

Case Presentation 11

A Case of Generalized Eruptive Histiocytosis in a 23-Year-Old Man

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Case Report

A 23-year-old man of Mexican descent presented in July of 2013 with an extensive papular eruption on his bilateral lower extremities. The papules ranged in size from 0.2-1.0 cm, both firm and soft, without scale or crust, and were distributed symmetrically. The lesions were overlying a confluent, red-brown, smooth, erythematous skin with a serpiginous border extending from mid-calf up to his thighs, with trace pitting edema (figure 1a and 1b). Over the next several months, the papules spread from his posterior calves up to his inguinal folds, increasing in size and number. He had no systemic signs or symptoms. The only medication that the patient took during this time was clonazepam, for a new diagnosis of anxiety. He did not try any topical or oral medications for the skin lesions. Besides anxiety, the patient also had a history of stress induced urticaria. He had no family history of skin diseases. A limited battery of laboratory tests were performed in Mexico, revealing a complete blood count within normal limits, a metabolic panel showing hypoalbuminemia and a normal lipid profile. Viral serologies and an autoimmune workup were not performed. Imaging studies were within normal limits.

Biopsies of the patient's lesions procured at different time points in the patient's clinical course demonstrated an extensive dermal histiocytic infiltrate, accompanied by concomitant interstitial mucin deposition (Figure 2A-2B). The histiocytoid cells ranged from being rounded and epithelioid to exhibiting a somewhat spindled appearance, especially at the base of the infiltrate. The cell nuclei were reniform and irregularly contoured in shape, with somewhat thickened nuclear membranes. There was a moderate degree of pleomorphism to the cell population, with some cells being quite large (50-100 microns), although the majority of the cells were monotypic, in the 12 to 15 micron size range (Figure 2c1 and 2c2). The cells had vesicular nuclei with multiple chromocenters and abundant eosinophilic to basophilic cytoplasm. The pleomorphism was less conspicuous at the base of the lesions. No significant mitotic activity was identified. Although the dominant histiocytic infiltrate was mononuclear, a few multinucleated cells were noted. There were many admixed neutrophils and plasma cells in the infiltrate although without emperipolesis by the larger histiocytic elements (Figure 3).

An extensive array of immunohistochemical stains were performed. The mucin deposition in the dermis was highlighted by an Alcian blue preparation. The infiltrate was positive for CD11c and CD14 (figure 3 and 4). A CD1A preparation showed positivity amidst reactive Langerhans cells. There was extensive immunoreactivity of the histiocytes for CD43 and CD68 with a considerable degree of positivity amidst the deeper-seated, dendritic spindled elements. A myeloperoxidase preparation was positive in neutrophils while the majority of the histiocytes were essentially negative. A CD79A highlighted reactive plasma cells. There was extensive staining throughout the infiltrate for Factor-XIIIA (figure 5) and CD34. The staining intensity was quite varied ranging from being weakly to strongly positive. An S100 preparation showed positivity amidst a few of the larger elements noted superficially, while most of the infiltrate was negative. Significant immunoreactivity was not identified for CD30 or a pan-cytokeratin. Similarly, a Langerin stain was negative. There was also rather striking immunoreactivity of the infiltrate for CD34.

Discussion

The histiocytosis syndromes are proliferative disorders of monocytes exhibiting varied terminal differentiation ranging from infiltrates of scavenger macrophage origin to a monocyte with dendritic cell properties. The macrophage has as its main function phagocytosis while the dendritic cells are further subcategorized according to their location in tissue and inherent antigen presenting properties. Dendritic cells (DCs) provide an essential link between innate and adaptive immunity by virtue of their antigen-presenting activity and cytokine production. The DCs can largely be divided into three subsets represented by the Langerhans cells (LCs), myeloid DCs (mDCs) and the plasmacytoid DCs (pDCs) respectively. The latter two DCs have also been designated DC1 and DC2 respectively. The mDCs exist in three main compartments:

peripheral tissue DCs, secondary lymphoid organ resident DCs and circulating blood DCs. In the skin the peripheral tissue DCs fall under the designation of dermal dendrocytes. Given a common CD34 positive stem cell origin for both LCs and myeloid DCs, it is not surprising that the myeloid DCs can differentiate into LCs. The mDCs are characterized by the production of a large number of soluble factors including IL-6, IL-8, IL-10, IL-12, and the expression of toll-like receptors (TLR) 2, 4 and 7. A critical function of the myeloid DCs is to prime T cells to help naïve B cells to produce large amounts of IgM and switch isotypes toward IgG and IgA. In contrast, LCs are not capable of regulating B cell differentiation. Myeloid DCs typically express a myeloid marker profile. In this regard, they are CD11c+ and lysozyme positive and show variable positivity for CD163 and CD68. They are typically myeloperoxidase negative. In addition more terminally differentiated myeloid markers such as CD14, CD83, and HLA-DR can be observed (4, 5). The myeloid DC is a somewhat malleable cell that can differentiate further to exhibit an overlapping phenotypic profile with the plasmacytoid dendritic cells such as MXA, CD56, and CD123; as a result of this overlapping phenotypic profile these cells fall under the designation of an interferon dendritic cell (IF-DC). The resident dermal DCs is typically factor XIIIA positive and does not have any overlapping phenotypic features with a plasmacytoid dendritic cell and hence is not considered an interferon dendritic cell. The exact role of the peripheral blood myeloid DCs is unclear however in human blood the majority of the myeloid DCs express BDCA-1 while a minor subset express BDCA-3. The third subset express neither BDCA-1 nor BDCA-3 although exhibit positivity for CD16.

In contrast, pDC are characterized by their plasma cell-like morphology based primarily on the eccentric disposition of the nucleus, production of large amounts of Type I interferons, and expression of TLRs 7 and 9. They can express CD2 and CD7 along with MXA, an interferon alpha inducible protein and TCL1 oncogene; pDCs are characterized by their expression of CD123 although CD123 is not specific for pDCs. CD123, the interleukin-3 receptor, is found on various pluripotent hematopoietic precursor cells promoting specific lines of differentiation. One of the most specific antigens expressed by pDCs is CD303 (BDCDA2). Like the myeloid DCs, they too may also express CD83, a cell surface molecule expressed by mature DCs. It should be noted that the exact lineage affiliation of pDCs remains undefined although a lymphoid precursor seems likely. They are however distinct from mDCs; they do not express myeloid specific markers such as lysozyme, myeloperoxidase, and CD11c. They are BDCA-2 positive. Their main role is one related to enhancement of innate immunity through the elaboration of interferon alpha. Plasmacytoid dendritic cells are not involved in antigen processing. Cutaneous clonal monocyte proliferations are derived from these aforesaid cell types and accordingly have been categorized into three classes based on the nature of the proliferating cell: Class I (Langerhans cell histiocytosis), Class II (macrophage/dermal dendrocyte related histiocytoses), and Class III (malignant histiocytosis) (Cardoso F et al, 2013).

In this case, histiocytes had a very distinctive phenotypic profile, whereby they were terminally differentiated CD14-positive monocytes (Figure 11) that also showed immunoreactivity for CD68, CD11C and Factor-XIIIA, without positivity for CD83 and myeloperoxidase. A minor component of the histiocytic infiltrate, namely the somewhat pleomorphic multinucleated cell were S100 positive, although without any concomitant immunoreactivity of Langerin and CD1A. The CD34 preparation was difficult to interpret because of the extensive staining of the reticulin network and blood vessels (Figure 10). Overall, the phenotypic profile was compatible with a form of histiocytosis composed of resident dermal dendritic cell derivation (Santegoets et al, 2008). The Factor XIIIA-positive, dermal dendritic histiocytoses are defined by juvenile xanthogranuloma, xanthoma disseminatum, Rosai-Dorfman disease, generalized eruptive histiocytosis, and Erdheim-Chester disease (Verma S, 2012; Purgina B et al, 2011; Perrin C et al, 1993). The pleomorphism present amidst the histiocytes is quite characteristic for all factor XIIIA dermal dendritic histiocytoses, and especially so for juvenile xanthogranuloma and Rosai-Dorfman disease (Verma S, 2012; Singh N and Mannan AA, 2013; Perrin C et al, 1993). In addition, the presence of other inflammatory cell elements, including plasma cells and neutrophils, is also an intrinsic feature of these diseases (Verma S, 2012; Singh N and Mannan AA, 2013; Perrin C et al, 1993; Sagransky M, Deng A, Magro C, 2012). In point of fact, there is considerable clinical and histopathologic overlap between these entities.

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Another important differential diagnosis, which is not a Factor XIIIa-positive, dermal dendritic histiocytopathy, is histiocytic sarcoma. Histiocytic sarcoma is an extremely rare, malignant neoplasm exhibiting morphologic and immunophenotypic evidence of histiocytic differentiation. It is diagnosed on the basis of highly atypical morphology of tumor cells and expression of histiocyte-associated markers. Although the infiltrate in this case did have a moderately atypical morphology and did express histiocytic markers, the clinical presentation and regression of the lesions aid in the exclusion of the diagnosis of histiocytic sarcoma (Takahashi, E. and Nakamura, S., 2013). All in all, the primarily monotypic histiocytic infiltrate, the immunohistochemical profile, the lack of staining for Langerhans cell markers, the absence of xanthomatous cells, and the clinical presentation including the regressive tendency of the lesions were most compatible with a diagnosis of generalized eruptive histiocytosis (GEH) (Sagransky M, Deng A, Magro C, 2012).

GEH is a rare type of Factor XIIIa-positive histiocytopathy, characterized by symmetric distribution of red-brown papules on the trunk, proximal extremities and face. The lesions tend to regress spontaneously, leaving behind hyperpigmented macules, a finding well exemplified by this case. It is primarily a disease of adults (Fernandez-Jorge B et al, 2006). Generalized eruptive histiocytosis (GEH) is an extremely rare, benign, non-Langerhans cell histiocytosis, which was first described in 1963 by Winkelmann and Müller, amidst three adult patients (Winkelmann RK and Muller SA, 1963). There have been a few cases described in children and overall, less than 50 cases have been reported worldwide. The onset of this disease in adults is typically in third to sixth decades of life; while in children, the commencement is before the age of four. GEH manifests in red to brown papules, typically less than 1.0 cm, distributed on the trunk, proximal extremities and occasionally, the face. The papules usually have a striking symmetrical disposition and rarely involve mucosal surfaces or viscera. Within several months, the lesions resolve, leaving behind hyperpigmented macules (Winkelmann RK and Muller SA, 1963; Lan Ma H et al., 2007; Cardoso F et al, 2013). The etiology of the condition is unknown but likely reflects a clonal disorder of myelomonocytic cells. It is unclear if GEH has the same association with underlying myeloproliferative disease as conditions such as histiocytosis X (Klemke CD et al, 2003; Sagransky M, Deng A, Magro C, 2013; Montero I et al, 2012). Diagnosis is made based on histopathologic and immunohistochemical examination. Herein, we present a case of GEH in a 23-year-old man, with detailed focus on the clinical presentation and histopathology, in order to improve understanding of the diagnosis of this disease.

Recent medical literature has suggested that GEH may be divided into 2 subsets: an early, indifferent stage of other histiocytic disorders and a specific condition without a subsequent disorder (Cardoso F et al, 2013; Fernandez-Jorge B et al, 2006). GEH is generally not associated with malignancy and the characteristic regression has been postulated to be mediated by massive apoptotic cell death (Tang et al, 2006). As there are no clinical or histologic parameters that may predict a patient's development of other, more severe forms of histiocytosis, close follow-up is essential (Fernandez-Jorge B et al, 2006). We were very struck by the symmetrical nature of the eruption both in the context of the papular component and the erythrodermic element. In reviewing the literature, it would appear that the appearance manifested by this case is typical for this disorder recognizing that typical is an oxymoron in the context of a condition that is so rare. Other forms of histiocytopathy do not have this distinctive pattern of papular erythroderma.

In summation we present an exceptional rare but classic presentation of generalized eruptive histiocytosis based on a careful integration of the clinical features, light microscopic findings and phenotypic profile.

Figure Legend



Figure 1a-c: Clinical photographs showing an extensive symmetrical eruption. There is background erythema with a supervening papular component, the latter apparent on higher magnification images of the skin rash.

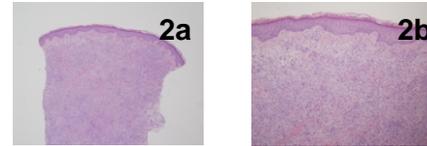
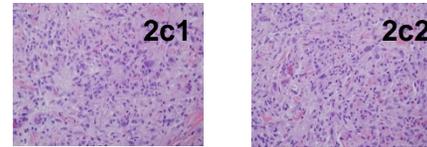


Figure 2a, b: Biopsies of patient's lesions show a dense histiocytic infiltrate in the dermis. A) hematoxylin & eosin, 100x magnification and B) hematoxylin & eosin, 200x magnification.



Figures 2c1 & 2c2: Significant pleomorphism of the histiocytes is revealed at higher magnification. Hematoxylin & eosin, 400x magnification.

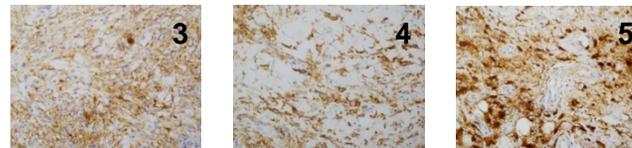


Figure 3: The histiocytes are extensively positive for CD11c by immunohistochemical staining. A) 40x magnification and B) 400x magnification.

Figure 4: The histiocytes are extensively positive for CD14 by immunohistochemical staining. A) 40x magnification and B) 400x magnification.

Figure 5: The histiocytes are extensively positive for Factor XIIIa by immunohistochemical staining. A) 40x magnification and B) 400x magnification.

Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations. The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 250 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr. Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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