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The Pseudoinflammatory Pattern Revisited

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ABSTRACT

In 1973, Dr. Martin C. Mihm, Jr. presented the finding that congenital melanocytic nevi, when viewed at low magnification, resemble superficial and deep perivascular dermatitis, forming the so-called "pseudoinflammatory" pattern. One year earlier, Dr. Richard A. Sagebiel had put forward the concept of "pseudovascular spaces" in melanocytic nevi. A retrospective look at these early studies confirms that alert observation at the microscope can lead to a deeper understanding of the fundamental biology underlying melanocytic tumors.

I first met Dr. Martin C. Mihm, Jr. in 1973, while I was feeling my way toward a career during a gap year away from undergraduate studies. To my great good fortune, I discovered dermatology early, by working at the Massachusetts General Hospital (MGH) as the world's first PUVA research technician under Dr. John A. Parrish, the farseeing leader of the Photobiology Unit (now the mighty Wellman Center for Photomedicine). Even before graduating from college, I had the opportunity to attend Marty's lectures to the residents and to witness up-close his exceedingly dynamic teaching style. The stimulating environment at MGH spurred me into the profession of medicine, and I returned in 1984 to begin a research fellowship and clinical residency in dermatology at Harvard. There, the first unforgettable lesson that Marty imparted was the "pseudoinflammatory" pattern seen in congenital melanocytic nevi (CMN). If one wonders why this seemingly picayune topic has stuck with me through the decades, my best explanation is that I was still relatively young and innocent back then. The notion of pseudoinflammatory nevi must have shocked my tender sensibilities and shook up my naïve assumptions; the very idea contravened and mashed up some of the most basic categories of pathology (inflammation and neoplasia), with "pseudo" thrown in for good measure.

The arrangement of lymphocytes around dermal blood vessels characterizes the common histopathologic pattern designated as superficial and deep perivascular dermatitis, which includes viral exanthems, dermal hypersensitivity reactions, and so on. In CMN, the arrangement of nevus cells around vessels can simulate perivascular infiltration by lymphocytes, when viewed at low magnification; hence, pseudoinflammatory. Because I received this pearl early on, I have gone through later life blithely assuming that it must be common knowledge among most dermatopathologists. However, looking into this topic more carefully now, I see that the concept is only sparsely represented in the medical literature, mainly in books by authors with an MGH connection. For example, *The Melanocytic Proliferations* by Crowson, Magro, and Mihm, in a table concerning the pathology of CMN, refers to the "Perivascular pattern resembling lymphocytic infiltrate." [1] Similarly, in *Pathology of Melanocytic Nevi and Melanoma*, Barnhill, Piepkorn, and Busam state, "perivascular and periadnexal cuffing of nevus cells in some congenital nevi may closely resemble an inflammatory process such as a gyrate erythema." [2] Even apart from its application to CMN, the term "pseudoinflammatory" is a bibliographic rarity; a PubMed search for "pseudoinflammatory" yields a meager 107 hits dating back to 1829 [3], mainly with reference to ophthalmology (pseudoinflammatory macular dystrophy) as well as assorted tumors of various organs, but not CMN.

So much for secondary sources, but where did the concept of pseudoinflammation in CMN first arise? The origin seems to be the magisterial 1973 paper on "Congenital melanocytic nevi

of the small and garment type: Clinical, histologic, and ultrastructural studies" by Mark, Mihm, Liteplo, Reed, and Clark [4]. In that monograph, Marty and his colleagues exhaustively compared 60 CMN with 60 acquired nevi. Among other characteristics of compound and dermal CMN, they listed "Arrayed in perivascular and perieccrine distribution, mimicking an inflammatory infiltrate." Several figures illustrated nevus cells surrounding and infiltrating dermal blood vessels and lymphatics. However, the authors did not use the provocative term "pseudoinflammatory pattern" in their study. Perhaps this concept would be more widely recognized now if Marty and his colleagues had written down that vividly memorable coinage.

To illustrate the pseudoinflammatory pattern here, note what might appear at low power to be lymphocytic infiltrates surrounding dermal blood vessels (Figure 1). However, when viewed at high power these cells exhibit considerable cytoplasm and a nested arrangement; they are clearly not lymphocytes but rather nevus cells (Figure 2).

The concept of pseudoinflammatory CMN may be catchy, but it is fair to ask whether it is also important. As is so often true of careful microscopic observations, the simple finding of a perivascular distribution of congenital nevus cells does indeed offer an intriguing glimpse into fundamental biologic processes with major implications for human disease. The perivascular, perineural, and periappendageal distribution of nevus cells in CMN probably reflects the embryonic migration of melanocyte precursor cells from the neural crest, whereby these structures' basement membranes serve as substrate, a royal road for the cellular journey to the target site in the skin. Angiotropism (i.e., migration along the external rather than intraluminal aspect of vessels) is seen in >94% of CMN [5]. Melanoma cells also employ angiotropism to exploit the process of embryonic locomotion. In extravascular migratory metastasis, melanoma cells co-opt the perivascular basement membrane used by normal melanocytes during the benign histogenesis of CMN. Reversing gears, melanoma cells can thereby spread back from the skin and travel to distant metastatic sites [6–8]. Seen in the light of this pathway, the pseudoinflammatory pattern exemplified by CMN has a wider relevance and qualifies as much more than a mere curiosity.

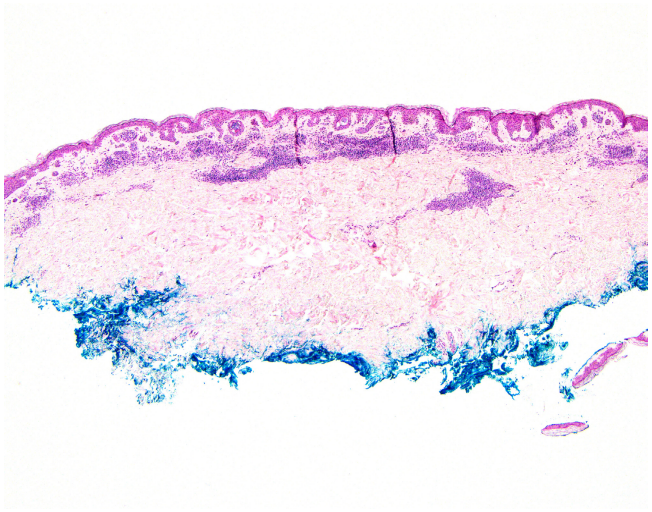

FIGURE 1 | Pseudoinflammatory pattern in congenital melanocytic nevus. Nevus cells resembling lymphocytes surround dermal blood vessels in a pattern simulating superficial and deep perivascular dermatitis (H&E, original magnification 40×).

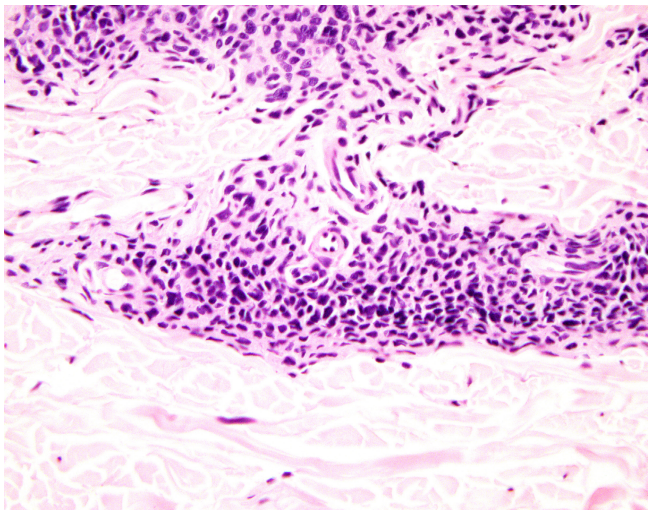

FIGURE 2 | Pseudoinflammatory pattern in congenital melanocytic nevus. Unlike lymphocytes, perivascular nevus cells have considerable cytoplasm and a nested arrangement (H&E, original magnification 400×).

Under the potent influence of such additional mentors as Drs. George F. Murphy and Raymond L. Barnhill, I was inspired to devote my career to academic dermatopathology. From 1990 to 1992 I trained as a dermatopathology fellow at New York Hospital/Cornell University under the tutelage of Dr. N. Scott McNutt. Scott himself had received his MD degree from Harvard Medical School (there having attended dermatopathology lectures by Dr. Wallace H. Clark) and had performed his pathology residency at MGH. After Boston, he worked for a decade as a pathologist at the VA Medical Center in San Francisco before moving to New York. In San Francisco, he became a good friend and colleague of Dr. Richard W. Sagebiel, a pathologist at St. Mary's Medical Center. Sagebiel had a special interest in melanocytic pathology, and taught McNutt much about this topic. During my time in New York, Scott would often point out "the pseudovascular spaces of Sagebiel" while we were viewing intradermal nevi. The eponym commemorated a 1972 study in which Sagebiel discovered a pseudovascular (his term) pattern in 10% of 350 melanocytic nevi [9]. This classic paper illustrated the separation of nevus cells away from the adjacent stroma and from each other, resulting in clefts that simulated vessels. To demonstrate the pseudovascular pattern here, note what might appear to be vessels surrounded by nevus cells. However, these are not actually vessels but nevus cells, arranged in nests that are so poorly cohesive that they simulate vessels with central lumina (Figure 3).

It seems we have been doubly deceived; not only is there pseudoinflammation around vessels, but also pseudoinflammation around pseudovessels. This raises the age-old question: Do two wrongs make a right? But here is a much more interesting question: Does pseudovascularity amount only to a quirky artifact of fixation, as Sagebiel indicated, or could it have a deeper significance? With the greatest respect to Sagebiel, I submit that he was too modest

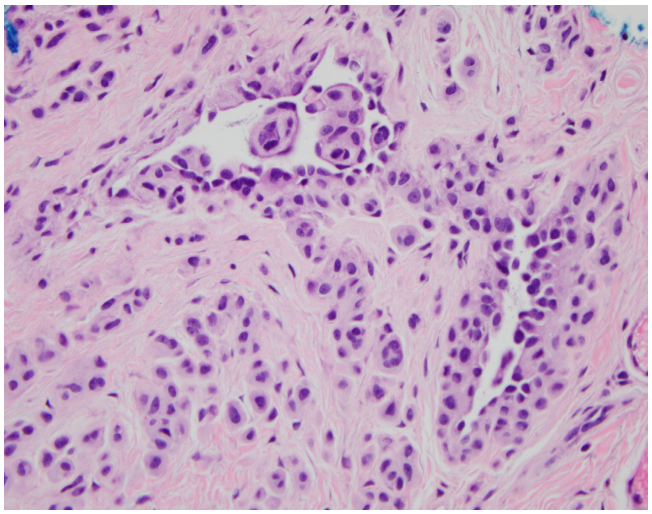

FIGURE 3 | Pseudovascular pattern in congenital melanocytic nevus. Nevus cell nests are so poorly cohesive as to simulate vessels (H&E, original magnification 400×).

in downplaying the importance of his discovery. Instead, I would categorize pseudovascularity in nevi as a "real artifact": yes, an artifact (for the spaces apparently do not exist in vivo), but one that reflects genuine underlying biology. In support of this idea, note that all the other tissue elements in the specimen retain their normal intercellular connections and cohesion. Therefore, this phenomenon is evidently not a generalized side effect of harsh histologic processing; instead, pseudovascularity points to a loss of cohesion by the nevus cells specifically.

The biology underlying the dyshesion of nevus nests may offer clues to fundamental processes critical in the progression of melanoma. As Miller and Mihm discussed [10], the histopathogenesis of melanoma can be modeled as a sequence starting (in some cases) with a wholly benign nevus and proceeding through dysplastic nevus, radial-growth-phase melanoma, and vertical-growth-phase melanoma, to metastatic melanoma. This complex series of biologic events depends on corresponding molecular lesions. One key aspect of the transition to the vertical-growth and metastatic phases is an altered expression profile of various cadherins by invasive melanoma cells [11]. This switch assists melanoma nests to disaggregate and the tumor cells thereby to gain access to vessels, which they then exploit to execute the metastatic program. Similarly, CMN nevus cells show a gradient of reduced E-cadherin expression at greater dermal depth, and changes in nevus cells' levels of E-cadherin may affect their motility in primary cultures [12]. The pseudovascular phenotype of nevi may reflect a shift in their expression of adhesion molecules, leading to focal disaggregation analogous to that seen in tumor progression. Thus, this benign phenomenon may open a window into basic mechanisms linked to melanoma invasion and metastasis.

One fascinating further possibility is that melanocytes may gain access to adhesive pathways by assuming some of the characteristics of true vessels. While this concept has not yet been validated in nevi, it is well-recognized in melanomas by virtue of "vasculogenic mimicry," whereby melanomas can form vessel-like lumina and laminin-associated channels; melanoma cells can even express endothelial genes such as vascular endothelial cadherin (CD144) and tyrosine kinase with immunoglobulin and epidermal growth factor-like domains 1 (TIE-1). This concept was popularized by Folberg and Hendrix [13] and subsequent data indicate that it is related to the vascular endothelial growth factor (VEGF) pathway elicited by more primitive, stem-like melanoma cells that are capable of differentiation plasticity [14]. Melanocytic nevi also exhibit plasticity, being able to mature into neural structures resembling Meissner corpuscles, so why should they not also make a fleeting attempt every now and then at forming a vessel? Time will tell, as investigators probe this issue more deeply in both benign and malignant melanocytic proliferations.

Thus, these two obscure topics, pseudoinflammation and pseudovascularity in melanocytic nevi, exemplify that apparently trivial findings may eventually lead to surprising and even illuminating insights. Behold the vast power of observation! This is the wondrous age of molecular medicine, granting scientists access to amazingly precise tools such as knockout mice, silencing RNA, CRISPR, and many other technological breakthroughs; for that reason, some researchers nowadays deride old-fashioned, observational studies as weak, indirect, and (shudder!) phenomenological. To the contrary, I would argue that active observation remains an essential foundation for hypothesis-driven, mechanistic biology. The practice of dermatopathology is deeply satisfying because it provides the lucky practitioner with unmatched daily stimulation at the microscope, and endless opportunities for both alert observation and informed speculation. True, at least in their earlier years our departed mentors lacked our most elegant contemporary methods. For that very reason, I believe that they deserve even greater admiration for the persistent curiosity, diligence, and ingenuity that they brought to their work. Marty Mihm was surely no exception. His celestial reputation as a peerless master of microscopic diagnosis and a founding father of experimental melanoma pathology will long endure.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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