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Congenital self-healing non-Langerhans cell histiocytosis*

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Abstract. Clinical, morphological, ultrastructural and immunological studies were performed in a case of congenital self-healing non-Langerhans cell histiocytosis. The patient showed several aspects that have not been published before: a large nodule in the vulvar region, vesiculobullous elements and pneumonia (asymptomatic). The relationship of the vesicles and pneumonia to the histiocytic disorder is not clear. Ultrastructurally, worm-like (comma-shaped) particles, dense bodies and Birbeck granules were not found. Histiocytes were Leu-6 negative, and S_{100} (partly), Leu M_3 and HLA-DR positive. Positive reactions were also obtained with anti-lysozyme and non-specific esterase. Several aspects of this case and of others described previously are discussed.

Key words: Non-Langerhans cell histiocytosis – Reticulohistiocytosis – Self-healing, congenital disease

Introduction

Congenital self-healing histiocytosis was first described in 1973 as reticulohistiocytosis [5]. This syndrome is characterized by multiple dermal histiocytic infiltrates that involute spontaneously.

Clinically one finds papulonodular skin lesions (which are present from birth); there are no systemic features and the disorder disappears within 6–12 months. Only 15 congenital cases have been described [2, 4, 5, 7, 8, 10–13, 15].

Congenital self-healing (reticulo)histiocytosis appears very serious, but the prognosis is excellent. It is unnecessary to treat these patients, since the course is self-limited and the side-effects of treatment may be more dangerous. In this article an additional patient suffering from a congenital self-healing non-Langerhans cell histiocytosis is described, with several aspects, as yet undescribed in this entity.

Case report

After an uncomplicated pregnancy and vaginal delivery a 3280 g female child was born; her mother had not been ill during pregnancy. The child looked healthy, but there were many small erosive, haemorrhagic (± 30–40) lesions and larger infiltrative plaques (a total of 6) on the skin, some of which showed central crusting. On palms and soles, haemorrhagic erosive bullous and vesicular lesions were seen. A brownish-red nodule about 40 mm in diameter was found on her vulva, partly covered by a yellow-greyish coating (Fig. 1). No oral lesions were seen and there was no purpura. Physical examination showed no abnormalities. Laboratory data, including complete blood count and serum immunoglobulins (IgG, IgM, IgA), were normal. Serology for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, syphilis and hepatitis B was normal. Bone marrow examination showed completely normal cells. A Tzanck smear (cytological examination of a scraping from the bottom of a vesicle) revealed no abnormalities. Herpes simplex and bacterial skin cultures from vesicular lesions were negative. X-rays of skull and skeleton showed no abnormalities.

Chest X-rays revealed interstitial shadowing in both upper lung fields with a fine interstitial aspect, indicating congenital pneumonia. The child was hospitalized for observation, although symptoms of pneumonal infection were not present. The skin lesions underwent a rapid and impressive involution; the child was not growing very well, possibly due to an intercurrent viral infection, but she recovered quickly.

At 6 weeks of age the chest X-ray showed marked improvement; the skin lesions also improved dramatically and showed healing with milia. The vulval nodule also involuted progressively (Fig. 2). Follow-up examination at age 2 years 3 months showed a normally developing child with no abnormalities.

Histology

An infiltrative truncal plaque was biopsied (4 mm biopsy). The epidermis showed acanthosis and hyperkeratosis. A focally dense nodular cellular infiltrate was situated in the upper part of the dermis without granuloma formation (Fig. 3). The dermal infiltrate consisted of large polygonal and elongated histiocytic cells with eosinophilic cytoplasm and vesicular nuclei, many assuming the characteristics of foam cells. Multinuclear giant cells (non-Touton type) were also encountered. There were variable numbers of eosinophilic leucocytes among the histiocytic cells. Mitotic figures were absent.

Immunohistochemistry

Immunoperoxidase staining was carried out on cryostat sections with anti-Leu-4, anti-Leu-2_a, anti-Leu-3, anti-Leu 6, anti-Leu-M_3, anti-HLA-DR and anti-Leu-14 (Becton and Dickinson, PO Box 7375, Mountain View, Calif., USA). The

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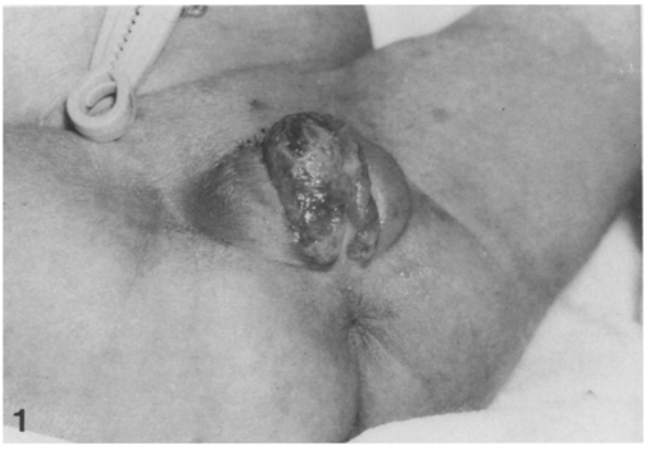

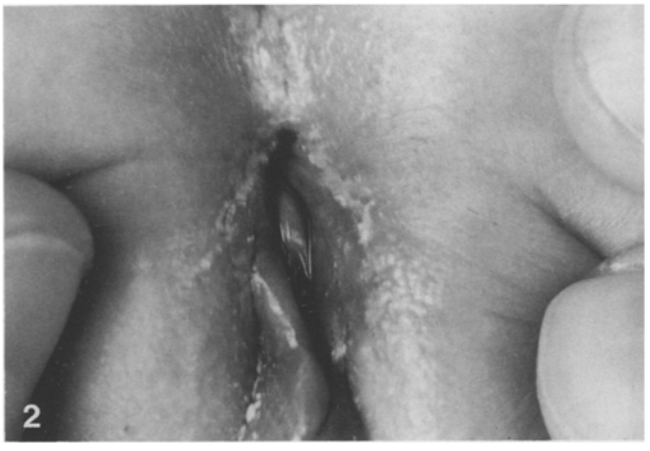

Fig. 1. Brownish-red nodule in the vulval region, covered by a yellow-greyish coating

Fig. 2. Spontaneous healing of nodule in the vulval region

Fig. 3. Focally dense infiltrate of histiocytes in the dermis. Haematoxylin-eosin, × 224

histiocytic infiltrate was Leu-6 negative, HLA-DR and Leu-M_3 positive. With anti-Leu-4 and Leu-3 very sporadic positive staining was found. With anti-Leu-2_a and Leu-14 no positive staining was observed. Histochemically, the infiltrating cells were characterized as S_{100} positive (about 30% of the cells), lysozyme weakly (variable) positive on paraffin sections. Tests were performed twice, including appropriate negative and positive controls.

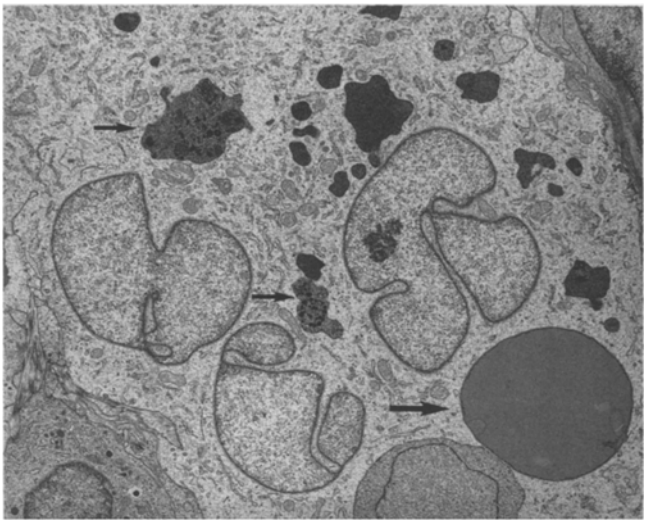

Fig. 4. Multinucleated giant cell with lysosomes *(thin arrow)* and lipid droplets *(thick arrow)*. Electron microscopy, × 228

Electron microscopy

The mononuclear histiocytic cells were ultrastructurally characterized by ruffled cell margins and round or reniform nuclei. The cytoplasm contained abundant characteristically membrane-bound lysosomes, varying in amount, size and density, lipid droplets, myelin figures and other cytoplasmic inclusions. The endoplasmic reticulum was represented by large, flattened profiles. The Golgi zones were prominent. The mitochondria were numerous and round. (The material was embedded in three blocks; ultrathin sections of each were examined extensively.) Langerhans granules were not identified in any of the ultrathin sections. Multinucleated giant cells showed the same characteristic features as the mononuclear histiocytic cells (Fig. 4). The abundance of dense lysosomes, lipid droplets and inclusions was even more prominent than in the mononuclear cells. There were no Langerhans granules, and neither comma-shaped nor regularly laminated (dense) bodies were detected in any of the sections.

Discussion

An additional patient with congenital self-healing non-Langerhans cell histiocytosis is described; the diagnosis is based on infiltrative plaques, histologically consisting of focal dermal, cellular infiltrates typed histologically, immunohistochemically and ultrastructurally as histiocytes.

Ørnvold et al. [13] described a case in which systemic signs of thrombocytopenic purpura and lymph node enlargement were present. Hashimoto et al. [6] reported a case of self-healing reticulohistiocytosis not present at birth but which developed after 17 days, disappeared within 3 weeks and was associated with neutropenia, lymphocytosis, atypical cells in bone marrow and hepatomegaly.

Our patient also suffered from a mild, asymptomatic congenital pneumonia. It was not clear if there was any association with the histiocytic skin eruption. Pneumonia has been described in histiocytosis X [14]. Clinically our patient also differs from the cases of self-healing reticulohistiocytosis by striking and plentiful erosive or vesiculobullous lesions and

only one large nodule in the vulval area. These remarkable vesiculobullous lesions disappeared within 2 weeks and the radiological evidence of pneumonia within 3 months. The inter-relationship of these features is unclear.

Histologically, a dermal infiltrate of histiocytes is found in all cases of congenital self-healing histiocytosis. In all cases, the epidermis is free of infiltrating cells. Usually eosinophils are scattered throughout the infiltrate. This histological picture is indistinguishable from histiocytosis X, although in that entity the epidermis may be involved. So far only infiltrates limited to the dermis have been reported in congenital self-healing histiocytosis. Electron microscopy cannot always differentiate between congenital self-healing non-Langerhans cell histiocytosis, reticulohistiocytosis, self-healing histiocytosis X and "persisting" histiocytosis X. All the other syndromes may demonstrate Langerhans granules within the histiocytes.

In self-healing reticulohistiocytosis Langerhans granules occur in approximately 10%–25% of the histiocytes. In our case no Langerhans granules were found, even after extensive surveys.

Only seven of the described cases of congenital self-healing reticulohistiocytosis have been investigated ultrastructurally [2, 5, 8, 10–13]. Electron microscopical features include dense bodies (in 5 out of 7 cases), worm-like particles (in 2 out of 7) and rod- or racket-shaped Langerhans granules, so-called Birbeck granules (in 4 out of 7; present in 10%–25% of the tumour cells) in the cytoplasm of the infiltrating cells. Laugier et al. [10] and Ørnvold et al. [13] found no Langerhans granules on electron microscopic surveys. This suggests, that there could be a continuous overlap between Langerhans cell and non-Langerhans cell histiocytosis.

Immunohistochemical investigations have been performed in four cases of congenital self-healing histiocytosis, including ours. The infiltrating cells have almost all the qualities of macrophages-monocytes normally found in the cells of malignant or benign histiocytic proliferations. The infiltrate in our case was typed as S_{100} (only 30% of the infiltrate cells), Leu M_3 positive and HLA-DR positive; a slightly positive reaction was achieved with anti-lysozyme serum. On the basis of these and ultrastructural findings, the infiltrating cells could be classified as histiocytes [9]. Histiocytosis-X is characterized by Leu-6 positive cells [3]. However, the dermal infiltrating cells in our case are Leu-6 negative. This important difference with respect to histiocytosis-X is compatible with the inability to detect Langerhans granules in extensive electron microscopic surveys.

Other diseases to be differentiated from self-healing non-Langerhans cell histiocytosis are juvenile xanthogranuloma and benign cephalic histiocytosis [1, 9]. These entities differ by distinct histological and clinical criteria. There is a close resemblance between juvenile xanthogranuloma and congenital self-healing non-Langerhans cell histiocytosis with regard to clinical behaviour and histological appearance. Histologically, juvenile xanthogranuloma differs due to the presence of Touton giant cells and an inflammatory reaction with fewer or a complete lack of eosinophils. Immunohistochemically, juvenile xanthogranuloma is completely S_{100} negative in contrast to congenital self-healing non-Langerhans cell histiocytosis, in which a part of the histiocytic infiltrate is S_{100} positive.

In conclusion, this group of proliferative histiocytic diseases is not clearly classified. Future investigations concerning immunological and ultrastructural parameters are indicated.

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