Seminars in Diagnostic Pathology ▮ (2016) ▮▮▮–▮▮▮

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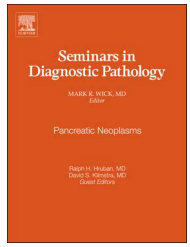

Contributions of Dr. Louis "Pepper" Dehner to the art of cutaneous pathology, the first pediatric dermatopathologist

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ARTICLE INFO

Keywords:
Pediatric pathology
dermatopathology
juvenile xanthogranuloma

ABSTRACT

Dr. Louis "Pepper" Dehner has been one of the most influential surgical pathologists of the last century. Authoring more than 450 publications, he is the premier modern pediatric pathologist. Perhaps, an area that he is less recognized and in which we would like to describe his contributions, is his role as a creator of the art of pediatric dermatopathology. Dr. Dehner has had at least 50 major publications describing, discovering, and orienting the discipline in the fields of fibrohistiocytic disorders of childhood, vascular tumors, and histiocytosis among many others. Dr. Dehner has clearly manifested that while many similarities between adult and pediatric surgical pathology exist, "children get different diseases." It is because of his mindful analysis and translation of the clinico-pathologic and biologic correlative between specific entities and advances in the field he has made that we are honored to describe some of his contributions to this particular area.

Introduction

As former fellows of Dr. Louis "Pepper" Dehner, it is most illustrative to describe a typical sign-out day with him. We would arrive, and Dr. WX shows Dr. Dehner a difficult biopsy of a child. "Please do not tell me anything about the clinical history, as I do not want any "contamination" in my thinking." Eventually, he comes to terms that he is looking at a skin biopsy from a little boy in the scrotum. There are dilated lymphatic channels with granulomatous inflammation and plasma cells within them. He answers to Dr. WX: "This is a great example of Melkerson–Rosenthal syndrome." Astonished, I turned to thinking: How in the world does he know? "Alejandro, what are the three most difficult diagnoses to make? (1) the one you haven't thought about; (2) the one you thought about, but erroneously came to the conclusion that was not; and (3) the one that hasn't been described …." We would try to avoid any comments about Civil War, Vietnam or presidential politics, in order to expedite going through the huge piles of slides that are in front of us. Dr. Dehner just finished a phone call with surgeon XY. He immediately says "Dr. XY should wear paper toilet continuously in his head. You know why? He has $%@ for brains."

The fibrohistiocytic diseases and problems in classification

Dr. Dehner has been one of the leading investigators to separate histiocytosis into two main categories, in accordance to

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http://dx.doi.org/10.1053/j.semdp.2016.08.004
0740-2570/

the cell that they morphologically and immunophenotypically resemble: the mature macrophage and the dendritic cells. Originally classified as histiocytosis X, non-histiocytosis X, and malignant histiocytosis, significant reordering and re-classifications have emerged.[1,2] More recently, the addition of molecular tools has served in the understanding that many of these entities have specific mutations, that could help achieve specific diagnoses and provide pathways for specific targeted-therapies.[3]

The so-called histiocytosis X has now been named Langerhans cell histiocytosis. Together with juvenile xanthogranuloma, they are grouped under the "dendritic cell-related" proliferations. The macrophagic proliferations include other distinctive entities such as Rosai–Dorfman disease, reticulohistiocytoma and reticulohistiocytosis, among others. The previously thought "malignant histiocytosis"[4] has now been reclassified, for the most part, as anaplastic large cell lymphomas (both ALK+ and ALK− variants) leaving the extraordinary rare group of histiocytic sarcomas under that category.

Juvenile xanthogranuloma

The largest, most eloquent and comprehensive article documenting the natural history, clinical presentation and histopathologic findings of juvenile xanthogranulomas (JXG) was written by Dr. Dehner in 2003 and published in the American Journal of Surgical Pathology.[5] Originally, JXG was described by Adamson and McDonagh in 1905 and 1912 as nevoxanthoendothelioma (although some credit belongs to Rudolf Virchow for reporting a child with "cutaneous xanthomas" in 1871).[6] As many tumors in the early part of the previous century, McDonagh believed that JXG arose from the "endothelium of the capillaries." He originally pointed that the clinical appearance of them resembled soft fibromas or connective tissue tumors and highlighted that, in many circumstances, the lesions resolved on their own. The value and clinical significance of this early description has remained intact for over 100 years.

The seminal publication of Dr. Dehner of 174 cases illustrates that most JXGs in children present as isolated skin lesions, and were slightly more common in boys compared to girls (57% vs 43%). JXG can present in any location in the body and as many as 75% present within the first year of life.[7] A deep soft tissue mass was noted in 16% of cases. Extracutaneous solitary presentations of JXG include orbital lesions, bone lesions and rarely visceral forms.[8] Multifocal involvement occurred in 12% of cases and approximately 4% of children had systemic dissemination. Most interesting was the fact that fatality could rarely occur, and usually in the form of a hepatitis with giant cell features. One of Dr. Dehner's point along this was the fact that primary cases of so-called "giant cell hepatitis" might actually reflect liver involvement by this disease, since as many as 50% of cases of them do not have a specific etiology.

The most important part of the study was the recognition of a wide variety of histologic appearances for JXG: while the more characteristic pattern of xanthomatized histiocytes, multinucleated giant cells with a wreath-like pattern, and spindle cells is evident in the skin (Fig. 1), such can be missed in extracutaneous or visceral locations (were multinucleated giant cells can be absent). Tahar et al. referred 4 distinctive patterns: xanthomatous, xanthogranulomatous, fibrohistiocytic and combined.[9] Indeed, the non-cutaneous forms can show only mononuclear cells and spindle cells, with only focal xanthomatized changes. Such cutaneous pattern reflects truly "the life cycle of the lesions with its capacity of self-healing and spontaneous regression," and the xanthomatized pattern represents the end stage of it. In some cases JXG can present with cellular atypia, including enlarged and hyperchromatic nuclei, high nuclear to cytoplasmic ration, and mitotic figures. Such finding should not be interpreted as malignant. Importantly, Dr. Dehner believes that a fundamental portion of JXG diagnosis relies on a very distinctive phenotype, which includes the expression of vimentin, the histiocyte marker CD68, and Factor XIIIa, grouping this process in the category of dendritic cell tumors. JXG, as we know, is invariably negative for Langerhans cell markers CD1a and Langerin. Although most are negative, some cases can show significant staining for S100 protein.

While uncommon, recent advances have shown that JXG can rarely occur in association with genodermatosis, and particularly with neurofibromatosis type 1.[10,11] A common link between neurofibromatosis, juvenile myelomonocytic leukemia, and JXG has been noted.[12] Other associations with JXG in children that were pointed in Dr. Dehner's series included pilomatrixomas and nevus sebaceous of Jadasohn. However, given the frequency of such lesions in children, they are most likely an incidental association, rather than a related neoplasm. It is not uncommon to see adult patients with juvenile xanthogranuloma, and hence the term "xanthogranuloma" is now advocated by many authors. Indeed, Dr. Dehner reported 44 adult cases of JXG in their series. Most isolated cutaneous lesions typically regress on their own, and no further treatment than monitoring is further advocated. Those patients with multiple lesions and recurrences show varying degrees of spontaneous remission. Most patients with systemic disease require chemotherapy. Isolated non-cutaneous lesions in the deep soft tissue or visceral organs or bone, should undergo complete resection.

The differential diagnosis of JXG is sometimes challenging, particularly in cases with few multinucleated giant cells, absence of wreath-like morphology, a predominant spindle cell component, or location in a deep seated area. Dermatofibromas/benign fibrous histiocytomas can sometimes have multinucleated giant cells and xanthomatized changes, and the immunophenotype is for the most part shared with JXG (Factor XIIIa+, CD68+). However, the border in DF is more infiltrative and there is collagen trapping at the edges. Similarly, most DFs show a spindle cell appearance, and a predominance of such type of cell is only seen in 3% of JXGs. Some cases of histiocytoses can also generate diagnostic difficulties. LCH is usually easier to distinguish, due to the presence of epidermotropic atypical Langerhans cells and different immunophenotype (CD1a+, Langerin+, S100+). The poorly defined category of indeterminate cell histiocytosis, however, includes neoplasms in children with an incomplete Langerhans phenotype (S100+, partial CD1a, and absence of Langerin). Diffuse and weak S100 staining can sometimes be present in some cases of JXG, as previously pointed out by Dr. Dehner.[13] Cases with substantial