially was published in 2014, and provides a 6-tier classification system for reporting pancreatobiliary cytology specimens that correlates with biologic behavior and management from studies largely involving adult patients.[20,21] To the best of our knowledge, the applicability of the PSC-RPBC in rare pediatric specimens arising from these locations has not been studied to date. However, in general, pediatric pancreatobiliary lesions differ from adult lesions in that the common neoplastic mucinous cysts in adults are rare in children, and the causes of pancreatitis (eg, gallstones and alcohol for adults) are different in children. The more likely etiology of a benign pancreatobiliary lesion in a child is a developmental cyst, hamartoma, or inflammatory process (Rosai-Dorfman disease, autoimmune/IgG4-related disease, or infection).[22] These benign lesions can be associated with severe pancreatitis, which can prove to be lethal if not treated emergently.[23]

In the spectrum of neoplastic lesions, pancreatoblastoma, pancreatic neuroendocrine neoplasm, solid pseudopapillary tumor, germ cell tumor, sarcoma, and lymphoma should be considered before a pancreatic ductal adenocarcinoma in a young patient (Table 1). For PSC-RPBC category IV neoplasms in children, category IV of "neoplastic: benign" would apply to serous cystadenomas and schwannomas, whereas category IV "neoplastic: other" would apply to neuroendocrine tumors and solid pseudopapillary tumors. Pancreatic neuroendocrine tumors can occur within the setting of genetic syndromes in children (eg, tuberous sclerosis, von Hippel-Lindau, and multiple endocrine neoplasia), as can serous cystadenoma (eg, von Hippel-Lindau).[24] Pancreatoblastoma is an important malignancy to consider in children and demonstrates focal beta-catenin and LEF1 nuclear positivity within squamoid areas, and also can be observed within the setting of familial adenomatosis polyposis–related syndromes and Beckwith-Wiedemann syndrome.[25] A special consideration in the malignant category is pancreatic undifferentiated rhabdoid carcinoma with SMARCB1 (INI1) loss and the absence of *KRAS* mutations, which can occur in young patients (Figs. 2E and 2F).[26] In cytology samples of biliary masses, an important consideration in the pediatric population is embryonal rhabdomyosarcoma, which can present clinically as a large multicystic mass, similar to sarcoma botryoides in the vagina, and may demonstrate small, round, blue cells with some rhabdoid features that are easy to overlook in liquid-based cytology and may be more apparent on a cell block. Thus, in rare pediatric pancreatobiliary specimens, it is important to consider these rare inflammatory, developmental, and neoplastic entities, which may be associated with systemic disease or genetic syndromes.

Soft-Tissue Cytology Reporting in Children (Dr. Lisa A. Teot)

Although to the best of our knowledge there currently is no formal cytological classification scheme for the reporting of soft-tissue tumors, these tumors are common in children and may be sampled by FNA and/or core needle biopsy prior to and to guide definitive treatment. The use of FNA and core needle biopsy is particularly helpful to avoid more invasive open biopsies of deep-seated tumors, and these ideally are combined with on-site evaluation to confirm the sampling of viable, lesional tissue and to appropriately triage material, thereby minimizing the risk of a nondiagnostic biopsy. The current World Health Organization classification for soft-tissue and bone tumors, published in 2013, provides a helpful framework for approaching soft-tissue lesions in both small biopsies and surgical resections based on salient morphologic, immunophenotypic, and molecular features,[27] which also can be applied to cytological material for accurate subclassification in various categories of tumors (eg, adipocytic, fibroblastic, nerve sheath, etc). Among the challenges

encountered in the diagnosis of pediatric soft-tissue lesions are morphologic and immunophenotypic overlap, particularly among patients with spindle cell and round cell tumors; the involvement of the same genes (eg, *EWSR1*) in translocations in different tumors; and the absence of characteristic molecular abnormalities in many tumors (Figs. 2G and 2H).[28,29] In addition, when comparing soft-tissue and bone tumors diagnosed in children with those found in adults, there are differences with respect to the subtypes observed and the treatment, which highlights the importance of specialized multidisciplinary care. One example is rhabdomyosarcoma, in which the embryonal and alveolar subtypes are more commonly noted in pediatric patients, whereas in adults the pleomorphic subtype is more common and generally is less responsive to treatment (Table 1).

A major advantage of preoperative cytological or small biopsy evaluation is the ability to perform ancillary studies and, in many cases, render a definitive diagnosis. Unlike an intraoperative frozen section pattern–based diagnosis (eg, spindle cell neoplasm), this allows for appropriate management, including surgical planning, and, for some malignancies, neoadjuvant chemotherapy and/or radiotherapy. For example, nodular fasciitis is a bland but somewhat cellular and often mitotically active benign spindle cell neoplasm that can be mistaken for sarcoma. Although the morphology and immunophenotype overlap with those of other benign and malignant spindle cell tumors, nodular fasciitis harbors the *MYH9-USP6* fusion, which can help to confirm the correct diagnosis on preoperative cytologic specimens or small biopsies and therefore prevent inappropriately extensive surgery.[30] In the near future, a revised version of the World Health Organization classification will be available, and will include key cytological features in the description of the entities in addition to updated immunohistochemical markers and molecular aberrations uncovered in some of the existing and new entities.

CONCLUSIONS

The unique ability to bring together cytopathologists from different practice settings who have expertise in pediatric lesions is one of the valuable aspects of an international symposium such as the 20th International Congress of Cytology in May 2019. This gathering helped to disseminate knowledge and discuss entities diagnosed in a pediatric population in light of evidence-based management guidelines. This educational offering helped to fill an important knowledge gap for cytopathologists. Understanding the need for the application of current classification systems in a pediatric setting provides timely and practical information that, to our knowledge, has not been addressed extensively in the peer-reviewed literature and in textbooks on the subject.

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AUTHOR CONTRIBUTIONS

Sara E. Monaco: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Zubair W. Baloch:** Data curation, formal analysis, investigation, resources, and writing–review and editing. **Esther Diana Rossi:** Data curation, formal analysis, investigation, resources, and writing–review and editing. **Lisa A. Teot:** Data curation, formal analysis, investigation, resources, and writing–review and editing. **Colleen Wright:** Conceptualization, project administration, supervision, visualization, and writing–review and editing.

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