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Case Report

A case of generalized eruptive histiocytosis in a 23-year-old man

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Abstract

Generalized eruptive histiocytosis (GEH) is an exceedingly rare type of Factor XIIIa-positive histiocytopathy, characterized by symmetric distribution of red-brown papules on the trunk, proximal extremities, and face. It is diagnosed by the integration of the clinical features, light microscopic findings, and phenotypic profile. Herein, we report an unusual presentation of GEH in a 23-year-old man, who had a striking papular and erythrodermic component to his lesions.

Case synopsis

A 23-year-old-man 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, were both firm and soft, and were without scale or crust. The papules were distributed symmetrically and were overlying a confluent, red-brown, smooth, erythematous skin with a serpiginous border extending from mid-calf up to his thighs (Figure 1 A,B,C). Trace pitting edema was present. 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.



Figure 1 a-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.

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 and 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 emperilopolesis by the larger histiocytic elements (Figure 3).

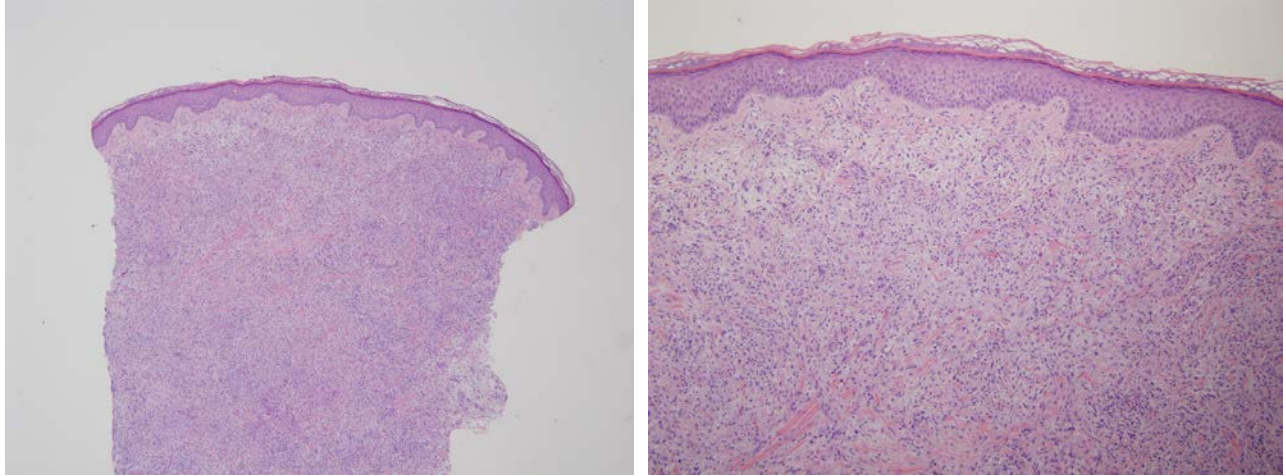


Figure 2 a,b. Biopsies of patient's lesions show a dense histiocytic infiltrate in the dermis. A) hematoxylin & eosin, 100x magnification and B) hematoxylin & eosin, 200x magnification

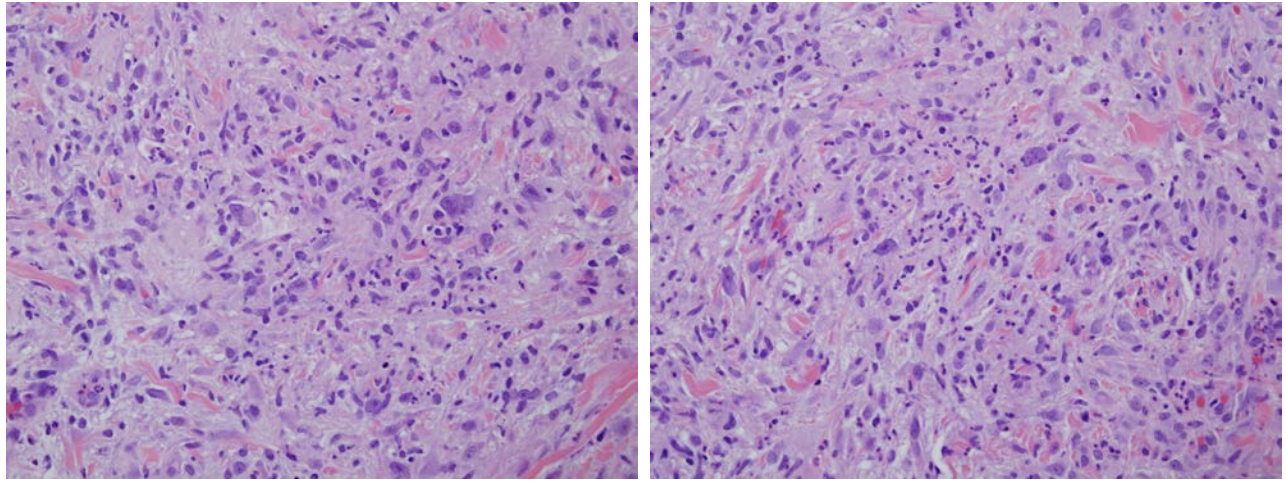


Figure 2 c, d. Significant pleomorphism of the histiocytes is revealed at higher magnification. Hematoxylin & eosin, 400x magnification

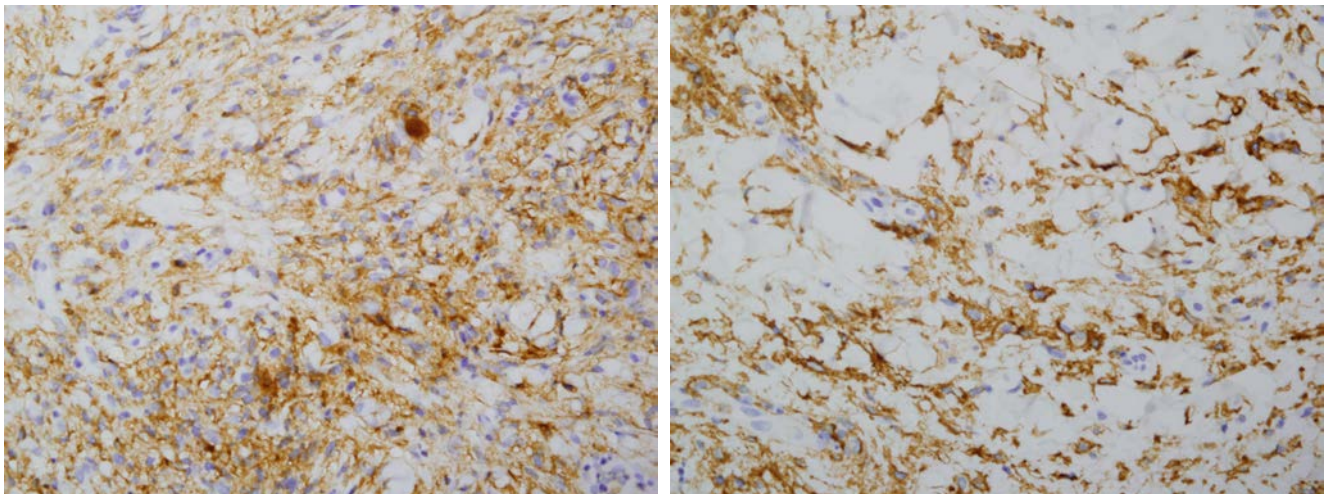


Figure 3. The histiocytes are extensively positive for CD11c by immunohistochemical staining. 400x magnification.

Figure 4. The histiocytes are extensively positive for CD14 by immunohistochemical staining. 400x magnification.

An extensive array of immunohistochemical stains was performed. The mucin deposition in the dermis was highlighted by an Alcian blue preparation. CD11C and CD14 stains highlighted the infiltrate (Figures 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 amidst neutrophils, whereas 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, but most of the infiltrate was negative. Significant immunoreactivity was not identified for CD30 or cytokeratin. Similarly, a Langerin stain was negative. There was also rather striking immunoreactivity of the infiltrate for CD34.

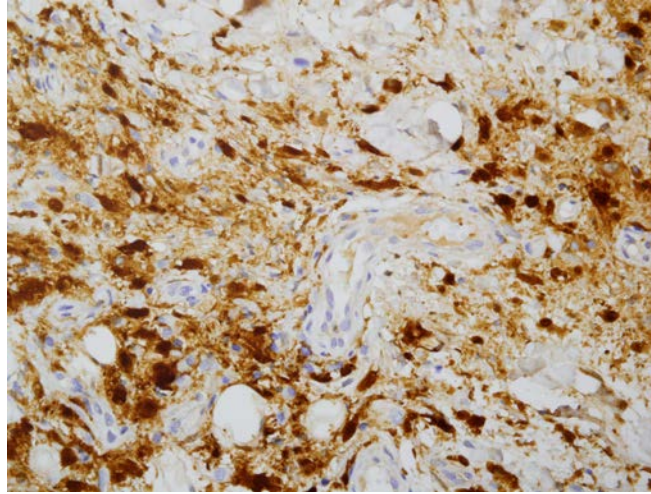


Figure 5. The histiocytes are extensively positive for Factor XIIIa by immunohistochemical staining. 400x magnification.

Discussion

The histiocytopathy syndromes are proliferative disorders of monocytes exhibiting varied terminal differentiation ranging from infiltrates of scavenger macrophage origin to monocytes with dendritic cell properties. The primary function of the macrophage is phagocytosis whereas 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 [1,2,3]. 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 mDCs exist in three main compartments and are therefore labeled as: 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 [4,5].

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) [6].

In this case, the histiocytes had a very distinctive phenotypic profile, whereby they were terminally differentiated CD14-positive monocytes 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 cells were S100 positive, although without any concomitant immunoreactivity of Langerin and CD1A [5]. The CD34 preparation was difficult to interpret because of the extensive staining of the reticulin network and blood vessels. Overall, the phenotypic profile was compatible with a form of histiocytosis composed of resident dermal dendritic cell derivation [4].

The Factor XIIIa-positive, dermal dendritic histiocytoses are defined by juvenile xanthogranuloma, xanthoma disseminatum, Rosai-Dorfman disease, generalized eruptive histiocytosis, and Erdheim-Chester disease [7,8,9]. 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 [7,9,10]. In addition, the presence of other inflammatory cell elements, including plasma cells and neutrophils, is also an intrinsic feature of these diseases [7,9,10,11]. In fact, there is considerable clinical and

histopathologic overlap between these entities. Another important condition in the 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 [5,12]. 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 [11].

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 [13,14]. Generalized eruptive histiocytosis (GEH) is an extremely rare, benign, non-Langerhans cell histiocytosis, which was first described in 1963 by Wikelmann and Müller in three adult patients [15]. 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, but 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 [6,15,16]. 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 [3,11,17]. 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 [6,13]. GEH is generally not associated with malignancy and the characteristic regression has been postulated to be mediated by massive apoptotic cell death [18]. 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 [13,19]. 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 rather unusual for this disorder, recognizing that unusual 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 [14,15,18].

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

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