

Histiocytoses.

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Summary

The histiocytoses are diseases caused by the proliferation of histiocytes in various organs, including the skin; they have a very variable clinical spectrum and prognosis ranging from an often fatal multisystem involvement to a self-healing single lesion in a single organ. The classification of histiocytosis, which is based on the origin cell and malignancy potential, divides them into Langerhans cell histiocytosis (Class I), non-Langerhans histiocytosis (Class II) and malignant histiocytosis (Class III). In each of these classes numerous clinical forms have been described, but these forms according to some Authors only represent different developmental stages of the same disease. Letterer-Siwe disease is the most frequent form among Class I histiocytoses and juvenile xanthogranuloma and Rosai-Dorfman disease are the most frequent forms among Class II Histiocytoses. In Class I histiocytoses the histologic examination is not able to distinguish between severe and mild forms; the observation of the skin lesions can help in this differentiation.

Key words

Histiocytosis, Langerhans cell, Letterer-Siwe disease, Hashimoto-Pritzker disease, Langerhans cell histiocytoma, juvenile xanthogranuloma, cephalic histiocytosis.

The histiocytoses are diseases caused by the proliferation of histiocytes in different organs; they have a very variable clinical spectrum and prognosis ranging from an often fatal multisystem involvement to a self-healing single lesion in a single organ. The stem cell from which the histiocytoses derive is a bone marrow CD34+ cell; from the latter under the influence of environmental cytokines derive CD1a+, S-100+, langerin+ Langerhans cells, macrophages that take different names depending on the tissue in which they reside and finally dermal dendritic cells with some phenotypic aspects of antigen presenting cells and of monocytes and macrophages, but CD1a negative. The classification of histiocytosis, which is based on the origin

cell and malignancy potential, divides them into Langerhans cell histiocytosis (Class I), non-Langerhans histiocytosis (Class II) and malignant histiocytosis (Class III).

Langerhans Cell Histiocytosis (Class I)

It includes the clinical diseases known as Letterer-Siwe disease, Hand-Schuller-Christian disease and eosinophilic granuloma of bone, gathered in the chapter of the so-called histiocytosis X; to these three clinical pictures it was added in 1973 another clinical picture known as Hashimoto-Pritzker disease (38). Before treating these diseases separately, let's see some general

characteristics, bearing in mind that the major differences are found in their clinic, while it is virtually impossible to distinguish between them from a histopathological point of view.

Etiology. No environmental factors responsible for the disease are known, but an epidemiological study of 177 cases (37) of Langerhans cell histiocytosis (LCH) highlights the possible role of maternal urinary infections, nutritional problems and blood transfusions in the first month of life. As regards the possible role of genetic fac-

tors there are reports discussing clinically identical LCH in monozygotic twins (44), mutations of B-RAF (61) and expression of the p16 protein (66).

Histopathology. The histologic appearance of the Langerhans cell (LC) is characteristic (Fig. 2): large size, 20-30 microns in diameter, abundant eosinophilic cytoplasm, nucleus with lax chromatin and a more or less profound incision for which its look varies from bean-shaped to lobulated.

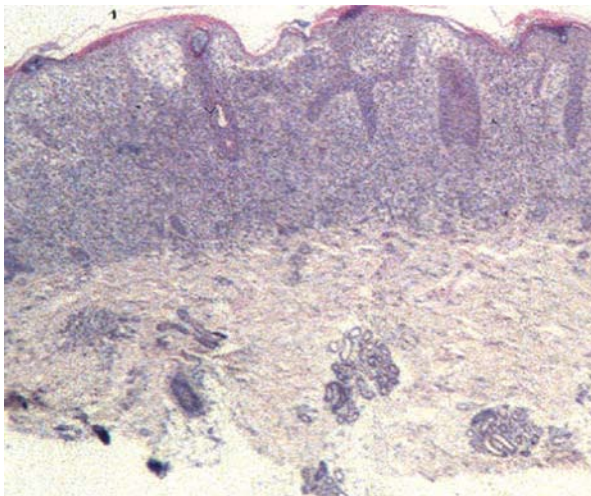


Fig. 1

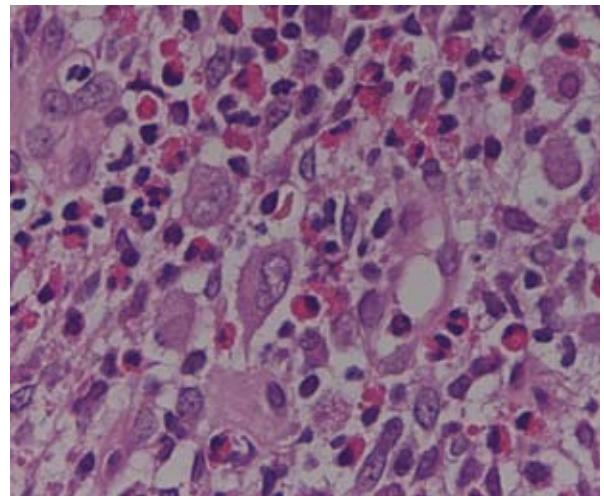


Fig. 2

Fig. 1, 2: Letterer-Siwe disease; you can see the significant edema of the superficial dermis (Fig. 1, H&E, 20x). In Fig. 2 (H&E, 400x) you can see the characteristic of the Langerhans cells: large cells with bean-shaped nucleus, abundant cytoplasm with definite borders; there are also many eosinophils.

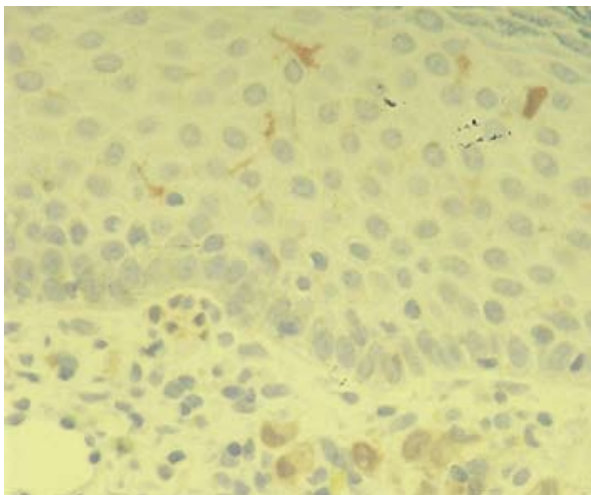


Fig. 3



Fig. 4

Fig. 3, 4: Positive stain with S-100 protein (Fig. 3, 250x) both in pathological Langerhans cells of the dermis and in normal ones of the epidermis. In Fig. 4 Birbeck granules inside the nucleus on electron microscopy.

In the recent lesions these cells usually constitute the majority of the infiltrate; in the older lesions, especially when the disease is in spontaneous or drug-induced remission, the cell may show lipid vacuoles until it takes an aspect similar to those observed in Hand-Schuller-Christian disease (2).

In addition to the LC there may be other cells, mainly lymphocytes and eosinophils (Fig. 2), and in some cases a granuloma-like infiltrate very similar to that found in eosinophilic granuloma of bone.

Initially, the infiltrate occupies the superficial dermis, where it is surrounded by a very edematous stroma (Fig. 1), and the middle dermis; the epidermis does not appear affected by the infiltrate. However, when the latter grows significantly, it extends upwards, eroding the epidermis, and in depth to reach in the larger nodules the muscular layer.

As regards the immunohistochemistry Langerhans cell reacts with S-100 (Fig. 3), CD1a, langerin, CD68, HLA-DR receptors; there are no significant differences in susceptibility to S-100, CD1a, langerin (76). The ultramicroscopic marker of LCH is represented by Birbeck granules (Fig. 4).

Skin lesions. The most characteristic and frequent skin lesion of LCH is a 1 mm in diameter papule with well-defined margins, sometimes purpuric. The purpuric appearance is not due to liver involvement or thrombocytopenia because it is present also when there is not a liver or bone marrow dysfunction as in the self-healing forms (7, 8). The other lesions observed in the LCH derive from this primary lesion, which can erode and become crusty or grow and become a nodule or ulcerate or overload of lipids becoming xanthomatous. The stromal edema that characterizes the primitive papule may explain the exudative, even



Fig. 5



Fig. 6

Fig. 5, 6: Please note the difference in morphology, distribution and number of skin lesions between Hashimoto-Pritzker disease (Fig. 5) and Letterer-Siwe disease (Fig. 6).

bullous with infiltrated base or pustular varicella-like lesions that are observed in the congenital form of Hashimoto-Pritzker. Lesional polymorphism is more evident in congenital forms where the lesions are fewer and less close to each other (Fig. 5), while the acquired forms are usually monomorphic with high prevalence of micropapular lesions (Fig. 6).

With regard to the distribution of the lesions, in the acquired forms prevail the seborrheic sites - scalp, behind the ears, central chest and paravertebral areas level with the trunk, diaper area (Fig. 6) -; on the other hand, in the congenital form of Hashimoto-Pritzker the lesions affect the entire skin surface without preferring seborrheic locations.

As regards the evolutionary trend of the lesions, when LCH lasts several months, the lesions characteristically appear in subintra-croscs.

The skin lesions are common in all forms of LCH, but have a different meaning for the dermatologist and the oncologist. The latter gives unfavorable prognostic significance to the presence of skin lesions (17, 22) because when these lesions are in addition to visceral lesions, are an expression of a greater spread of the disease. On the other hand, the dermatologist, when recognizing the pathognomonic lesions of LCH (9), knows that they may be the expression of an exclusive skin involvement and that may resolve spontaneously; it is indeed difficult for the dermatologist to be the first specialist to diagnose a multisystem LCH, while he knows and must remember that an initially pure cutaneous form can turn into a multisystem disease (29).

Until a few decades ago the pessimistic interpretation of the significance of skin lesions prevailed and any histopathological diagnosis of LCH led to prescribe an aggressive systemic chemotherapy even when there were only skin lesions.

To change this interpretation were important the reports in 1981 of Osband et Al. (57) who first treated with thymic extracts systemic forms of LCH, in 1973 of Hashimoto and Pritzker regarding the self-healing congenital form, and finally the increasingly frequent reports of purely cutaneous and self-healing LCH forms (7, 8). It is thus held more and more the concept that there

are self-healing forms of LCH: usually we are dealing with pure cutaneous forms already present at birth or that arise within the first months of life, but there are also self-healing forms affecting the adult or other organs such as lymph nodes, bones, lungs and liver (4, 8, 31, 33).

Because the skin lesions are not seldom the first to appear and as the initially pure cutaneous forms of LCH may later become multisystem, the dermatologist has the difficult task of trying to identify the predictive signs of multisystem involvement.

From this point of view it seems useful to consider the distribution of the skin lesions, their number and diameter, the existence or absence of polymorphism and the presence of more or less deep ulcerated lesions.

We already said that in the multisystem forms of LCH the lesions are distributed in seborrheic locations while in the self-healing forms any cutaneous site can be affected. Important is the number of skin lesions that can be counted in the self-healing forms where there can also be an isolated lesion - LC histiocytoma -, while in the multisystem forms the skin lesions are sometimes so numerous as to cover the whole skin: in these cases, when more than 60% of the skin is affected by ulcerated lesions, there may be as in burns a dysfunction of the skin. Also the diameter and the polymorphism of the skin lesions is important: in the multisystem forms you usually see 1 mm in size, monomorphic papules, while in the self-healing forms there is considerable polymorphism ranging from grossly nodular lesions to varicella-like pustular lesions with infiltrated base till to nodular Kaposi-like lesions.

Letterer-Siwe disease

Letterer-Siwe disease, potentially the severest form in this group, has a debated pathogenesis, being according to some Authors a monoclonal proliferation of Langerhans cells (72), according to others a reactive form (25).

Usually the disease does not start before 3 months of age and after the 18th month (19). It is clinically characterized by the already described papules (Fig. 6, 7) distributed in seborrheic sites;



Fig. 7



Fig. 8

Fig. 7, 8: Purpuric micropapules of Letterer-Siwe disease typically distributed in seborrheic sites (Fig. 7). In Fig. 8 a nodular xanthomatous lesion of Letterer-Siwe disease, as you can see in its remission phase.



Fig. 9



Fig. 10

Fig. 9, 10: Gingival granulomatous lesions of Letterer-Siwe disease.

the granulomatous or xanthomatous (Fig. 8) nodular lesions are rare, the latter being sometimes visible in the drug-induced or spontaneous remission phase of the disease.

As regards the prognosis, we distinguish multisystem rapidly fatal forms, multisystem forms with or without organ dysfunction and self-healing forms, usually affecting only one organ, mainly skin or bone.

Multisystem forms are the most frequent in this group; they affect the bone, usually of the skull - being responsible for osteolytic areas and in severe cases deformation of the skull - the gum

with granulomatous mass and loss of teeth (Fig. 9- 10), the spleen, liver, lymph nodes, lung, and middle ear.

Hand-Schüller-Christian disease

It differs from the previous form for a more subtle course and for affecting older children, usually between the second and the sixth year (19).

The most characteristic manifestations are bone lesions (Fig. 11), diabetes insipidus and



Fig. 11



Fig. 12

Fig. 11, 12: Hand-Schüller-Christian disease with lesions of the bone and the soft tissue (Fig. 11); there are also skin lesions (Fig. 12) similar to those of Letterer-Siwe disease.



Fig. 13



Fig. 14

Fig. 13, 14: Eosinophilic granuloma of bone with swelling of the right frontal region (Fig. 13, circled) and osteolysis with clear-cut borders of the underlying bone (Fig. 14).

exophthalmos. Bone lesions affecting mainly the skull are associated with swelling of the soft tissues; radiologically you can observe osteolytic areas that give rise to images reminiscent of a map.

A significant increase in diuresis betrays pitressin-sensitive diabetes insipidus.

Exophthalmos is linked to the presence of retrobulbar granulomatous lesions; the latter are sometimes associated with bone lesions of the orbital cavity.

In addition to these classic lesions there may be splenoepatomegaly, lateral cervical adenopathy, lung and bone marrow involvement, usually without organ dysfunction.

When present, the skin lesions (Fig. 10) are similar to those of Letterer-Siwe disease, but less numerous and localized to the scalp and in the sternal and vertebral region. The course is chronic with possible spontaneous or therapy-induced remission.

Eosinophilic granuloma of bone

It is usually diagnosed after the second year of life and has a favorable evolution towards remission, spontaneous or favored by curettage or by radiotherapy. Any bone can be affected, but the skull is the elective seat (Fig. 13, 14). It may be associated with lymphadenopathy, which is sometimes the initial symptom of the disease (19) and nodular and ulcerative skin lesions, especially in periorificial sites.

Acquired pure cutaneous LCH

With this term we refer to a LCH exclusively localized to the skin at the time of diagnosis and not present at birth: these cases are typically diagnosed by dermatologists, but their frequency is underestimated because we believe it is possible that the forms with fewer lesions (Fig. 17) receive



Fig. 15



Fig. 16

Fig. 15, 16: Acquired pure cutaneous LCH; the only difference as compared with Letterer-Siwe disease is the minor number of lesions. When the lesions are very few, the disease can be misdiagnosed. In the child as in Fig. 15 and 16 1 month after the pure cutaneous onset the liver was affected without organ dysfunction.

ve a trivial diagnosis as seborrheic dermatitis or diaper rash (Figg. 18-23).

This form closely resembles Letterer-Siwe disease by age of onset, monomorphic lesions (Fig. 15, 16) distributed in seborrheic sites and subinfrant crops of lesions: the only difference is the minor number of lesions that can often be counted (2).

In 50% of cases these forms remain pure cutaneous and spontaneously and completely regress after about six months: during this period of time subinfrant crops of lesions continue to appear with a waxing and waning clinical course till the complete regression.

In another 50% of cases after a few weeks, more rarely after a longer period of time, the involvement of other organs such as the liver and the bone marrow becomes evident; the involvement of other organs is usually discrete and is not associated with organ dysfunction; however, although exceptionally, the involvement of other organs can be fatal.

Therefore, we saw that Letterer-Siwe disease, Hand-Schuller-Christian disease, eosinophilic granuloma of bone and acquired pure cutaneous LCH are not clearly separate entities, but have several contact points and may evolve one into the other.



Fig. 17: The child as in Fig. 17 presented only few - a dozen - skin lesions and spontaneously recovered within 4 months.



Fig. 18



Fig. 19



Fig. 20



Fig. 21



Fig. 22



Fig. 23

Fig. 18, 19, 20, 21, 22, 23: Acquired pure cutaneous LCH. The child was previously followed due to a deep hemangioma of the back (Fig. 22). When aged 3 months she presented some papules on the hemangioma and simultaneously on the scalp (Fig. 18) and in the diaper area (Fig. 20). The histological examination confirmed the diagnosis of LCH; she presented spontaneous crops of papules for 6 months without involvement of other organs and then spontaneously healed (Fig. 19, 21, 23).

Hashimoto-Pritzker disease (congenital self-healing LCH)

Hashimoto and Pritzker in 1973 (38) described an exclusively cutaneous form of histiocytosis, present at birth and self-healing. Initially considered a non-Langerhans histiocytosis, later it has been inserted among LCH in its own right. It is not exceptional because in 1991 46 cases of the disease had been already described (7).

It is characterized by presence at birth, exclusive involvement of the skin, involvement of any cutaneous site even outside of the seborrheic locations, low number of lesions that can usually be counted, polymorphic lesions and spontaneous regression (Fig. 24, 25). The polymorphism of the lesions is not evident in the individual patient; however, in different patients lesions as papules, blisters or pustules with infiltrated base, nodules, eroded or bleeding lesions may be present.

Physicians should not forget that all of these features may be present, albeit exceptionally, in LCH like Letterer-Siwe.

Nor physicians should forget that pure cutaneous, self-healing forms of LCH can be found also in children after birth (8), in the adult (25) and in the elderly (65).

In addition to congenital self-healing forms with multiple element also exists **solitary cutaneous congenital histiocytoma**, reported for the first time by Esterly et Al. in 1985 (30); fifty cases of this form have been so far reported (11). Present at birth in almost all cases, it prevails in the male in the ratio of 3/2 compared to the females, its average diameter is 12.5 mm (4-30) and the epidermis is involved in 73% of cases (Fig. 26-29). In 67% of cases LC histiocytoma regresses spontaneously in months after the biopsy; in the other cases when removed, it does never recur (11).



Fig. 24



Fig. 25

Fig. 24, 25: Hashimoto-Pritzker disease: at birth 5-6 papules and nodules (Fig. 24) spontaneously regressed within 4 months (Fig. 25).



Fig. 26



Fig. 27



Fig. 28



Fig. 29

Fig. 26, 27, 28, 29: Congenital solitary cutaneous LC histiocytoma: in all the cases the epidermis is affected. The nodule in Fig. 26 was removed by shaving and did not recur (Fig. 27).

Treatment of Langerhans cell histiocytosis

When, based on skin lesions, the diagnosis of LCH is made by the dermatologist, it is important after histological confirmation to rule out the involvement of other organs with the aid of the oncologist. The oncologist examination is useless only in the case of congenital solitary cutaneous histiocytoma: when the lesion is removed by shaving, it is not necessary an enlargement of the removal, aware that recurrences have not been so far reported; on the other hand, when the lesion is large, a biopsy to be certain of the diagnosis is enough, aware that LC histiocytoma will spontaneously regress. Therefore, the child will be monitored clinically, sparing X-rays and examinations involving albeit a minimal risk for him.

In case of multiple lesions in the congenital form, after excluding the involvement of other organs, a symptomatic treatment will be prescribed, for example antiseptic sponging in case of eroded lesions, waiting for their spontaneous regression in weeks or months (35, 36).

In case of acquired pure cutaneous Langerhans cell histiocytosis the oncologist monitoring will be much more careful: skin lesions continue to recur for months especially during infectious episodes; after the final regression of skin lesions the risk of generalization of the disease does exist but is very low (48).

The possibility of spontaneous regression exists even in case of involvement of other organs in

addition to the skin and it has been documented in the case of lymph node (9), pulmonary (4) and liver (31) involvement. However, in the multisystem forms before starting chemotherapy, it will be useful to test the response to corticosteroids. In the multisystem forms with organ dysfunction vinblastine is indicated alone or in combination chemotherapy.

In case of resistance to therapy bone marrow transplantation may be indicated (28, 78).

Histiocytosis with dermal dendrocytes (Class II)

Unlike the LCH, which constitute a fairly homogeneous group of diseases, non Langerhans histiocytosis include diseases less similar to each other characterized by benign proliferation of monocyte-macrophage cells. According to Winkelmann (74) and Gianotti and Caputo (36) non Langerhans histiocytosis includes juvenile and adult xanthogranuloma, benign cephalic histiocytosis, papular xanthoma, multicentric reticulo-histiocytosis, xanthoma disseminatum, reticulo-histiocytoma, generalized eruptive histiocytoma, sinus histiocytosis, progressive nodular histiocytosis, necrobiotic xanthogranuloma. Weitzman and Jaffe (71) divided non Langerhans histiocytoses into two groups:

1. group of juvenile xanthogranuloma arising from a prevailing proliferation of dermal



Fig. 30

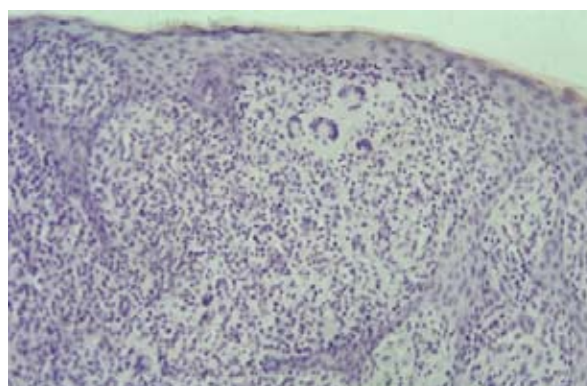


Fig. 31

Fig. 30, 31: Juvenile xanthogranuloma with the typical appearance of a yellow nodule (Fig. 30), consisting of a proliferation of xanthomatous histiocytes and giant cells (Fig. 31, H&E, 100x).

dendritic cells and including juvenile and adult xanthogranuloma, benign cephalic histiocytosis, generalized eruptive histiocytosis, disseminated xanthoma, progressive nodular histiocytosis, systemic juvenile xanthogranuloma and Erdheim-Chester disease;

2. group independent of juvenile xanthogranuloma, mainly resulting from a proliferation of macrophage cells and comprising reticulohistiocytoma, sinus histiocytosis, multicentric reticulohistiocytosis, sinus histiocytosis with massive lymphadenopathy. Indeterminate cell histiocytosis is considered separately.

Juvenile xanthogranuloma

Juvenile xanthogranuloma (JXG) is the most frequent variety of non Langerhans histiocytosis and for this reason it was the first to be described

(47). It consists of a proliferation of dermal dendritic histiocytes (Fig. 29, 30) and has a meaning similar to that of other frequent benign proliferations of childhood as hemangioma and mastocytosis; the frequency of these proliferations is such that they can be casually concomitant (Fig. 32, 33). JXG shares with hemangioma (Fig. 32) and mastocytosis (Fig. 33) both the clinical course – initial growth followed by slow regression – and the large clinical spectrum ranging from a single nodule of the skin or isolated xanthogranuloma representing approximately 70% (27, 69) of cases – thus justifying the term xanthogranuloma in contrast with mastocytosis, more often characterized by multiple lesions – to numerous nodules covering much of the skin surface and affecting internal organs; the rarity of the latter event does not alter the essential benignity of the disease.

JXG is present at birth in 5-17% of cases (27, 39, 64) and appears within the first year of life



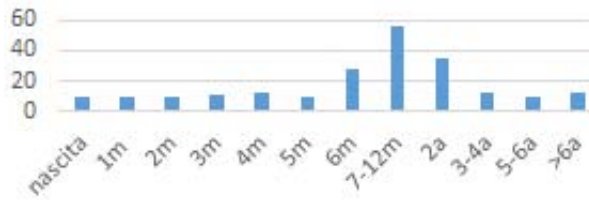
Fig. 32



Fig. 33

Fig. 32, 33: JXG of the foot associated with hemangioma (Fig. 32); JXG of the face and mastocytosis of the trunk (Fig. 33).

TABLE 1: Age of onset of JXG in 215 subjects aged < 13 years (116 M; 99 F).



in 40-70% of cases (64, 67). However, JXG can start even in adults (adult xanthogranuloma) with a peak incidence at the end of the third decade of life (67) but with cases started at 80 years (59). In our series consisting of 216 cases (116 males and 99 females) aged less than 13 years 55% of cases occur between 6 months and 24 months (Table 1).



Fig. 34



Fig. 35

Fig. 34, 35: Juvenile xanthogranuloma with xanthomatous nodule of the elbow and non xanthomatous nodule of the temporal region (Fig. 34); the latter on histological examination showed to be JXG and recurred after removal with a xanthomatous papule (Fig. 35, arrow).



Fig. 36



Fig. 37

Fig. 36, 37: A 2-year-old child with a 4 centimeters nodule of the ankle (Fig. 36); the magnetic resonance imaging (Fig. 37) showed a well demarcated nodule extending in extra-fascial site, compressing and displacing the vascular bundle and the Achilles tendon; on histological examination the nodule was diagnosed JXG.



Fig. 38



Fig. 39



Fig. 40



Fig. 41

Fig. 38, 39, 40, 41: Nodular (Fig. 38), plaque (Fig. 39), agminated (Fig. 40) and generalized (Fig. 41) juvenile xanthogranuloma.

Histologically, JXG despite the absence of a capsule, is a well demarcated neoformation of histiocytes and occupies the papillary and reticular dermis sparing the epidermis; the latter appears flattened and thinned. In addition to histiocytes rapidly getting xanthomatous, in the neoformation there are Touton giant cells with the characteristic crown of nuclei, lymphocytes, neutrophils and eosinophils (Fig. 31). On immunohistochemistry the histiocytes are S-100 negative, but vimentin and factor XIIIa positive (45, 64). On electron microscopy there are not Birbeck granules; on the other hand, worm-like bodies and lipid droplets not delimited by membranes can be seen (19).

The clinical appearance of the initial JXG is a fibrangiomatic papule that within a few weeks becomes frankly yellow (Fig. 34, 35). The yellow color is missing, however, as well as in early lesions, even in the deep lesions (Fig. 36) and in those which, although rarely, never become xanthomatous (12).

The number, diameter and shape of the lesions change significantly; in addition to the superficial nodules (Fig. 30, 32, 38) there are plaque lesions (Fig. 39) sometimes extended to 10 cm and more and in 5% of cases deep nodules (Fig. 36) covered by normal skin (64); there are also agminated (Fig. 40) and generalized cutaneous (Fig. 41) forms.



Fig. 42



Fig. 43

Fig. 42, 43: Juvenile xanthogranuloma of the scalp (circled) associated with peripheral neurofibromatosis.

The nodules are mainly located on the head, neck and upper torso. Xanthogranuloma nodules may be found also in other organs (systemic JXG) with unfavorable prognosis, but their incidence is rare, as can be inferred from the fact that the most frequent extracutaneous location, that is the eye, is present in only 0.4% of cases (40); this location is less rare in children under the age of 2 with multiple lesions.

JXG is not associated with disorders of lipid metabolism. On the other hand, it is associated not infrequently with neurofibromatosis 1 (Fig. 42, 43), but the presence of a nodule of JXG goes unnoticed due to the importance of neurofibromatosis (13); the same is true for other nevus lesions as congenital melanocytic nevus, nevus anemicus, hairy nevus, frontal vortices that are more common in neurofibromatosis 1.

More important, but fortunately rarer is the association XGG, neurofibromatosis and chronic myeloid leukemia: the coexistence of JXG increases significantly the risk of leukemia, with

respect to the exclusive presence of neurofibromatosis (79).

Juvenile xanthogranuloma (Fig. 45) must initially be differentiated from molluscum contagiosum, histiocytoma, Spitz nevus (Fig. 44) and from xanthoma-like mastocytoma with negative Darier sign (Fig. 48): with the passage of weeks the appearance of the typical yellow color clarifies the diagnosis; the characteristic yellow color may become more evident with the pressure of the fingers or with dermoscopy (Fig. 47) with slight pressure showing the typical appearance of rising sun; sometimes the differential diagnosis from Spitz nevus can be difficult, because dermoscopically also in juvenile xanthogranuloma a wishish grid as in Spitz nevus can be seen (Fig. 47).

The clinical course of JXG is typical: in all its varieties an initial stage of growth, in which the xanthomatous appearance may be missing or not evident, is followed by a phase of obvious xanthomatization and slow regression.



Fig. 44



Fig. 45

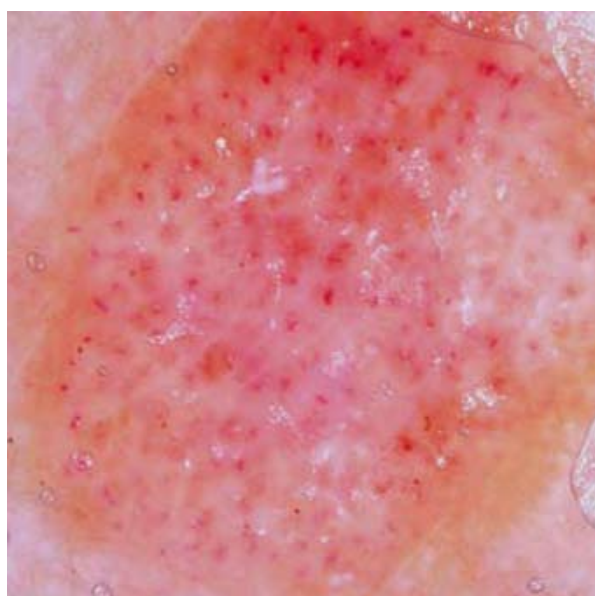


Fig. 46

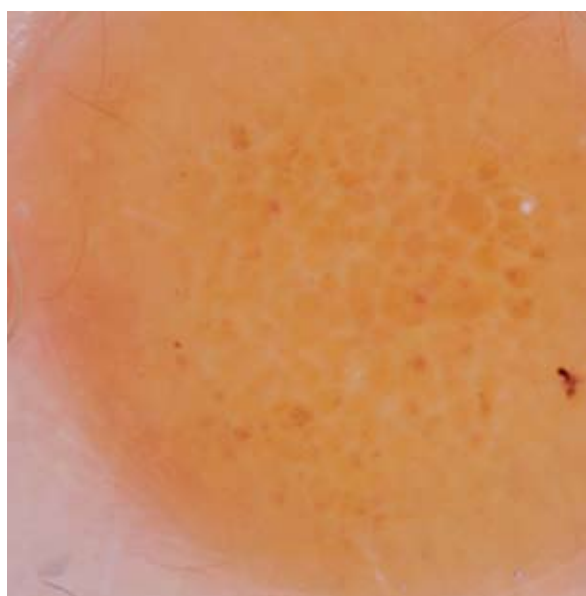


Fig. 47



Fig. 48



Fig. 49

Fig. 44, 45, 46, 47, 48, 49: Spitz nevus can present clinical (Fig. 44) and dermoscopic (Fig. 46) findings similar to those of JXG (Fig. 45, 47). Xanthoma-like mastocytoma with negative Darier sign at the moment of the first examination (Fig. 48), after 1 month rightly diagnosed due to blister formation (Fig. 49).



Fig. 50

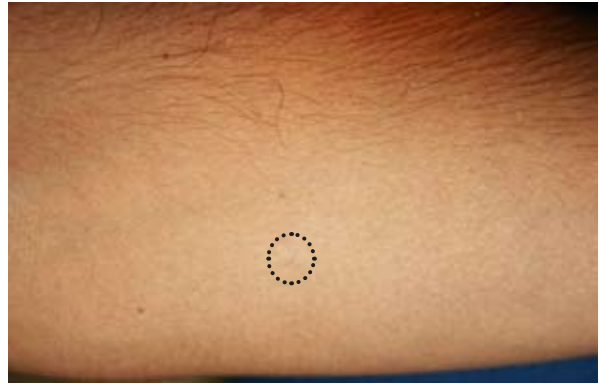


Fig. 51



Fig. 52



Fig. 53



Fig. 54



Fig. 55

Fig. 50, 51, 52, 53, 54, 55: Regression of JXG (Fig. 50) with atrophic residua (Fig. 51, circled). The 3-month-old child as in Fig. 52, besides a hemangioma, presents on the buttock an initial xantogranuloma, that later on becomes xanthomatous (Fig. 53, 54) and finally regresses (Fig. 55) long before of hemangioma.

The latter is complete in a couple of years with scarce atrophic residua (Fig. 50, 51); the regression of JXG is therefore more rapid than that of other childhood proliferation as mastocytosis and hemangioma (Fig. 52, 53, 54, 55), which often require ten years.

In the majority of cases of juvenile xanthogranuloma, when the clinical diagnosis does not require a confirmation, it is not necessary its removal, given the tendency to spontaneous regression of the neof ormation, nor are necessary laboratory tests.



Fig. 56



Fig. 57



Fig. 58

Fig. 56, 57, 58: Cephalic histiocytosis: 1-3 mm, skin-colored, asymptomatic papules (Fig. 56) with tendency to spontaneous regression as you can see in the child as in Fig. 57, at the age of 2, that recovered at the age of 4 (Fig. 58).

Benign cephalic histiocytosis

Described first time by Gianotti et Al. (35), it is similar to JXG but with smaller lesions. The lesions start after the sixth month of life (19) on the upper part of the face and then tend to involve the rest of the face, more rarely other sites. The characteristic lesion is a 1-3 mm papule (Fig. 56, 57), persisting for years, but finally resolving without going through xanthomization; only the largest lesions leave slightly atrophic sequelae.

The histologic examination shows in the superficial and mid dermis a well-delimited infiltrate of non xanthomatous histiocytes, usually without giant cells. On electron microscopy, it is characterized by the presence of worm-like, comma-shaped, arch-shaped, and S-shaped bodies (19).

The disease should be differentiated from flat warts and micronodular juvenile xanthogranuloma. Flat warts begin later on, after the second year of life, are flat and have an asymmetrical distribution due to infection by contiguity. Xanthogranuloma of the head may be indistinguishable

at first, before xanthomization, but the histological and ultrastructural examinations are decisive.

Treatments are neither necessary nor helpful due to its tendency to the spontaneous regression and the inefficacy of the topical treatment.

Progressive nodular histiocytosis

The disease, described for the first time in a 9-year-old boy (68), is characterized by yellow-brownish papules and deep nodules reminiscent of XGG; however, the lesions do not regress but progressively increase in number: the general condition is not affected, but the esthetical consequences have a significant impact on the quality of life. Histologically, the epidermis is spared and the dermis is occupied by an infiltrate of foamy S110-, CD1a-, CD68+ and Factor XIIIa+ histiocytes. The prognosis is different in the child that spontaneously recovers and in the adult that presents mucous lesions and may have a progressive disease. There is no effective therapy.



Fig. 59: Generalized eruptive histiocytosis with diffuse red papules (Can et Al., EJPD 21, 157-9, 2011).

Generalized eruptive histiocytosis

It is a rare, papular, not xanthomized histiocytosis, with a tendency to spontaneous regression. It prevails in the adults (51) but has been described also in children from the first month of life (70). It is characterized by subintra-eruptions of pink (Fig. 59) or brownish-red, large, hard papules, localized to the face, trunk, and root of the limbs.

The histologic examination shows in the superficial and mid dermis a rather monomorphic, poorly delimited infiltrate of non xanthomatous histiocytes, presenting a nucleus with loose chromatin and abundant pale cytoplasm. There are no giant cells.

Electron microscopy demonstrates dense bodies, often onion bulb-shaped like in Hashimoto-Pritzker disease. There are sometimes worm-like bodies, but never Birbeck granules (18).

As we will discuss later, generalized eruptive histiocytosis may represent an early stage of

other diseases of this group (77): this hypothesis was suggested thanks to the observation of a well characterized from a clinical, histological and ultramicroscopic point of view pediatric case, then evolved in a classic disseminated xanthoma.

Xanthoma disseminatum

It is a normolipemic mucocutaneous xanthomatosis owing to the proliferation of histiocytes positive for factor XIIIa and negative for S-100 and CD1a, mainly affecting children and young adults. The skin lesions are coarse papules and yellowish or red-brownish nodules affecting the face, neck and trunk and flowing in the axillary and inguinal folds. Lesions of the eye, mucous membrane, respiratory and nervous system coexist with pitressin-sensitive diabetes being present in 40% of cases. Next to self-limiting forms there are persistent and progressive forms (21). From a histological point of view, besides foamy histiocytes, there are giant cells, lymphocytes and neutrophils infiltrating the superficial dermis or the whole dermis and the subcutaneous fat tissue. In the severe progressive cases cyclophosphamide was used with some success (21).

Papular xanthoma

It was described both in adults (73) with a worse prognosis and in children (16, 20) with a self-healing tendency. It shares with JXG and xanthoma disseminatum some clinical and histological findings.

Clinically, there are few yellowish or red-brownish papules or nodules, mainly on the back (Fig. 60, 61).

Histologically, the infiltrate predominantly consists of foamy histiocytes (Fig. 62) and giant cells. The histiocytes are S100-, CD1a-, factor XIIIa+, CD68+. The prognosis is different in children that spontaneously recover and in adults that present mucosal lesion and a potentially progressive disease.

There is no an effective treatment in the severest cases and the therapy is unuseful in the self-healing cases of childhood.



Fig. 60



Fig. 61

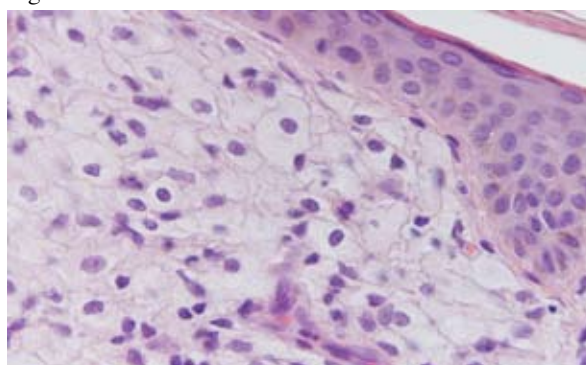


Fig. 62

Fig. 60, 61, 62: Childhood papular xanthoma: papules and nodules getting frankly yellow under the pressure of the fingers (Fig. 61); histologically (Fig. 62) foamy histiocytes just below the epidermis.

Erdheim-Chester disease

It is a xanthomatous and sclerosing histiocytosis. It affects the skin with xanthomatous lesions in a minority of cases, but primarily the long bones, especially of the lower limbs, causing osteolysis and osteosclerosis; in 50% of the patients the internal organs such as the lungs, kidney, liver, nervous system are affected sometimes massively leading to exitus (26).

The histological examination shows S-100-, CD1a-, factor XIIIa+, CD68+ histiocytes. Many treatments were tried but without confirmed results.

Indeterminate cell histiocytosis

It is a histiocytosis that affects mainly or only the skin with multiple lesions (Fig. 63, 64) and has a favorable course in most of the cases (75);

its skin lesions are reminiscent of generalized eruptive histiocytosis.

The histological examination shows a non epidermotropic infiltrate of Langerhans-like histiocytes (Fig. 65), giant cells and lymphocytes (75). What is peculiar is that histiocytes, as well as showing positivity for phagocyte markers, are also S-100, CD1a and HLA-Dr positive; however, the histiocytes are langerin negative and on electron microscopy there are no Birbeck granules. It is not therefore a Langerhans cell histiocytosis, as confirmed clinically by the absence of extracutaneous involvement and histologically by the lack of epidermotropism and intercellular edema in the papillary dermis (3).

Its constituting cells could be indeterminate histiocytes which remained in the dermis without completing their migration into the epidermis where acquiring Birbeck granules and positivity for langerin would become Langerhans cells; therefore, they could be precursors of Langerhans



Fig. 63



Fig. 64

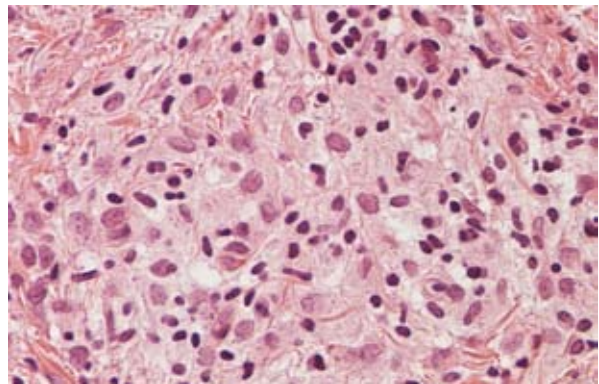


Fig. 65

Fig. 63, 64, 65: Indeterminate cell histiocytosis in an adult (Fig. 63, 64). The histological examination shows Langerhans-like histiocytes and lymphocytes.

cell (52, 53). More recently it has been suggested that these dendritic cells are members of the dermo-epidermal dendritic system responsible for presenting antigen, in transit from the skin to the paracortical areas of the regional lymph nodes (5, 63).

Multicentric reticulo-histiocytosis

It is a rare histiocytosis that affects adult women, but sometimes the child (58), begins with a seronegative polyarthritis and later affects the skin and mucous membranes; in 20% of cases it is associated to a malignancy. The skin lesions are pink papules and yellow-brownish nodules that affect predominantly the extensor surfaces of the hands and forearms; in 50% of cases there are mucosal lesions affecting mainly the oral cavity. The cutaneous infiltrate consists of histiocytes

with ground glass cytoplasm, with variable xanthomization, S-100-, CD1a- factor XIIIa+, CD68+, giant cells, lymphocytes and eosinophils. When it is not associated with a malignancy the prognosis is good because after several years the disease stabilizes. There is no effective therapy.

Sinus histiocytosis (Rosai-Dorfman disease)

Among the non Langerhans histiocytoses sinus histiocytosis is one of the most frequent with 423 cases reported up to 1990 (32). This name was given by Rosai and Dorfman (60) due to the presence of a histiocytic infiltrate in the sinuses of lymph nodes; also when localized to the skin the histology is characterized by groups of histiocytes contained in lymphatic lacunae (1).

Sinus histiocytosis is a disease reactive to infections, and the Epstein-Barr virus is the cau-

sative agent most often cited (32, 43, 55). The disease affects young adults without difference of sex and usually manifests with a major laterocervical bilateral lymphadenopathy, often associated with general symptoms. In addition to the lymph nodes other organs can be affected and between these the most frequent is the skin, which can also be the only affected organ: in 1998 19 cases of exclusively cutaneous Rosai-Dorfman disease had been described (24). The skin lesions are generally yellowish or purpuric papules, nodules and plaques; the skin lesions, usually multiple, can also consist of a single plaque (1). In addition to the lymph nodes and skin paranasal sinuses, salivary glands, liver, genitourinary and central nervous system, and still others may be interested.

The histological examination is pathognomonic both for the location of histiocytes and for the phenomenon of emperipolesis, i.e. phagocytosis of lymphocytes and, to a lesser extent, of neutrophils, plasma cells, and red blood cells by histiocytes. It's interesting to note that on immunohistochemistry histiocytes, in addition to being positive for the markers of macrophages (EBM11, HAM56 and Leu M3, FcIgG and receptors for C3) and monocytes (OKM5 and Leu M1) are also positive for S-100, for some of the epitopes of CD1 and factor XIIIa. The clinical course is variable and ranges from healing in a year up to death in 10% of cases (32); many therapies have been tried without success.

Necrobiotic xanthogranuloma

It is characterized clinically by the association with paraproteinemia and histologically by necrobiosis and xanthogranulomatous infiltrate (42); the paraproteins would combine with lipids and precipitating in the skin would cause a foreign body granulomatous reaction. Clinically, it is characterized by yellow-reddish, ulcerated, infiltrated lesions mainly in the periorbital region; the histology shows histiocytes, Touton cells, needle-shaped clefts due to precipitation of cholesterol and foci of necrobiosis. The therapy is that of paraproteinemia, i.e. steroids and plasmapheresis.

Unifying hypothesis of non Langerhans histiocytoses

Some Authors (77) proposed a unifying concept for non Langerhans histiocytoses, assuming that the clinical, histological and immunohistochemical differences depend from the more or less advanced stage of the same disease and are not expression of different diseases. From a clinical point of view, for example, the earlier lesions are reddish papules or nodules whereas the older lesions are yellowish as a consequence of xanthomatization of histiocytes.

So from a histological point of view in the mature lesions of XGG there is the simultaneous presence of histiocytes and giant cells while in benign cephalic histiocytosis you can see monomorphic mononuclear histiocytes; but if you make serial biopsies, in the later stages of the latter disease you can see more polymorphic aspects reminiscent of XGG.

Also from the immunohistochemical point of view you can observe differences related to the more or less advanced stage of the disease: so KiM1p is positive in all the histiocytes while KP1 (CD68) is positive in multinucleated and xanthomatous cells, while it is negative in the vacuolated and spindle histiocytes; similarly, factor XIIIa is intensely positive in vacuolated histiocytes, while in the more mature lesions with polymorphous infiltrate becomes negative or remains positive only in the central region.

Malignant histiocytosis (Class III)

It includes monocytic leukemia, histiocytic lymphoma, which derives from tissue histiocytes and therefore, at least initially, gives a localized tumor, and proper malignant histiocytosis with generalized involvement of the reticuloendothelial system. Monocytic leukemia may present on the skin leukemia lesions, histologically consisting of monocytes positive for nonspecific esterase (6) and nonspecific lesions. Histiocytic lymphoma can affect primitively the lymph nodes or other organs: in the latter case the skin may be primitively affected. Lymphoma is radiosensitive.

Malignant histiocytosis is clinically characterized by severe general symptoms, painful lymphomegaly and hepatosplenomegaly; ulcerated skin lesions can be present. It is often confused with other histiocytosis (50). When the treatment starts early, the response to radiochemotherapy is good (56).

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