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REVIEW
Uncommon Histiocytic Disorders: The Non-Langerhans Cell Histiocytoses

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Background. Histiocytic disorders are currently identified by their component cells. The non-Langerhans Cell Histiocytoses (non-LCH) are a group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of Langerhans cells (LCs). The non-LCH consist of a long list of diverse disorders which have been difficult to categorize. A conceptual way to think of these disorders that make them less confusing and easier to remember is proposed based on immunophenotyping and clinical presentation. ***Results.*** Clinically the non-LCH can be divided into 3 groups, those that predominantly affect skin, those that affect skin but have a major systemic component, and those that primarily involve extracutaneous sites, although skin may be involved. Immunohistochernically many of the non-LCH appear to arise from the same precursor cell namely the dermal dendrocyte. Juvenile Xanthogranuloma (JXG) is the model of the dermal dendrocyte-derived non-LCH. Other non-LCH with differing clinical presentation and occurring at different ages but with an identical immunophenotype appear to form a spectrum of the same disorder, deriving from the same precursor cell at different stages of maturation. They should be considered as members of a JXG family. Non-JXG family members include Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). ***Conclusion.*** The non-LCH can be classified as JXG family and non-JXG family and subdivided according to fairly clear-cut clinical criteria. Utilization of this type of approach will allow better categorization, easier review of the literature and more accurate therapy decision-making. Pediatr Blood Cancer 2005;45:256–264.

Key words: histiocytic disorders; Langerhans cell histiocytosis; non-Langerhans cell histiocytosis

INTRODUCTION

Histiocytic disorders are currently identified by their component cells. In the right clinical context, lesional cells that are CD1a+/Langerin+/S100+ can be identified as Langerhans cell histiocytosis (LCH) cells without looking for ultrastructural Birbeck granules. The non-Langerhans cell histiocytoses (non-LCH) are a diverse group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of Langerhans cells (LCs). Although some may have a hemophagocytic component, the definition excludes primary and secondary forms of hemophagocytic lymphohistiocytosis (HLH).

In general, the type of histiocyte that makes up the majority of a given lesion, can be matched to a counterpart in the normal developmental cycle of the histiocyte (Fig. 1). Much of this knowledge arises from study done in vitro, however, and how much is applicable in vivo is unclear. In fact, from recent studies, the view is emerging that the cells of the mononuclear phagocytic system, including LCs, may evolve from a number of different precursors including monocytes, lymphocytes and possibly even mesenchymal cells (Leenen P-personal communication). At present, however, it still appears that most histiocytes arise from the CD34+ stem cell which, driven by cytokines in the cellular microenvironment, develops along two major pathways, to CD14 negative or positive cells. The CD14− cell in the presence of TNFα and GM-CSF develops into the LC while the CD14+ cell develops either into the interstitial/ dermal dendrocyte or the monocyte/macrophage depending on the cytokine-environment [1]. There is continuing modulation between cells in the various developmental pathways, driven by changes in the microenvironment [2]. From a clinical point of view, it remains useful to divide histiocytic disorders into those

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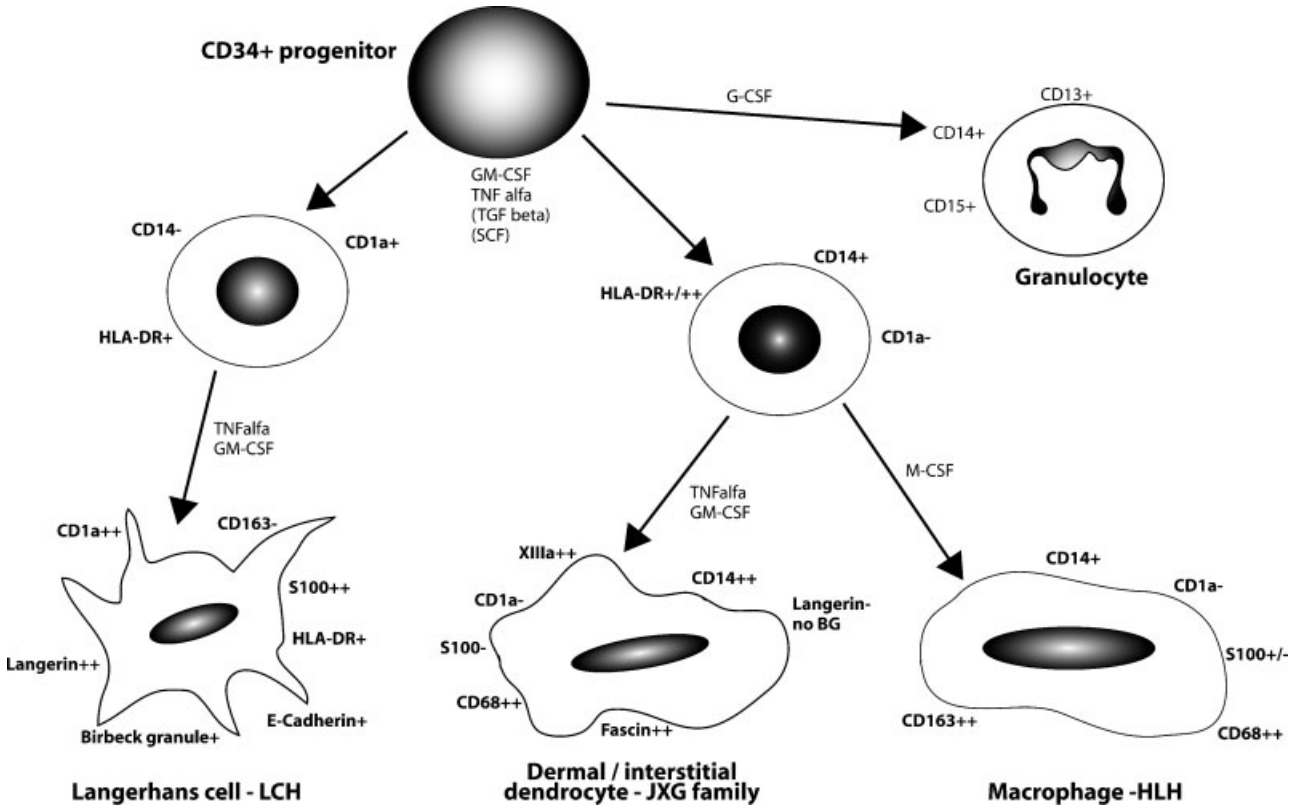

Fig. 1. Schematic representation of histiocyte developmental pathway.

arising from dendritic cells such as LCs and dermal dendrocyte and those arising from the macrophage line.

The dermal dendrocyte has as one of its hallmarks positive immunostaining for factor XIIIa and seems to be the precursor cell of many of the non-LCH [3]. The dermal dendrocyte can be found in cutaneous and extracutaneous sites, which would explain the occurrence of the extracutaneous forms of the diseases. It has been suggested that these cells should more correctly be termed interstitial dendritic cells [4].

The non-LCH are generally benign proliferative disorders which clinically can be divided into three major groups—those that predominantly affect the skin, those that affect the skin but have a systemic component as a major part of the disease, and those such as Erdheim–Chester disease (ECD) and sinus histiocytosis with massive lymphadenopathy (SHML) (Rosai–Dorfman disease) that primarily involve extracutaneous sites, although skin may be part of the disease spectrum.

THE JUVENILE XANTHOGRANULOMA (JXG) FAMILY

The non-LCH histiocytoses consist of a long list of diverse disorders, which have been difficult to categorize and even more difficult to remember. Based on study by Zelger et al. [5] and later Chu [6], we would like to propose a conceptual way to think of these disorders that make them less confusing and easier to remember. The proposal is based on studies that have shown that the lesional cell of most of the non-LCH have the identical immunophenotype, being Factor XIIIa positive, particularly at the early stages, as well as CD68, CD163, fascin and CD14 positive, S100 and CD1a negative. This suggests that these diseases form a spectrum of the same disorder and that they derive from the same precursor cell [6–8]. Zelger et al. [5], Chu [6], and others have since referred to these disorders as the JXG family. Only a few of the non-LCH appear to derive from a different cell line, the most important examples of these non-JXG family disorders are SHML (Rosai–Dorfman disease) and multicentric reticulohistiocytosis, (MRH). This concept of the JXG family is similar to what is found in LCH in which a wide spectrum of clinical forms of disease share the identical immunophenotype.

In their attempt to formulate a unifying concept for the non-LCH, Zelger et al. [5] described five major morphologic types of histiocytes namely scalloped, vacuolated, xanthomatised, spindle-cell, and oncocytic [5]. They found that JXG is usually polymorphous with all five types of histiocytes recognizable morphologically, and that the other cutaneous histiocytoses are usually largely monomorphous and could be defined by a specific histiocyte, as well as by the clinical features of the disease. Chu [6] took the concept forward by suggesting that the various cell types form a continuum along a pathway

of maturation, from the early scalloped cell through vacuolated to xanthomatized to the mature spindle shaped cells (Fig. 2). Chu also suggested that the more mature the histiocyte, the more resistant the disease to adjuvant therapy. Thus he felt that benign cephalic histiocytosis (BCH), generalized eruptive histiocytosis (GEH) and JXG represent the most immature end of the spectrum, occurring earlier in life and presenting with disease that usually resolves spontaneously. At the more mature end of the spectrum is xanthoma disseminatum (XD) in which the disease resolves but usually only after many years, and at the later stage is dominated by spindle-shaped histiocytes. At the extreme end of the spectrum is progressive nodular histiocytosis (PNH), a disease of mature spindle-shaped cells, which is very resistant to treatment [9]. The disease is progressive and although spontaneous involution may occur after many years, patients may be left with severe disfigurement [8,10]. Although these concepts remain unproven, considerable evidence exists to support them. Numerous cases have been described that show one type of lesion beside another [11,12], as have patients with lesions that follow a time cycle with progression from immature histiocytes to the more mature cells [13–15]. Lesions of BCH have been shown pathologically to mature to lesions typical of JXG, and some authors now refer to BCH as early JXG [8]. Similarly GEH has been shown to be a precursor of JXG, XD, and of PNH. Finally strong expression of MS-1 protein, a high molecular weight protein specific for sinusoidal endothelial cells and dendritic perivacular histiocytes, was found in all non-LCH cells tested, but not LCH. The strong cytoplasmic MS-1 expression in small lesional histiocytes, with expression confined to a rim surrounding the xanthomatized center of large xanthomatoid and multinucleated cells, also suggests a common maturation pathway for these cells and for these disorders [5]. A similar picture has been seen in LCH with recurrences, sometimes years later at the site of an earlier proven LCH lesion, but with a phenotype that suggests that the constitutive cells are more mature than the previous LCH cells, with loss of CD1a/Langerin, upregulation of surface HLA-DR, and increased fascin expression (Jaffe R, personal communication).

If we accept the concept that disorders that are clinically present quite differently may be due to the same basic cell type at different stages of maturation, then the long list of non-LCH disorders may be made more understandable and certainly easier to remember and to teach, by considering them in the context of early, middle and late maturation stage as schematically represented in Figure 3.

Whether histiocyte morphology can be used for pathologic diagnosis however as suggested by Zelger [3] is controversial, and some pathologists believe that the morphology is too variable to be used in this fashion, as might be expected if the diseases are occurring from cells at varying stages along a continuum.

DIAGNOSIS OF THE NON-LCH

Histopathology

Histopathology is used to diagnose the presence of a non-LCH, but differentiation between the different subtypes is based mostly on immunohistochemistry and the clinical setting.

The basic histopathology of the non-LC histiocytoses shows well circumscribed nodules with a dense infiltrates of histiocytes. Those that involve skin usually mainly infiltrate the dermis. Present in the lesions are multinucleate giant cells in variable numbers, and there is a variable degree of predominantly perivascular and perilesional inflammatory cells. Touton giant cells (seen in 85% of cases of JXG, in a recent series) [15], but not limited to JXG, are characterized by a wreath of nuclei around a homogenous eosinophilic cytoplasmic center, while the periphery shows prominent xanthomatization. Electron microscopy has revealed a variety of non-specific organelles including dense bodies, worm-like bodies and popcorn bodies amongst others [16]. In MRH and solitary reticulohistiocytoma multinucleate giant cells and histiocytes containing an eosiniphilic ''ground glass'' material are characteristically found [8,10].

Immunohistochemical Differentiation

The diagnosis is made by subdividing the non-LCH disorders initially according to their immunohistochemical characteristics. In this way, histiocytic lesions are divided into LCH, JXG family, and those that are neither LCH nor JXG family. Thus lesional cells, taken in context, that are positive for factor XIIIa, CD68, CD163, fascin, CD68, and CD14 and that are negative for CD1a, S100, Langerin and/or Birbeck granules are diagnostic of the JXG family. MRH, on the other hand is defined by histiocytes and multinucleated giant cells that are factor XIIIa negative, CD68 positive and appear to derive from the macrophage line, as do the constitutive S100+ cells of SHML (Rosai–Dorfman disease).

The final group of conditions that lack markers for LCH, JXG, or macrophage lineage, but are clearly dendritic in nature have been referred to as dendritic cell histiocytosis when CD1a negative [17], and as indeterminate cell histiocytosis when they are CD1a positive but lack Birbeck granules on EM. Cases usually occur de novo but lesions occurring at the same site as previous LCH but which appear to have lost the CD1a positivity, have been seen (Jaffe R, personal observation). In a small group of cases, there appears to be more local recurrence than would be expected for LCH [17].

The histiocyte morphology will be most helpful in excluding non-JXG solitary lesions such as reticulohistiocytoma. It is tempting to suggest that all other solitary lesions in the JXG family such as spindle-cell and

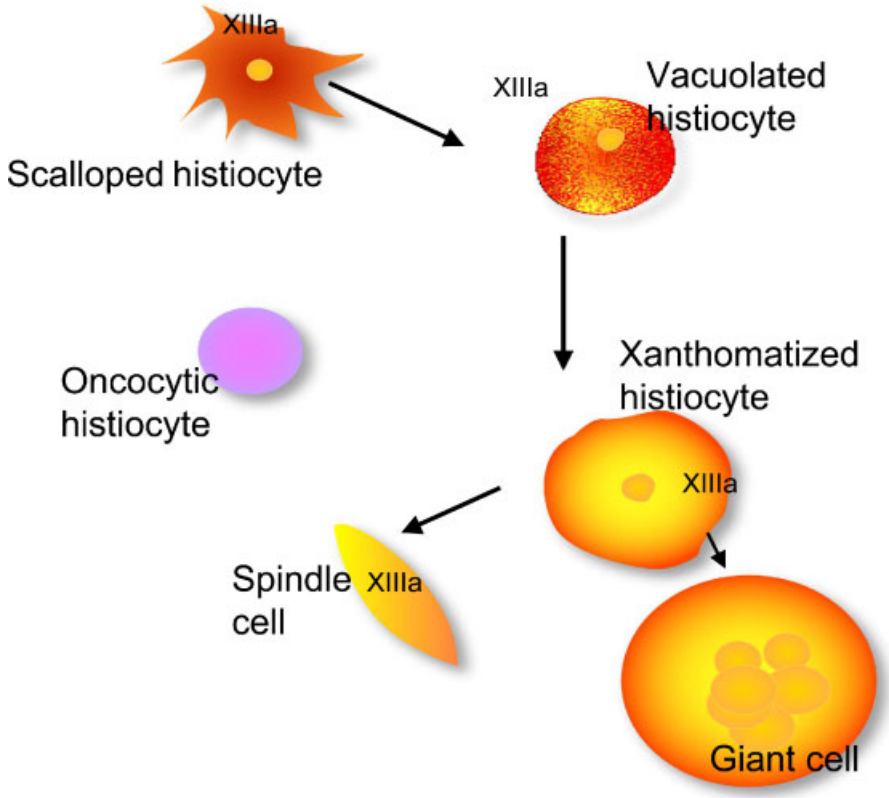

Fig. 2. Schematic representation of suggested maturation pathway of lesional histiocytes of the non-Langerhans cell histiocytosis (Non-LCH) [3,6]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

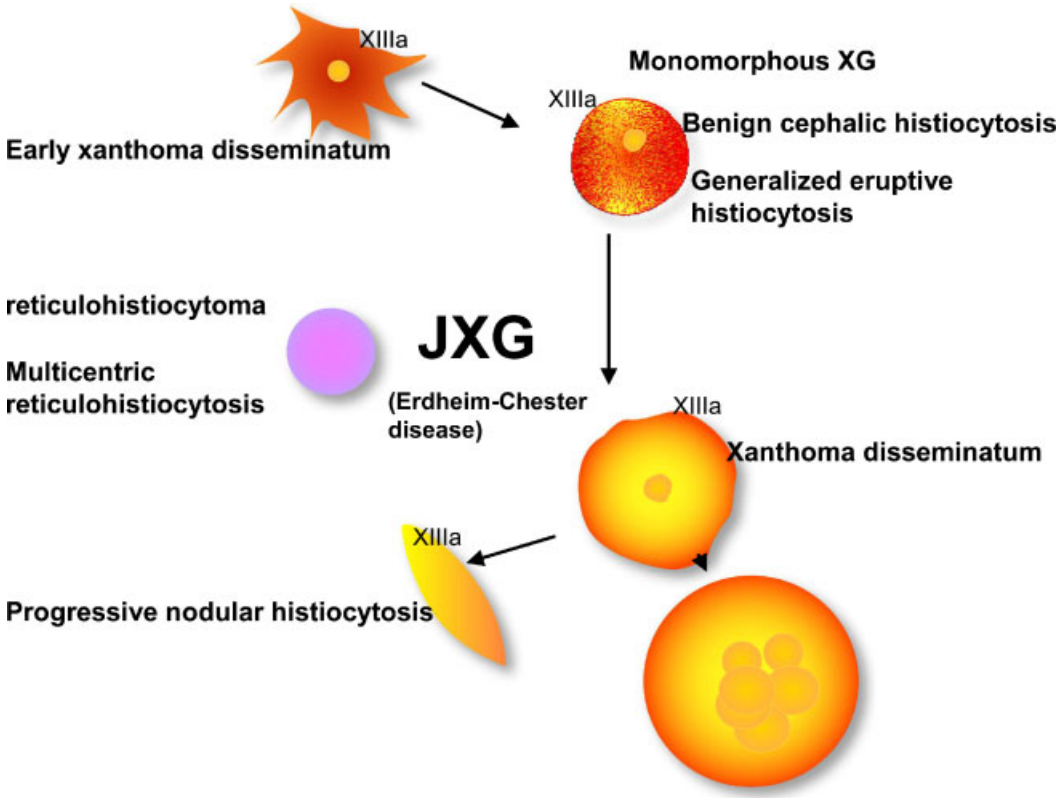

Fig. 3. Schematic representation of juvenile xanthogranuloma (JXG)-family by stage of histiocyte maturation [3,6]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

scalloped cell xanthogranulomas, simply be called solitary xanthogranuloma irrespective of histiocyte morphology. The therapy for all solitary lesions is primarily surgical excision and subdivision appears to serve no useful function.

Clinical Diagnosis

Once the diagnosis of ''JXG family'' is made on immunohistochemistry, the various diseases can be defined by the clinical setting, that is, whether they are solitary, multiple, or disseminated, the areas of the body involved and the age of the patient (Tables I and II) [8,10–12,15,16,18–29].

Thus, JXG is divided into cutaneous and extracutaneous forms. Multiple cutaneous lesions confined to the head and neck area in a young child is BCH, multiple skin lesions occurring in adolescence or young adults with prominent involvement of flexures as well as viscera and mucosa, and comprising mainly xanthomatized cells is XD, multiple lesions appearing in crops, generally sparing the flexures and occurring in normolipemic patients is GEH, while multiple lesions arising in skin of an older patient and progressing to form large nodules, with no evidence of spontaneous regression and comprising mainly spindle-shaped histiocytes, is PNH [5,6].

The reason for the variations in presentation of what appears to be the same disorder, may be due to differing immune responses to what may essentially be the same initiating factor/s. Cytokines can activate macrophages and modulate their phenotype, and the clinicopathologic variations seen are likely to be due to differing ''cytokine microenvironments'' [5]. A variation in host response could explain the predilection of specific diseases according to the age and gender of the patient. Thus, the majority of BCH and JXG occur in young children, XD characteristically affects males in their late teens or early twenties, PNH affects elderly patients of either gender [5], and MRH usually begins in the fourth decade and predominantly affects women [30]. All of these disorders have been rarely described in children however.

TABLE I. Non-Langerhans Cell Histiocytoses

Cutaneous non-LCH
The Juvenile xanthogranuloma family
Benign cephalic histiocytosis
Juvenile xanthogranuloma
Generalized eruptive histiocytoma
Adult xanthogranuloma
Progressive nodular histiocytosis
Non-JXG cutaneous histiocytoses
Solitary reticulohistiocytoma
Non-LCH dendritic cell histiocytosis
Indeterminate histiocytosis
Cutaneous with a major systemic component
JXG family
Xanthoma disseminatum
Non-JXG family
Mulicentric reticulohistiocytosis
Systemic non-LCH
JXG family
Erdheim–Chester disease
Non-JXG family
Sinus histiocytosis with massive lymphadenopathy (R-DD)

All of the disorders considered here are uncommon and pose significant diagnostic challenges. From a clinical point of view, however, they share some important characteristics [6,8].

In general, non-LCH in very young children are usually widespread but tend to be benign and self-limited. However, fatalities do occur in a minority of patients with systemic JXG (see later). With increasing age, JXG is more likely to be present as a solitary lesion but most still involute spontaneously.

In adults, non-LCH including adult XG, most commonly occur as solitary lesions which tend however, not to undergo spontaneous involution. The majority are cured by excision. Generalized lesions in adults are less common, but when they occur they rarely regress spontaneously, and chemotherapy and radiation therapy often have no or little impact on the course of the disease [6]. Finally, all of these disorders may be associated with underlying infectious, autoimmune or malignant diseases, the likelihood of which increases with increasing age [5] and is most commonly seen in MRH [10].

Cutaneous Non-LCH Disorders

Juvenile xanthogranuloma (JXG). JXG is the commonest of the non-LCH.

It is a benign proliferative disorder which usually resolves spontaneously. The pathogenesis is unknown, and the initiating stimuli may be one of many infectious or physical factors [11,31].

JXG is a disease of the young child. Median age of onset is 2 years [15], but lesions may be present at birth. Most JXG presents with solitary lesions which vary in size, but children less than 6 months of age tend to present with multiple lesions with a predisposition for the head and neck. The male preponderance is much higher (12:1) in young infants with multiple skin lesions [15].

JXG is associated with other diseases including neurofibromatosis type 1 and juvenile chronic myelogenous leukemia [32], today more correctly called juvenile myelomonocytic leukemia (JMML). In these patients the JXG usually precedes or occurs at the same time as the JMML. Cutaneous JXG usually follows a benign course with gradual involution months to several years [11]. Lesions may resolve completely or may leave a residual atrophic or hyperpigmented scar.

Extracutaneous involvement occurs in around 4% of children [15] and 5%–10% overall [19]. Median age at

TABLE II. Clinical Features Important in Diagnosis of the Non-Langerhans Cell Histiocytoses

Diagnosis	Age range	No. of lesions	Appearance	Sites of predeliction	Natural history
JXG	0–18 (median 2 years)	Single:multiple 9:1	Reddish progressing to yellow brown	Head and neck can be any site	Gradual involution
	<6 months, >M	Multiple-disseminated	Same	Same	Involution
Giant JXG	Young >F	Single	>2 cm	Upper extremity/ upper back	Involution
Systemic JXG (4% of JXG)	Median age 0.3 years	Single to multiple	Almost 50% have no skin lesions	Subcutis, liver, spleen, lung, CNS, ocular (iris)	May involute N.B. CNS, ocular JXG fatalities 4%–10%
Adult XG	18–80 (median 35 years)	Single	Same as JXG	Upper body (not legs)	No involution
BCH	Young child	Few to multiple	Reddish-tan papules	Head and neck	Involution or progression to XG
GEH	Young adult	Multiple-disseminated	Reddish-tan papules appears in crops	Face, trunk, arms spares flexures	Involution or progression to XG, XD, PNH
PNH	40–60 years M & F	Multiple-disseminated	1. Xanthomatous skin 2. Deeper subcut nodules	Any	Progression to disfigurement
XD	Late teen-young adult usually <25 years, >M	Disseminated	Yellow/reddish brown grow forming plaques and nodules	Any skin, eyelids flexures, mucosae viscera inc. CNS transient DI	Slow involution over years or progression rare fatalities
MRH	40+ >F 85% white	Multiple	Pink-reddish brown or yellow	Dorsum hands, 'coral bead' peri-ungual vermicular around nostrils face, pinna, arms, legs Symmetric erosive polyarthritis-usually precedes rash	Progression may involute after years Disabling arthritis in some patients
ECD	7–84 (mean 53 years)	Mainly systemic	Xanthelasma xanthoma	Symmetrical long bone sclerosis proptosis, lung, kidney retroperitoneal fibrosis, CNS including DI	High fatality rate—lung fibrosis resp/ cardiac failure
SHML	Mean 20.6 years wide range	Mainly systemic	Firm indurated papules	Cervical adenopathy 80% "B"symptoms 43% extranodal—skin, soft tissue, upper resp bone, eye, CNS (dural-based),other	Exacerbations and remissions often self-limited (years) 5%–11% fatalities

JXG, juvenile xanthogranuloma; BCH, benign cephalic histiocytosis; GEH, generalized eruptive histiocytosis; XD, xanthoma disseminatum; PNH, progressive nodular histiocytosis; MRH, multicentric reticulohistiocytosis; SHML, sinus histiocytosis with massive lymphadenopathy; ECD, Erdheim–Chester disease.

presentation is 0.3 years [19]. Almost half of the patients have no associated skin lesions. The commonest site of extracutaneous involvement is a solitary mass in the subcutis and/or deeper soft tissues (deep JXG) [15] followed by liver, spleen, central nervous system (CNS), and lung (systemic JXG) [15,19,33]. Most systemic lesions undergo spontaneous involution, however, ocular and CNS involvement may cause significant problems. Fatalities have been reported in systemic JXG. In one series, 2 of the 36 children died of progressive CNS disease [19], while in another 2 neonates died of hepatic failure [15]. Ocular JXG occurs in the very young child, with 92% of patients being less than 2 years of age, and may occur without concomitant skin involvement [34]. Eye involvement is usually but not always unilateral, and commonly presents with an asymptomatic iris tumor, a red eye with signs of uveitis, unilateral glaucoma, spontaneous hyphema, or heterochromia iridis [32]. Other areas of the eye may be less commonly involved. Early diagnosis and treatment determine the final visual

outcome. The diagnosis should not depend on finding typical skin lesions, and JXG should be part of the differential diagnosis of young children presenting with unilateral hyphema, glaucoma, or exophthalmos.

BCH

BCH is a rare histiocytic disorder, which heals spontaneously and is not usually associated with systemic involvement. BCH may be an early version of JXG [8]. Patients are typically young children with multiple tan papules on the cheeks, forehead and upper trunk. One patient with BCH and diabetes insipidus is described [35], but the condition is usually benign, self limited, and requires no therapy.

GEH [16,36,37], and PNH [8,38], are members of the JXG family that occur mainly in adults with rare descriptions in childhood. GEH is likely an early manifestation of some of the other members of the JXG family and must be distinguished from the eruptive histiocytomas associated with hyperlipidemia. The major clinical features of all the disorders are summarized in Table II.

CUTANEOUS HISTIOCYTOSIS WITH A SIGNIFICANT SYSTEMIC COMPONENT

JXG Family

XD [21,22] is a disorder with widespread cutaneous xanthomatous lesions which tend to involve flexural areas. It characteristically has a prominent mucosal and visceral component. XD patients tend to be younger at presentation most being less than 25-years-old. Ocular, CNS, and meningeal involvement can cause significant morbidity (DI, exophthlmos, hydrocephalus, ataxia), but the DI tends to be transient. Upper respiratory tract involvement can cause airway obstruction.

Non-JXG Family

Multicentric Reticulohistiocytosis (MRH). MRH is a rare multisystem disorder characterized by cutaneous involvement and a destructive osteoarthropathy. MRH is a disease of older adults, predominantly female, 85% of reported adults were white [22]. Rare cases in children have been described [23,39]. The disease is associated with underlying malignancy in about 28% of cases, hyperlipidemia in 30%–58%, and autoimmune disease in 6%–17% [23,24,40]. Clinically 2/3 present with arthritis, with skin lesions appearing at an average of 3 years later. In 20%, the skin nodules which are firm, flesh-colored to red, brown or yellow papules are the presenting feature [23]. Pathognomonic lesions are ''coral bead'' periungual papules, papules on the pinna and vermicular lesions bordering the nostrils [10]. Fifteen [39] to 50% [24] progress to a mutilating osteoarthropathy and disabling deformities. Some patients, including most of the children, have self limited disease with non-deforming arthritis [23].

SYSTEMIC NON-LCH DISORDERS

JXG Family

Erdheim–Chester Disease (ECD). ECD is a rare histiocytic disorder which morphologically and imunohistochemically appears to be a member of the JXG family that involves the long bones in a characteristic bilaterally symmetrical fashion [27,29]. It is distinguishable from LCH (S100+, CD1a+, Langerin+/Birbeck granules present) by the characteristic XG immunostaining (factor XIIIa+, CD68+, CD163+, fascin+, S100−, CD1a−, Langerin−, Birbeck granules absent). The typical skeletal involvement and X-ray findings distinguish ECD (predominantly middle-aged adults, mean age 53 years) from systemic JXG (mainly young children) since both have identical immunophenotyping. Pediatric cases of ECD have been rarely described, including a 20-month-old child seen by one of the authors (RJ).

Characteristic features of ECD are thus bilateral symmetrical long bone involvement [41], associated with extraskeletal organ involvement in more than 50% of cases. These include kidney, retroperitoneum, skin, brain, and lung in decreasing order of frequency, while retroorbital tissue, pituitary gland, and heart are involved less frequently. Skin findings include pruritic rash, xanthelasma and periorbital xanthomata in the face of normal plasma lipids. Other manifestations include bilateral exophthalmos, sometimes with visual impairment, pituitary involvement presenting with diabetes insipidus in 30% of cases and CNS disease resulting in neurologic defects including ataxia, behavioral disorders and even spastic paraplegia [42]. Dysuria, abdominal pain and bilateral nephromegaly from renal/ureteral obstruction by retroperitoneal fibrosis may occur. The prognosis of ECD appears to be significantly worse than that reported in other histiocytoses. In one review, 22 of 37 patients died of progressive disease, with a mean follow-up of less than 3 years, despite therapy. The cause of death in the majority appeared to be lung fibrosis leading to respiratory or cardiac failure [28,29] or renal failure from retroperitoneal fibrosis.

SYSTEMIC (EXTRACUTANEOUS) NON-LCH THAT ARE NOT JXG FAMILY

SHML (Rosai–Dorfman Disease)

SHML or Rosai–Dorfman disease is a non-neoplastic, polyclonal, usually self limited disease due to accumulation of S100+, CD1a−, CD68++, Fascin++, CD163++ histiocytes [43]. Pathologically, lymph nodes show massive sinus infiltration of large histiocytes admixed

with lymphocytes and plasma cells. Intact erythrocytes, lymphocytes, and plasma cells may be engulfed by histiocytic cells, a process known as emperipolesis [25]. Although emperipolesis is not unique to this condition, its occurrence in histiocytes that express S100 in the appropriate clinical and pathologic setting, is considered diagnostic of SHML. The mean age of onset is 20.6 years, but with a wide age distribution [25].

The commonest presentation is with bilateral painless cervical adenopathy associated with fever, night sweats, malaise, and weight loss. Other nodal groups may also be involved [26] and involvement of extranodal tissue such as skin, soft tissue, upper respiratory tract, bone, eye, retroorbital tissue and other sites is found in 43% of cases, and may be present without the peripheral lymphadenopathy [26,44]. Involvement of CNS poses a significant diagnostic and therapeutic challenge, usually occurring without extracranial lymphadenopathy and clinically and radiologically resembling meningioma [45,46]. While skin involvement occurs commonly, disease limited to skin is uncommon and is generally known as cutaneous Rosai–Dorfman (CRD) disease rather than SHML, which implies nodal involvement. CRD has a benign course with spontaneous resolution in most. The clinical course of SHML is unpredictable with episodes of exacerbation and remission which may extend over many years. The outcome is usually good and disease is often self limiting, nonetheless about 5% of patients die from disease. A subset of patients with immunologic abnormalities at or prior to presentation, have a less favorable prognosis [26]. The management was recently reviewed [47].

CONCLUSION

The non-LC histiocytic disorders may be clinically divided into those mainly affecting skin (the cutaneous histiocytoses), those with skin plus a major systemic component, and those that are mainly systemic.

The non-LC histiocytoses comprise a wide variety of uncommon diseases. Despite their clinical diversity, the majority appear to originate from a common precursor and to form part of a spectrum of a single disorder. Subdividing them initially according to immunohistochemical criteria into JXG family members and non-JXG, and then applying fairly clear-cut clinical criteria, makes diagnosis and decisions with regard to therapy easier.

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