Unusual variants of non-Langerhans cell histiocytoses

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Histiocytic syndromes represent a large, heterogeneous group of diseases resulting from proliferation of histiocytes. In addition to the classic variants, the subset of non-Langerhans cell histiocytoses comprises rare entities that have more recently been described. These last include both forms that affect only the skin or the skin and mucous membranes, and usually show a benign clinical behavior, and forms involving also internal organs, which may follow an aggressive course. The goal of this review is to outline the clinical, histologic, and ultrastructural features and the course, prognosis, and management of these unusual histiocytic syndromes. (J Am Acad Dermatol 2007;57:1031-45.)

Histiocytic syndromes represent a large, puzzling group of diseases resulting from proliferation of cells called histiocytes.[1]

The term "histiocyte" includes cells of both the monocyte-macrophage series and the Langerhans cell (LC) series, both antigen-processing and antigen-presenting cells deriving from $CD34^+$ progenitor cells in the bone marrow.

In 1987, the Histiocyte Society proposed a classification of histiocytic syndromes based on 3 classes: (1) class I, corresponding to LC histiocytoses (LCH); (2) class II, encompassing the histiocytoses of mononuclear phagocytes other than LC (non-LCH); and (3) class III, comprising the malignant histiocytoses.[2]

In addition to the classic variants listed in Table I, the group of non-LCH includes unusual or extremely rare disorders that have more recently been described (Table II). Indeed, among the latter, indeterminate cell (IC) histiocytosis (ICH) is a disease in which the predominant cells have the characteristics of both LC and macrophages[3] and whose actual existence as a separate entity is still debated.[4] Moreover, this heterogeneous group comprises both forms affecting only the skin or the skin and mucous membranes, such as hereditary progressive mucinous histiocytosis (HPMH) and progressive nodular histiocytosis (PNH), and forms involving also internal organs, such as Erdheim–Chester disease (ECD) and sea-blue histiocytic (SBH) syndrome (SBHS). The former usually have a benign clinical behavior, whereas the latter may follow a progressive course.

Thus, the purpose of this review is to schematically outline the clinical, histologic, and ultrastructural findings and the course, prognosis and management of these uncommon histiocytic syndromes on the basis of both our personal experience and an accurate review of the literature. The clinical characteristics, course, and management of these unusual variants of non-LCH are summarized in Table III, whereas their histopathologic, immunohistochemical, and ultrastructural features are indicated in Table IV. Markers and antibodies used for immunohistochemistry are listed in Table V.

Abbreviations used:

BCH:	benign cephalic histiocytosis
ECD:	Erdheim-Chester disease
GEH:	generalized eruptive histiocytosis
HPMH:	hereditary progressive mucinous histiocytosis
IC:	indeterminate cell
ICH:	indeterminate cell histiocytosis
JXG:	juvenile xanthogranuloma
LC:	Langerhans cell
LCH:	Langerhans cell histiocytoses
MR:	multicentric reticulohistiocytosis
PNH:	progressive nodular histiocytosis
PX:	papular xanthoma
SBH:	sea-blue histiocyte
SBHS:	sea-blue histiocytic syndrome
XD:	xanthoma disseminatum

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Table I. Classic forms of non-Langerhans cell histiocytosis, abbreviations used

GEH, generalized eruptive histiocytosis
BCH, benign cephalic histiocytosis
JXG, juvenile xanthogranuloma
PX, papular xanthoma
XD, xanthoma disseminatum
NX, necrobiotic xanthogranuloma
SHML, sinus histiocytosis with massive lymphadenopathy
MR, multicentric reticulohistiocytosis

Table II. Unusual variants of non-Langerhans cell histiocytosis, abbreviations used

ICH, indeterminate cell histiocytosis
PNH, progressive nodular histiocytosis
HPMH, hereditary progressive mucinous histiocytosis
ECD, Erdheim-Chester disease
SBHS, sea-blue histiocytic syndrome

INDETERMINATE CELL HISTIOCYTOSIS

Definition

In 1985, Wood et al[5] first described as ICH an unusual, distinctive variant of cutaneous histiocytosis whose cardinal features, distinguishing it from LCH, were: (1) lack, on ultrastructural study, of Birbeck granules; (2) absence, on histology, of epidermotropism; and (3) lack of extracutaneous involvement.

Furthermore, advances in the immunophenotypic characterization of histiocytic dendritic cells and macrophages subsequently led to the demonstration that the IC expressed both LC and monocyte/macrophage markers, ie, S-100/CD1 and CD68/CD14, respectively.[6] Various hypotheses have been proposed on the origin of IC, ie, whether IC are immature precursors of LC, LC are precursors of IC, or both are independent types of dendritic cells.[7]

Age of onset and incidence

ICH affects predominantly adults, showing no sex- or age-specific predilection, although about one third of the cases so far reported in the literature are pediatric.[4,8-15]

Since the original description of Wood et al,[5] only about 20 cases of ICH had been reported, until a recent study on a large collection that included 18 patients with ICH.[4]

Clinical findings

Two clinical subtypes seem to predominate: a solitary nodular form[11-14,16] (Fig 1, *A*) and a multiple papulonodular form[3,5,6,8-10,15,17-26] (Fig 1, *B*). The former is usually characterized by a single, soft red asymptomatic nodule about 1 cm in diameter; the latter presents with a widespread eruption of multiple, firm asymptomatic lesions ranging in size from a few millimeters to 1 cm, varying in color from dark red to brownish and covered by intact skin.

The multiple nodular form has also been documented as part of nodular scabies, a persistent reaction after acute scabies infestation, possibly representing a prolonged response of IC and lymphocytes to mite antigens.[27,28] On the other hand, the development of generalized eruptive ICH at the site of already healed pityriasis rosea has also been described, further suggesting that ICH may occur as a lymphohistiocytic reaction to various antigens.[9] However, in our view, such cases should be regarded as distinct from classic ICH.

Mucous membranes are always spared. Usually, there is no visceral involvement and the patients are in good general health.

Laboratory findings

Routine laboratory tests and radiographic investigations usually show nonabnormalities.

Histopathologic, immunohistochemical, and ultrastructural findings

Light-microscopic evaluation reveals an infiltration of histiocytic cells in the whole dermis and sometimes within the epidermis. The proliferating cells show an abundant, pale eosinophilic cytoplasm and large, irregularly folded or twisted nuclei. A few mitotic figures and multinucleated giant cells may be observed. Clusters of lymphocytes are admixed (Fig 2).

Immunohistochemically, the proliferating cells are KP1 $(CD68)^+$, S-100^+, $CD1a^+$, and factor $XIIIa^-$.[5,16,18,20,24] In summary, these cells display similar histologic and antigenic features to LC. Ultrastructurally, however, they differ in that Birbeck granules are absent.[12,18,20,24]

Course and prognosis

Based on a review of the literature that includes the recent report by Ratzinger et al,[4] 15 patients presenting with solitary lesions and showing a benign clinical course exist[11-14,16]; among these, two patients presented at birth with a solitary nodule that spontaneously regressed[12] or was removed by shave excision[13] without relapse, respectively.

On the other hand, 24 cases with widespread cutaneous lesions have been described,[3,5,6,8-10,15,17-26] the majority of which having an indolent or self-limited course; indeed, in a number of reported cases treatment and follow-up were not stated.[3,6,8,18,20,21]

Table III. Cutaneous findings, associated abnormalities, course, and treatment of unusual variants of non-Langerhans cell histiocytosis

	ICH	PNH	HPMH	ECD	SBHS
Age/sex	Adults > children	Children > adults	Heredity; beginning in adolescence or childhood; mainly women	Middle-aged and older adults	Sometimes familial; beginning in adolescents or young adults
Type of lesion	Dark-red to brownish papules or nodules	Yellow-brown or yellow-pink papules or nodules	Skin-colored, red, or yellowish papules or nodules	Red-brown papules merging into plaques; the lesions may become slack and atrophic	Nodules and waxy plaques; macular brownish hyperpigmentation
Pattern	Solitary nodular form; multiple papulonodular form	Generalized, with random distribution	Multiple lesions; symmetric distribution	Multiple lesions; symmetric distribution	Multiple lesions
Localization	No preferentially involved sites	Sometimes, prominent facial involvement	Face, hands, forearms, legs	Eyelids, axillae, groin, neck, trunk, face	Prominent facial involvement; trunk, hands, feet
Mucous membrane involvement	No	Yes (oral, laryngeal, conjunctival)	No	Yes (laryngeal, oral, conjunctival)	No
Systemic symptoms/ involvements	Usually none; possible association with hematologic disorders	Usually none; few reports of association with various systemic disorders	None	Fever, weakness, weight loss/ bone (patchy osteosclerosis), neurological, and pulmonary involvement; diabetes insipidus	Liver, spleen, bone marrow, lung, lymph node, retinal or nervous involvement
Clinical course	Usually benign; in few cases, evolution in hematologic disorders, notably leukemia	Progressive course of the skin lesions without spontaneous involution, but benign clinical behavior	Slowly spreading to other regions of the body; slowly increasing number of the lesions; no spontaneous resolution	Usually progressive, with a high mortality	Usually benign for the idiopathic form; related to that of the primary disorder for secondary forms
Management	Usually none; in few cases, various chemotherapy regimens	Intralesional and systemic corticosteroids; cyclophosphamide–all with unsatisfactory response; surgery	Usually none; in few cases, surgery	Systemic corticosteroids; radiation; various chemotherapy regimens; surgery–all usually with poor response	None

ECD, Erdheim-Chester disease; *HPMH*, hereditary progressive mucinous histiocytosis; *ICH*, indeterminate cell histiocytosis; *PNH*, progressive nodular histiocytosis; *SBHS*, sea-blue histiocytic syndrome.

Three cases with fatal outcome have, however, been described: one adult patient who died of mast cell leukemia,[24] another one with non-Hodgkin's lymphoma converted to ICH who developed terminal acute monocytic leukemia,[25] and an infant with a malignant histiocytic nonleukemic behavior.[15] A case of systemic ICH with ocular involvement, treated with polychemotherapy and corneal

Table IV. Laboratory investigations, histopathologic, immunohistochemical, and ultrastructural findings of unusual variants of non-Langerhans cell histiocytosis

	ICH	PNH	HPMH	ECD	SBHS
Laboratory findings	NS	NS (notably, normal lipid metabolism	NS (notably, normal lipid metabolism	↑ ESR; ↑ ALP	Leukopenia; thrombocytopenia; anemia
Histopathology	Dermal infiltration of HC with eosinophilic cytoplasm and folded nuclei; presence of multinucleated giant cells and lymphocytes	Dermal infiltration of HC with vacuolated clear cytoplasm; presence of Touton-like giant cells and aspects of "collagen trapping"	Dermal nodular aggregates of epithelioid or spindle-shaped HC; deposition of mucinous material	Dermal infiltration of foamy HC; presence of Touton giant cells	Dermal micronodular infiltrate of HC containing granules staining blue-green with Giemsa
Immunohistochemistry	KP1(CD68)$^{+++}$, S-100^{++}, CD1a^{+}, factor XIIIa^{-}	KP1(CD68)$^{+++}$, factor XIIIa^{+++}, CD1a^{-}, S-100^{-}	KP1(CD68)$^{+++}$, factor XIIIa^{+++}, CD1a^{-}, S-100^{-}	KP1(CD68)$^{+++}$, factor XIIIa^{++}, CD1a^{-}, S-100^{-}	KP1(CD68)$^{+++}$, S-100^{-}
Electron microscopy	LC-like HC but lacking BG	HC with indented nucleus and cytoplasm rich in ER, Golgi C, mitoch, lys, comma-shaped bodies	HC with bizarre-shaped nucleus and cytoplasm rich in myelin and zebra bodies	HC with cytoplasm filled with lipid vacuoles, cholesterol crystals, myeloid bodies, lys, phagos	Granules present as round dense bodies, and rodlike bodies

ALP, Alkaline phosphatase; *BG*, Birbeck granules; *C*, complexes; *ECD*, Erdheim-Chester disease; *ER*, endoplasmic reticulum; *ESR*, erythrocyte sedimentation rate; *HC*, histiocytic cells; *HPMH*, hereditary progressive mucinous histiocytosis; *ICH*, indeterminate cell histiocytosis; *LC*, Langerhans cell; *lys*, lysosomes; *mitoch*, mitochondria; *NS*, not significant; *phagos*, phagosomes; *PNH*, progressive nodular histiocytosis; *SBHS*, sea-blue histiocytic syndrome.

Table V. Panel of antibodies used

Marker	Dilution	Source	Main reactivity
S-100 protein*	1:400	Novocastra Laboratories Ltd, United Kingdom	Dendritic cells, including Langerhans cells, nerves, and melanocytes
CD1a	Ready to use	DAKO, Cytomation, Denmark	Dendritic cells, including Langerhans cells
KP1(CD68)	1:50	DAKO, Cytomation, Denmark	Monocytes and macrophages
Factor XIIIa*	1:400	DAKO, Cytomation, Denmark	Dermal dendrocytes, monocytes, and macrophages

A standard alkaline phosphatase anti-alkaline phosphatase complex method has been used for immunohistochemical studies.
*Polyclonal, others monoclonal.

transplantation, has recently been observed but a long-lasting follow-up was lacking.[26] In addition to the cases mentioned above, chemotherapy regimens, including vinblastine and 2-chlorodeoxyadenosine, respectively, were necessary in two other cases with extensive and disfiguring cutaneous disease despite the absence of visceral involvement.[5,17,22]

We observed two adult male patients with ICH having widespread cutaneous eruptions without evidence of systemic disease at onset.[29] In these patients, oral cyclophosphamide gave a good clinical response. However, during a 6- and a 4-year follow-up period, respectively, several recurrences occurred. These were characterized by more resistant cutaneous manifestations, and required repeated cycles with different intravenous antineoplastic regimens, including first etoposide and subsequently a combination of vinblastine and metylprednisolone. During the

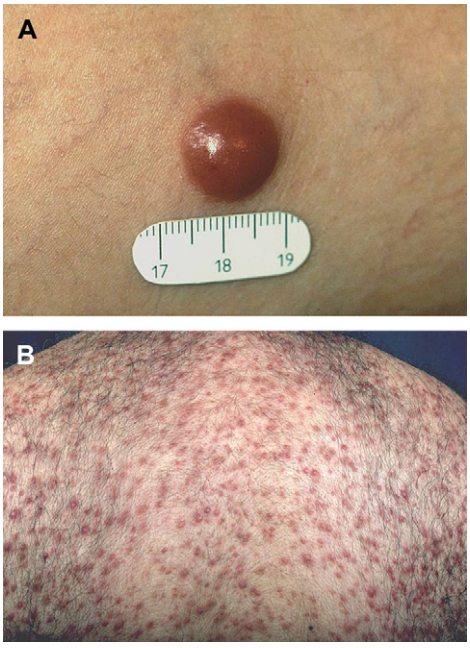

Fig 1. Indeterminate cell histiocytosis. Solitary nodular (**A**) and multiple papulonodular (**B**) forms.

last relapse, the first patient responded favorably to a course of treatment with 2-chlorodeoxyadenosine, after the above chemotherapeutic regimens had failed to induce a satisfactory clinical remission.[29] The other one developed acute myelogenous leukemia 5 years after ICH onset and died during high-dose chemotherapy, consisting of cytosine-arabinoside plus idarubicin (unpublished data). Thus, based on our experience, it seems suitable to reconsider the prognosis of ICH, its clinical course being not always so benign as thought in the past, and to strictly monitor the possible onset of an aggressive hematologic disorder.

Differential diagnosis

The cutaneous lesions observed in ICH are not characteristic. Solitary lesions are very similar to those observed in congenital self-healing reticulohistiocytosis of Hashimoto-Pritzker and in juvenile xanthogranuloma (JXG), and multiple lesions may look like those present in generalized eruptive histiocytosis (GEH) or in multicentric reticulohistiocytosis (MR).[30] A definite diagnosis of ICH is based on the histologic, immunohistochemical, and ultrastructural features of the cells constituting the infiltrate.

Management

As mentioned above, in the majority of cases the condition does not need any treatment, because its course is usually benign. However, several cases, including our two,[9] required chemotherapy regimens.[5,15,17,22,24-26]

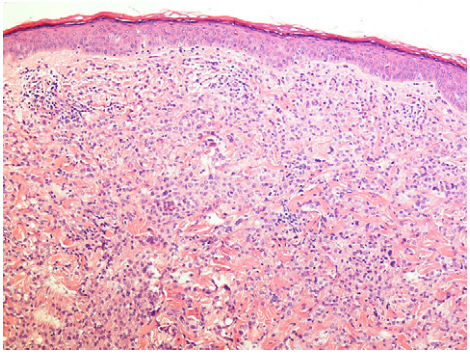

Fig 2. Indeterminate cell histiocytosis. Histology showing dermal infiltration of histiocytic cells, with scattered lymphocytes. (Hematoxylin-eosin stain; original magnification: ×100.)

Comment

Sidoroff et al[3] stated that, clinically, the multiple papulonodular form of ICH is indistinguishable from GEH, a rare non-LCH characterized by an indolent, usually self-healing clinical course. As a consequence, they speculated that GEH seems to be an early, indeterminate stage of various non-LC histiocytic syndromes, most notably including ICH, benign cephalic histiocytosis (BCH), JXG, PNH, xanthoma disseminatum (XD), and MR.

This view on non–LCH has recently been overemphasized by some of the above authors, who proposed that the prototype of this group is xanthogranuloma, all other non-LCH being only variants on xanthogranuloma.[4] Based on this unifying concept, ICH is regarded as representing various macrophage disorders identified at various time points in the inflammatory response. On the contrary, we defend the view on ICH as a separate entity; however, we suggest lumping it into a clinicopathologic spectrum where GEH, BCH, and JXG are the benign counterpart, whereas PNH, XD, and MR represent more aggressive forms or forms that can be associated with extracutaneous involvement.

PROGRESSIVE NODULAR HISTIOCYTOSIS

Definition

PNH is a normolipemic non-LCH affecting the skin and mucous membranes with no signs of spontaneous regression of the lesions. "Progressive nodular histiocytosis" is the name suggested in 1985 by one of us[30] to encompass several cases reported in the literature with similar clinical and histopathologic features,[31-34] including the first one described as "progressive nodular histiocytoma" by Taunton

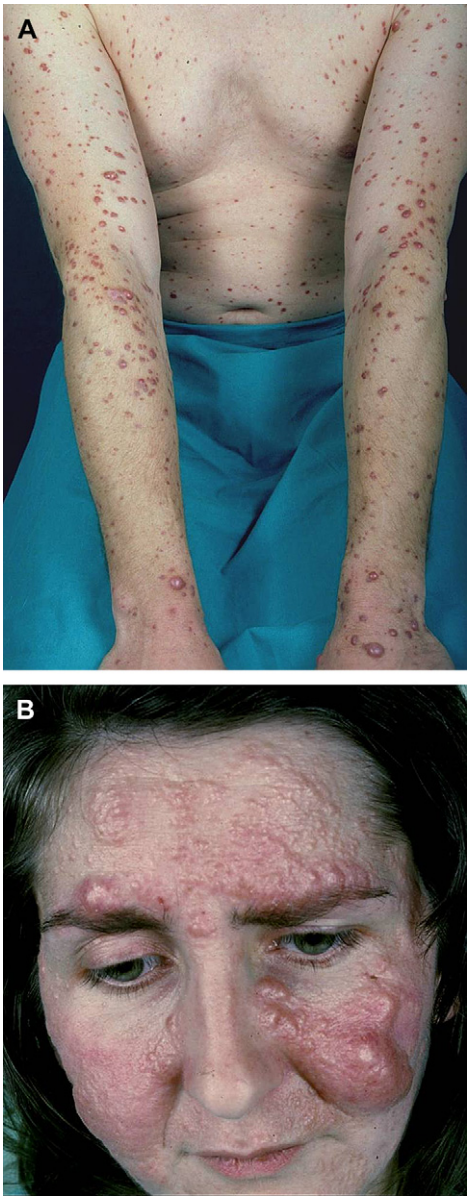

Fig 3. Progressive nodular histiocytosis. **A**, Multiple papulonodular lesions over upper extremities and trunk. **B**, Leonine appearance for coalescing of lesions on face.

et al[35] in 1978. Up until now, very few universally accepted reports of PNH existed, and these have received diverse nomenclature.[31-43]

Clinical findings

Clinically, the disease is characterized by the progressive appearance of hundreds of lesions of two different types, namely superficial papules and deep nodules[31-43] (Fig 3, *A*).

The most common lesions are yellow-brown or yellow-pink papules varying in size from 2 to 10 mm, widely and randomly distributed on the body, the flexural areas being spared. These lesions may be present in the oral, laryngeal, and conjunctival mucosae. The second type of lesion is a large dermal nodule, with overlying telangiectasia, which gives it a red-brown color. The nodules range in size from 10 to 50 mm and are more common on the trunk. Several large nodules over pressure points may show necrosis.

Neither type of lesion is prominent around the joints, but both are often seen around the genitalia.[34] Sometimes, there is a tendency for lesions to coalesce on the face, producing intense ectropion and a leonine appearance[30,32,36,38] (Fig 3, *B*).

Café au lait spots and arthritis are absent.

Laboratory findings

Laboratory findings, including cholesterol and triglyceride levels and lipoprotein values, are generally within normal limits.

Histopathologic, immunohistochemical, and ultrastructural findings

Histology shows a dermal infiltrate composed of histiocytes with abundant, vacuolated clear cytoplasm and a variable number of multinucleated, notably Touton-like, giant cells (Fig 4). Among these histiocytes, many lymphocytes and some plasma cells are observed. In some areas, a storiform pattern is seen and an appearance of "collagen trapping" as a result of splaying of collagen bundles is prominent at the infiltrate edge. In biopsy specimens taken from an older lesion, fibrosis is evident and Touton-like giant cells are nearly absent.[34,35]

Immunohistochemically, infiltrating histiocytes are strongly positive for CD68 and factor XIIIa but negative for CD1a and S-100. However, lack of factor XIIIa expression has also been found.[37]

Under the electron microscope, the histiocytes have a large indented nucleus and a scanty cytoplasm. The latter is rich in endoplasmic reticulum, Golgi complexes, and mitochondria, but also contains numerous membrane-bound, electron-dense lysosomes. In addition, there are irregularly shaped, electron-dense granules, some with a comma shape and others with a central electronlucent area. Rare lipid droplets are also seen. Birbeck granules are typically absent. One of us[33] observed intracytoplasmic granules having a unique and highly complex ultrastructure in a patient with papular histiocytosis closely resembling PNH. They had a wall consisting of two parallel unit membranes separated by a light space of approximately 150 A° and a portion formed as a result of the enlargement of the space between the two unit membranes and containing vesicles. However, these structures have not been found in PNH by other investigators.[34,37]

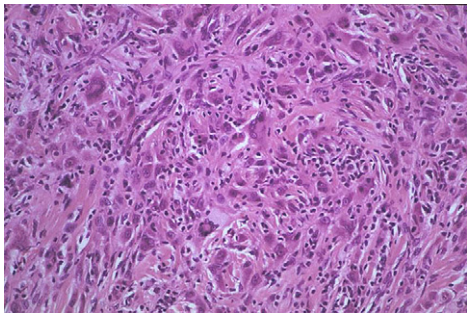

Fig 4. Progressive nodular histiocytosis. Histology revealing dermal infiltrate of histiocytes with abundant, vacuolated clear cytoplasm and several multinucleated, notably Touton-like, giant cells. (Hematoxylin-eosin stain; original magnification: ×400.)

Course and prognosis

Despite the progressive and deforming nature of the lesions with no signs of spontaneous involution, patients remain in good general health. Spontaneous regression of lesions has only occasionally been reported.[31,33,36] PNH has been reported in association with systemic disorders in two patients only: one[38] had chronic myeloid leukemia, hypothyroidism, and purine and lipoprotein metabolic changes, the other[42] was a child with precocious puberty, growth hormone deficiency, and a hypothalamic tumor.

Differential diagnosis

As stated above, PNH may be included within a clinicopathologic spectrum also comprising several entities from which PNH should be distinguished. The histologic and immunohistochemical findings in PNH are similar to those in JXG, GEH, and BCH. However, in typical JXG, one or several papules and nodules of 0.5 to 1.0 cm in diameter are present at birth or appear during the first 6 months of life and almost always undergo spontaneous resolution by 2 or 3 years of age. JXG can occur in adults, but also in adults the lesions regress spontaneously. Also in GEH, the lesions, which appear rapidly, usually clear spontaneously leaving brown macules or normal—appearing skin. Giant cells are not seen on histology. BCH can be excluded by the distribution of lesions, early onset, and lack of Touton giant cells. XD, where lesions occur in flexures and tend to coalesce, and where respiratory involvement is common, can also be excluded on clinical grounds. In MR, there is involvement of the hands and mucosal and visceral lesions and destructive arthritis. Papular xanthoma (PX) involves the skin and occasionally the mucosa. It generally resolves spontaneously after a few years.[30] Histologically, the lesions consist mainly of foamy cells, with essentially no nonlipidized histiocytes. Many intracytoplasmic lipid droplets are seen on electron microscopy. HPMH is an inherited disease. Typically, the lesions are smaller and histologic studies demonstrate the presence of mucin. Lepromatous leprosy may be ruled out because of the absence of intracellular bacilli. Finally, lipogranulomatosis of Farber is an inborn error of lipid metabolism with deposition of free ceramide and ganglioside in the brain, liver, lymph nodes, kidneys, and lungs. The disease, marked by onset in early infancy, usually follows a rapidly progressive course with lipid—laden histiocytic granulomas that involve the skin and mucous membranes. Large papules become confluent into deep nodules on the mucous membranes and around joints.[44,45]

Management

Treatments, including intralesional[34] and systemic[36] corticosteroids and cyclophosphamide, were unable to modify the progressive course of the disease. Surgical procedures were performed to remove enlarging lesions from the membrane mucous sites or the largest nodules of the face, with no evidence of recurrence.[32,34,35] Carbon-dioxide laser produced cosmetically acceptable results in one patient,[37] whereas it was followed by recurrence of the lesions over the scar tissue in another one.[38]

Comment

In our view, PNH may be considered the last stage of particular forms of other non-LCH such as GEH, PX, XD, and MR, according to the concept of clinicopathologic spectrum mentioned above.

HEREDITARY PROGRESSIVE MUCINOUS HISTIOCYTOSIS

Definition

HPMH was first described in 1988 by Bork and Hoede[46] as a new non-LCH resembling PNH in its clinical course, but differing from it by several clinical and histopathologic characteristics, notably an autosomal-dominant inheritance and mucinous degeneration.

Age of onset and incidence

The disease is very rare and affects almost exclusively women; only 11 patients from 6 different families,[46-51] in addition to two sporadic cases,[52,53] have been reported. Indeed, we observed a male patient and his daughter both affected by HPMH (unpublished data). In HPMH, the cutaneous manifestations begin in adolescence or childhood.

Clinical findings

The skin lesions consist of a few to numerous skin-colored to red-brown, pinhead to pea-sized

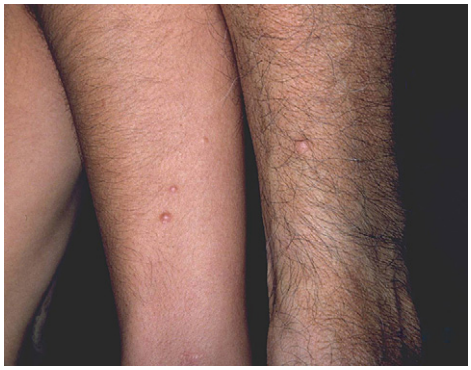

Fig 5. Hereditary progressive mucinous histiocytosis. Skin-colored to red-brown, dome-shaped nodules on forearms of father and daughter.

papules and dome-shaped nodules with a predilection to localize on the face, hands, forearms, and legs (Fig 5). The distribution is symmetric. There are no overlying telangiectases. The lesions do not tend to ulcerate or to merge into plaques. The mucous membranes are always spared. No visceral involvement has been reported.

Laboratory findings

General investigations do not show any pathologic changes. Results of extensive laboratory examinations reveal normal findings; particularly, there are no abnormalities in lipid metabolism.

Histopathologic, immunohistochemical, and ultrastructural findings

Histologically, the lesions consist of nodular aggregates of tightly packed epithelioid or spindle-shaped histiocytes with large nuclei and abundant cytoplasm in the papillary and mid dermis (Fig 6). Neither involvement of the epidermis nor inflammatory cells are seen, but a relatively high number of mast cells has been observed by some authors.[47] Moderate to extensive dermal deposition of mucinous material is demonstrated in long-standing tumors. Staining with toluidine blue reveals a marked metachromasia of the histiocytic cells. In accordance with some authors,[53] immunohistochemical studies performed by us showed positive labeling of the histiocytic cells with KP1 (CD68), and factor XIIIa, but S-100 protein and CD1a were negative. In contrast, other investigators[50] found that the histiocytes were negative for both KP1 (CD68) and factor XIII.

Ultrastructurally, the histiocytes have large, convoluted, often bizarre-shaped nuclei and one or two prominent nucleoli; the abundant cytoplasm contains numerous myelin bodies and zebra bodies, suggesting lysosomal storage phenomena, and an

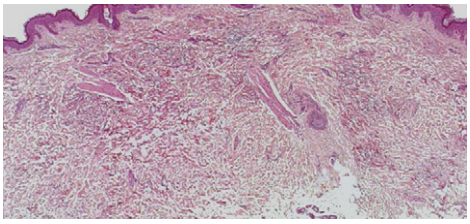

Fig 6. Hereditary progressive mucinous histiocytosis. Histologic pattern consisting of aggregates of tightly packed histiocytes in whole dermis. (Hematoxylin-eosin stain; original magnification: ×25.)

enlarged and dilated rough endoplasmatic reticulum. Typical pleomorphic granules, as described by one of us,[33] wormlike bodies, or Birbeck granules are absent.[46-53]

Course and prognosis

The disease shows a progressive course marked by a slowly increasing number of lesions, slowly spreading to other regions of the body and with no spontaneous regression; however, there is no evidence of extracutaneous illness, the general health remaining good with age.

Differential diagnosis

The main differential diagnoses of HPMH include the majority of non-LCH in addition to some nonhistiocytic disorders. In PNH, lesional cells may lipidize, contain pleomorphic inclusion bodies, and do not produce mucin.

GEH can be differentiated by onset late in life, tendency of the lesions to resolve spontaneously, predominance of epithelioid histiocytes in the lesions, and lack of mucin production. HPMH differs from MR in nearly all clinical aspects, especially the localization of cutaneous nodules and clinical course; moreover, there are no associated articular symptoms, and, histologically, the typical ground-glass appearance of the histiocytes is not observed. Among nonhistiocytic disorders, acral persistent papular mucinosis differs from HPMH in that it is not hereditary, children are not affected, and the lesions show mucinous degeneration with a scant histiocytic infiltrate.[54]

Multiple dermatofibromas are larger clinically, and multiple lesions are uncommon over the upper limbs or hands, but inheritance and mucin production in HPMH are essential diagnostic features.

Management

Considering its benign clinical behavior, most of the patients with this disease received no therapy[46,47,51]; in two cases, some of the tumors were surgically

removed for cosmetic reasons.[47,53] Indeed, in several reports the treatments were not stated.[49,50,52]

Comment

The nature of the disease is poorly elucidated. Its progressive spreading with age, with no tendency to spontaneous regression and its electron microscopy aspects, led to the assumption that HPMH might be a new lysosomal storage disease affecting solely the skin.[46,47] It has been hypothesized that the stored material was a new phospholipid, eg, a sphingomyelin that could not be detected by the methods available at that time.[46,47] On the other hand, the same authors stated that a proliferation and accumulation of macrophages as a result of an up to that time unknown stimulus could not be ruled out. Currently, the storage nature of HPMH cannot yet be confirmed.

ERDHEIM—CHESTER DISEASE

Definition

ECD is a rare, multisystem non-LC histiocytoxanthomatosis first described by William Chester[55] and Jakob Erdheim in 1930.

Age of onset and incidence

ECD primarily affects middle-aged and older adults.[55] The term "Erdheim-Chester disease" was first coined by Jaffe[56] in 1972 and, since reporting began in the literature, there have been approximately 180 cases recorded.

Clinical findings

The disease can involve almost any organ system; thus, the clinical presentation of patients with ECD differs on a case-to-case basis, mostly because of the variety of organ systems that may be involved and the level of disease activity present in each case. Radiographically documentable skeletal involvement is always present and focal bone pain, particularly involving the lower extremities, is the most common presenting symptom in patients with ECD, with an incidence of approximately 50%.[57] Indeed, many patients in whom radiographics findings are typical of ECD may be asymptomatic. Pathognomonic radiographic changes in the long bones consist of bilateral and symmetric patchy osteosclerosis involving the metaphysis and diaphysis with epiphysial sparing and loss of a clear definition between cortex and medulla. Distal femur and proximal tibia and fibula are the most frequently affected sites, whereas the disease usually spares the axial skeleton and flat bones.[57,58] In addition to the sclerotic changes, lytic lesions can be seen in up to 30% of cases.[59] Pathologic bone fracture, compression of the femoral neck, and the development of bone abscesses with cutaneous perforation have all been proposed as potential mechanisms involved in the manifestation of bone pain in ECD.[57] Second in frequency to bone involvement, diabetes insipidus, as a result of hypothalamic/posterior pituitary disease, has been reported in up to one third of patients, often preceding the diagnosis of ECD by several years.[57,59] Other neurologic involvement is rare but is often the source of significant morbidity.[57,59-61] It may manifest clinically with cerebellar signs, typically lower extremity ataxia, upper motor neuron deficits, and focal neurologic deficits.

Bilateral painless exophthalmos as a result of retro-orbital histiocytic infiltration is also common, serious cases often progressing to visual impairment. Although retroperitoneal and renal involvement occurs in one third of patients and may manifest clinically as abdominal pain, dysuria, and hydronephrosis, the majority of cases are asymptomatic.[57,58] Pulmonary involvement is uncommon, occurring in approximately 20% of reported patients, and is characterized by a progressive course commonly manifesting with dyspnea.[62] Radiographic changes consist of diffuse interstitial infiltrates and pleural and/or interlobular septal thickening.[62-64] Although uncommon, lung disease contributes disproportionately to morbidity and mortality associated with ECD, respiratory failure and cardiac failure representing the most common causes of death.[57,62] The skin involvement is present in one fourth of the cases and consists of xanthomatous lesions clinically identical to those observed in XD or PX. The cutaneous manifestations resembling XD are papules red-brown in color (Fig 7) at first and then becoming yellowish. These lesions, initially isolated, gradually tend to coalesce and merge into plaques, mostly on the main folds. The hard-elastic texture of the initial lesions tends to slowly diminish with time, and the skin may become slack and atrophic, especially on the folds and face. The distribution of the lesions is typically symmetric and the preferentially involved regions are, in order of frequency, the eyelids, the axillae, the groin, the neck, the trunk, and the face.

Skin manifestations resembling PX are more rare and consist of 2 to 15 mm, rounded, yellow to pink-yellow, asymptomatic papulonodular lesions most frequently involving the back and the head.

Laboratory findings

Laboratory findings are typically nonspecific and inconsistently include mild elevations of both erythrocyte sedimentation rate and C-reactive protein. An elevation in alkaline phosphatase has been reported in up to 19% of cases.[57]

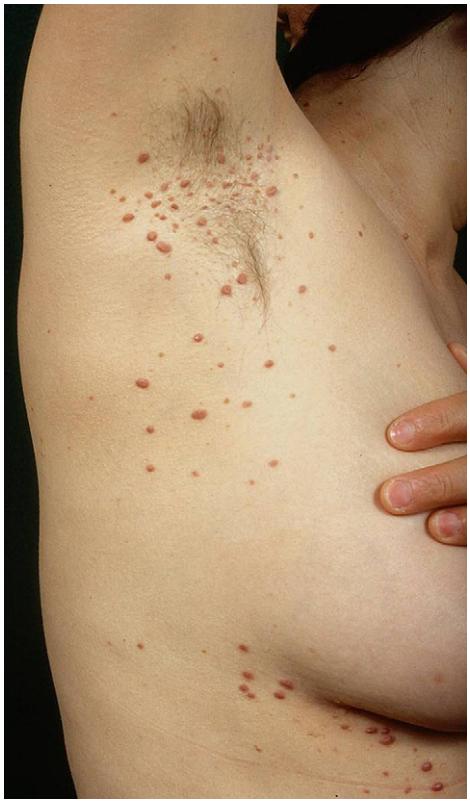

Fig 7. Erdheim-Chester disease. Red-brown papules resembling those of xanthoma disseminatum.

General symptoms of fever, weakness, and weight loss are common.

Histologic, immunohistochemical, and ultrastructural findings

Histologically, the skin lesions are characterized by a dermal infiltration that is almost entirely composed of foamy histiocytes (Fig 8) in association with small numbers of lymphocytes, plasma cells, and neutrophils. Touton giant cells are constantly present, but vary in number. Immunohistochemically, foamy histiocytes express the following immunophenotype: KP1(CD68)$^{+}$, factor XIIIa^{+}, CD1a^{-}, and S-100^{-}.

Under the electron microscope, foamy cells are characterized by an abundant cytoplasm completely filled with lipid vacuoles and sometimes containing cholesterol crystals and myeloid bodies. The majority of the histiocytes show the typical features of the macrophages, namely indented nuclei, abundant cytoplasm containing dilated rough endoplasmic reticulum, coated vesicles, and numerous lysosomes and phagosomes. These cells also display slender cytoplasm processes at the periphery. Multinucleated giant cells are produced by aggregation of these

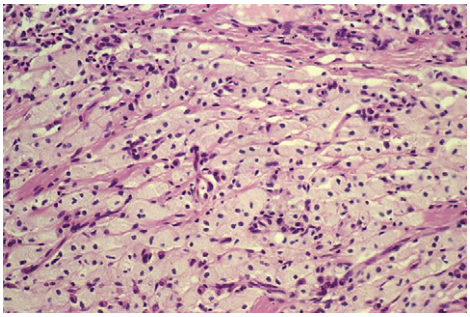

Fig 8. Erdheim-Chester disease. Histologically, skin lesions are characterized by dermal infiltration almost entirely composed of foamy histiocytes. (Hematoxylin-eosin stain; original magnification: ×400.)

macrophages. Birbeck granules are absent and comma-shaped bodies are seen only occasionally.

Course and prognosis

The course of ECD is usually progressive with a high mortality. The prognosis depends mainly on the extent and distribution of the extracutaneous disease.

In a review of 59 patients, Veyssier-Belot et al[57] reported that 22 (59%) of 37 patients with follow-up had died of the disease, 8 (36%) in less than 6 months, the mean survival duration having been just less than 3 years.

Differential diagnosis

ECD is often misdiagnosed because of its rarity and variety of end—organ involvement. The differential diagnosis is extensive and includes the diseases listed in Table VI. Among the differential diagnoses of particular interest for dermatologists, LCH may be distinguished histologically based on the characteristics of the infiltrate. This includes diagnostic LC with typical convoluted, often reniform, nucleus and abundant, slightly eosinophilic cytoplasm. Immunohistochemically, LC are positive not only for S-100 protein but also for CD1a, whereas, under the electron microscope, they contain Birbeck granules. The absence of well-formed granulomas on histology is helpful in excluding the diagnosis of sarcoidosis. Sinus histiocytosis with massive lymphadenopathy, also referred to as Rosai-Dorfman disease,[65] is a rare form of histiocytic proliferation that classically appears in childhood as massive, painless bilateral enlargement of cervical lymph nodes. Affected lymph nodes show a sinusoidal infiltrate of lymphocytes, plasma cells, and characteristic histiocytes with abundant vacuolated cytoplasm; the histiocytes are similar to those seen in ECD, differing mainly in that they frequently contain

intact lymphocytes within their cytoplasm (ie, emperipolesis). Moreover, in all the 3 disorders mentioned above, bilateral and symmetric osteosclerosis in long bones is lacking.

Management

Treatment regimens for ECD have included steroids, radiation, chemotherapy, and surgery, although no therapeutic clinical trials have been performed because of the rarity of the disease. Steroids are the most commonly used treatment modality, usually with poor response, although cases of remission of localized disease have been reported.[66] Radiation therapy has been used to shrink lesions of ECD, the rationale being based largely on its use in a similar disease such as LCH. Chemotherapy, including vinca alkaloids, anthracyclines, and cyclophosphamide, and surgical debulking of tumors have also been used but with discouraging results.[57] Effectiveness of interferon alfa in ECD has recently been reported.[67]

Comment

The origin of ECD is unknown.[68] It is undetermined whether ECD is a monoclonal proliferative disorder or whether it is a polyclonal reactive disease.[68,69] Although ECD has been known to occur in patients who also have LCH,[70] the two diseases are generally regarded as representing distinct entities. From a dermatologic perspective, ECD may be considered as a variant of XD with bone and visceral involvement and, thus, having an aggressive clinical behavior.

SEA-BLUE HISTIOCYTIC SYNDROME

Definition

In 1970, Silverstein et al[71] coined the term "sea-blue histiocyte syndrome" to describe a primitive idiopathic storage disease in which many organs were infiltrated by the so-called SBH. SBH are large macrophages whose cytoplasm is filled with granules staining blue or blue–green with Giemsa. Up until now, approximately 60 cases of SBHS have been published. In addition to the primary form of SBHS, it is now clear that there are secondary forms related to a wide variety of conditions, including diseases with a high rate of intramedullary cell death and storage diseases. The common feature is the accumulation of unsaturated lipids within histiocytes as a result of increased production or to a failure of catabolism. The former group includes various blood disorders such as chronic myeloid leukemia,[72] idiopathic thrombocytopenic purpura,[73] severe autoimmune neutropenia,[74] and myelodysplastic syndromes[75] in which cells are cleared at an increased rate by the reticuloendothelial system. The latter group encompasses a variety of inherited metabolic defects including sphingomyelinase deficiency, most notably Niemann-Pick disease.[76-78] Moreover, long-term parenteral alimentation with fat emulsion[79] and severe hypertriglyceridemia[80] have rarely been reported to produce the accumulation of SBH within the marrow. Finally, SBH have exceptionally been found in the infiltrate of mycosis fungoides.[81,82]

Table VI. Differential diagnosis of Erdheim-Chester disease

Xanthoma disseminatum
Juvenile xanthogranuloma
Langerhans cell histiocytosis
Sinus histiocytosis with massive lymphadenopathy
Sarcoidosis
Amyloidosis
Gaucher's disease
Niemann-Pick disease
Mastocytosis
Paget disease
Fluoride intoxication
Adult progressive diaphysial dysplasia
Whipple's disease
Mucopolysaccharidoses
Hermansky-Pudlak syndrome
Malakoplakia

Modified by Tashjian et al.[61]

Clinical findings

In the primary form of SBHS, the most common symptoms are hepatosplenomegaly and bone marrow involvement resulting in hemorrhagic diathesis, then lung infiltrates, lymphadenopathies, and, less frequently, retinal or nervous involvement.[83,84] Cutaneous changes are very rare, having been observed in a few patients only.[85-89] They include facial macular brownish hyperpigmentation[87] and nodular lesions.[85,86,88,89] Nodular lesions have been observed on the face, trunk, hands, and feet. Eyelid infiltrative swelling and facial waxy plaques are the most prominent cutaneous features, resulting in a puffy appearance[86] (Fig 9). The disease may be familial.[85]

Histopathologic, immunohistochemic, and ultrastructural findings

Histologically, cutaneous nodular lesions show an edematous dermis with a sparse micronodular infiltrate composed of large, pale, monomorphous histiocytes containing vacuoles and granules (Fig 10, *A*). These granules become clearly visible as inclusion bodies of varying size and shape after staining

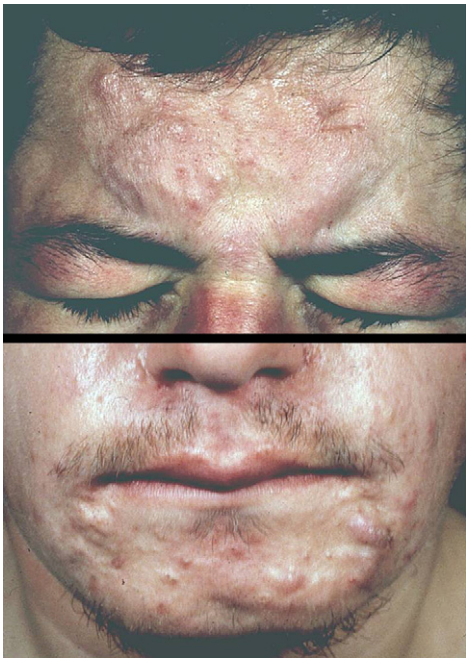

Fig 9. Sea-blue histiocytic syndrome. Facial waxy plaques resulting in puffy appearance. Courtesy of Prof M. Pippione.

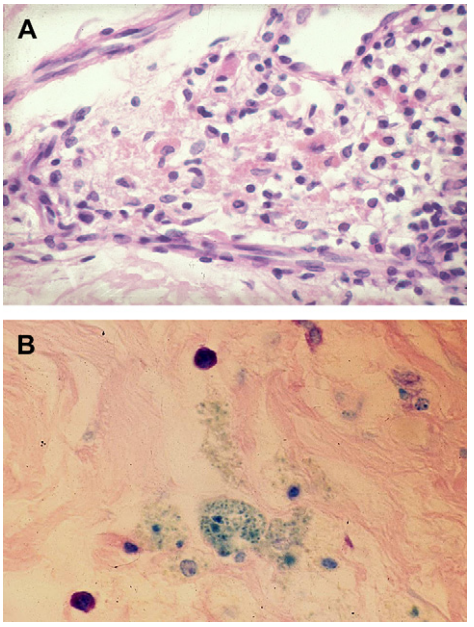

Fig 10. A, Histology of sea-blue histiocytic syndrome. Sparse infiltrate composed of large, monomorphous histiocytes within edematous dermis. (Hematoxylin-eosin stain; original magnification: ×200.) **B**, Granules within cytoplasm of infiltrating cells appear clearly visible (blue-green) after staining with Giemsa. (Original magnification: ×400.) Courtesy of Prof M. Pippione.

with Giemsa (blue-green) (Fig 10, *B*) and toluidine (dark-blue without metachromasia), and are highly birefringent under polarized light.[86] Immunohistochemically, the histiocytes are KP1 $(CD68)^{+}$ and S-100^{-}; in the literature, they have not been tested for CD1a or for factor XIIIa.

Ultrastructurally, the granules present as round dense bodies, membranous or lamellated structures, occasionally showing a fingerprint appearance, and bodies containing dense rodlike formations.[85,86] The presence of the rodlike bodies appears to be a striking feature in SBHS, although their significance and origin remain obscure.

Course and prognosis

The idiopathic form of SBHS pursues a relatively benign clinical course, usually with no progression apart from the skin lesions. In secondary forms, the course is related to that of the primary disorder.

Differential diagnosis

The main differential diagnoses of primary SBHS include the secondary forms of SBHS. This requires conditions associated with presence of SBH, notably lymphoproliferative disorders and storage diseases, to be ruled out. Because of the puffy appearance of the face observed in primary SBHS, leonine facies as a feature of mycosis fungoides should be excluded, also taking into account that SBH has exceptionally been reported in association with this disease.[81,82] Moreover, a leonine appearance is sometimes seen in PNH.[30,32,36,38] Finally, lepromatous leprosy should be considered and ruled out based on the absence of intracellular bacilli.

Management

No treatment capable of stopping the progression of the cutaneous disease has so far been reported.

Comment

The pathogenesis of the material stored within SBH is still unclear, but phospholipids, glycosphingolipids, and ceroids have been identified. Although no consistent enzymatic defect has been identified in these patients, a biochemical derangement in lipid metabolism has been hypothesized.[71,90,91]

Some authors have proposed that a partial sphingomyelinase deficiency is a possible cause of SBHS.[92,93]

CONCLUSIONS

The clinical, histologic, and ultrastructural findings and the course, prognosis, and management of 5 unusual histiocytic disorders have been reviewed. Although their classification still remains controversial, we suggest lumping all these entities into the wide group of non-LCH. In ICH, the proliferating cells express both macrophage markers, such as KP1

(CD68), and LC markers, such as S-100 and CD1a. Thus, ICH was proposed to be a separate entity showing an overlap between LCH and non—LCH. We defend the view of ICH as a distinctive entity, but we suggest including it into a spectrum comprising several classic non-LCH on the basis of the strict clinicopathologic and ultrastructural similarities between the latter and ICH.

According to this concept, PNH may be classified into the group of non-LCH, possibly representing the last stage of other non-LCH.

HPMH was proposed to be a storage disease, but this hypothesis cannot yet be confirmed. On the other hand, the dermal deposits of mucin could justify including it in the group of cutaneous mucinoses. However, this form sometimes resembling PNH in its clinical course better fits the diagnostic criteria for non-LCH. ECD could be regarded as a separate entity, distinct from non-LCH because it is a multisystem disorder. Indeed, the fact that the cutaneous manifestations of ECD are usually identical to those of XD makes it conceivable to consider it a form of non-LCH. Finally, the primary form of SBHS is considered to be a primitive idiopathic storage disease, whereas the secondary forms are related to a number of conditions, including diseases with a high rate of intramedullary cell death and storage diseases. Their common feature is the infiltration of many organs by the so-called SBH, making SBHS a true histiocytic syndrome.

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