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CASE REPORT

Indeterminate Cell Histiocytosis in a Pediatric Patient: Successful Treatment with Thalidomide

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Abstract The 15-year-old male patient presented several 2–6 mm large livid reddish-yellowish, shiny, compact papules on the head, trunk and extremities, which had developed within the last 4 months. Histology showed normal epidermis with dense dermal infiltrate of histiocytes accompanied by few eosinophils, Touton or foamy giant cells. The histiocytes were S100 positive, CD1a negative and did not contain Birbeck granules ultrastructurally. Chest X ray, EEG, skull MRI did not show pathology. Opthalmology, neurology, oto-rhino-laryngology did not reveal alterations. Based upon the clinical symptoms and the histopathology, the diagnosis of indeterminate cell histiocytosis was confirmed. Cryotherapy and cauterization did not stop the progression of the disease, however, under thalidomide treatment no new symptoms developed and the lesions healed with pigmentation.

Keywords Indeterminate cell histiocytosis · Thalidomide · Pediatric patient · Immunohistochemistry · Electronmicroscopy · Birbeck granules

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Abbreviations

ICH	Indetreminate cell histiocytosis
MRI	Magnetic Resonance Imaging
EEG	Electroencephalogram
CD1a	Cluster of Differentiation 1a
CD4	Cluster of Differentiation 4
CD68	Cluster of Differentiation 68

Introduction

Histiocytoses are characterized by pathological proliferation of cells of the mononuclear-macrophage system and the dendritic cells. This heterogeneous group of disorders is differentiated on the basis of clinicopathological, immunohistochemical and ultrastructural features, and present with different prognosis [1]. Histiocytoses are closely related entities, with Langerhans cell histiocytosis representing one group of histiocytoses and non-Langerhans cell histiocytosis representing another. Langerhans cell histiocytoses include four overlapping syndromes: Letterer-Siwe disease, Hand-Schüller-Christian disease, Hashimoto-Pritzker disease and eosinophilic granuloma [2]. Non-Langerhans histiocytes differ morphologically, phenotypically, and ultrastructurally from the Langerhans cells [3–5]. Rare clinical entities, as the indeterminate cell histiocytosis (ICH) are composed of histiocytic cells with some shared morphological and phenotypical features to Langerhans cells but they do not contain Birbeck granules [6].

The indeterminate cell histiocytosis has been described predominantly in adults, and in fewer than a dozen cases in children [7].

While thalidomide can be a good treatment option for Langerhans cell histiocytoses, there are no previously

reported pediatric patients with ICH regarding successful therapy with this drug.

Case Report

The skin symptoms of the 15-year-old male ballet dancer student developed and rapidly extended to the head, trunk and extremities within the last month, when he presented with several 3–8 mm large reddish-brownish, later yellowish papules. (Fig. 1). Apart from mild seasonal pollen allergy he was healthy. Laboratory tests were normal and excluded hematological malignancy or hyperlipidemia. The chest-X-ray, skull MRI, EEG, ophthalmology, neurology and oto-rhino-laryngology did not show pathology.

Histologically the lesion resembled to xathogranuloma, composed from dermal infiltrate of foamy histiocytes intermingled with eosinophils, Touton or foamy giant cells, few plasma cells and lymphocytes (Fig. 2). The histiocytes were CD68, CD4 and S100 positive but CD1a negative (Fig. 3 a-d) and did not contain Birbeck granules ultrastructurally while many of them had lipoid bodies (liposomes) and few myeloid structures (Fig. 4).

These data and the skin limited symptoms excluded the generalized eruptive histiocytoma, the Langerhans cell histiocytoses, the Rosai-Dorfman disease, juvenile xanthogranuloma, sinus histiocytosis with massive lymphadenopathy and we categorized the case to the inhomogenous group of indeterminate cell histiocytosis (ICH). Because of the rapid progression of the skin symptoms under the next 5 months while he was treated by topical 5-fluorouracil and repeatedly by cryotherapy, and cauterization we introduced a thalidomide medication (100 mg/day). The closely controlled 7 month long treatment was well tolerated and did not influence his dancing activities. The progression stopped already after the first month of therapy and the symptoms gradually healed (Fig. 5) with pigmentation in 8 months after the thalidomide therapy initiation without recurrences in the following 3 years.

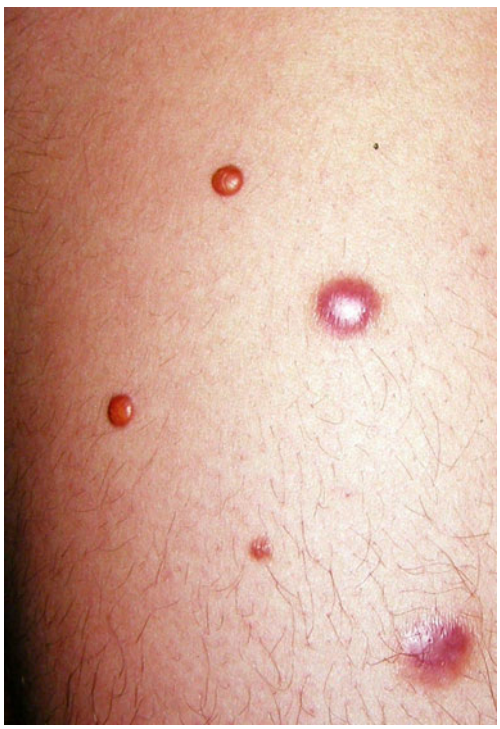

Fig. 1 Multiple reddish-brown, partially yellowish papules on the lower extremites

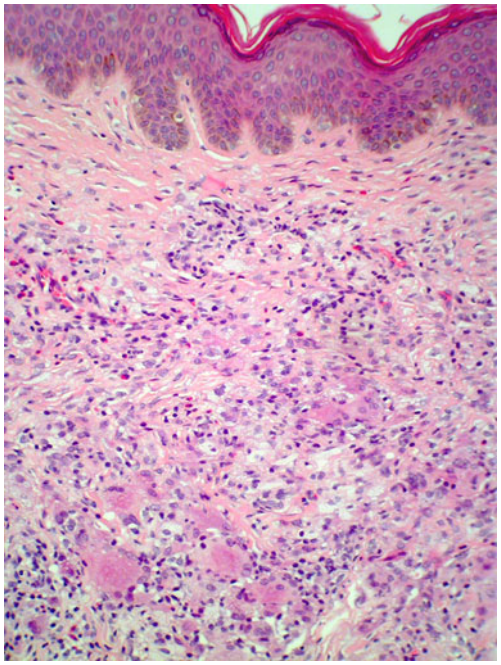

Fig. 2 Note the admixe of eosinophils and the partially xanthomatous or Touton type giant cells within the vacuolated, xanthomatized histiocytic dermal infiltrate. Haematoxylin and eosin (original magnification×250)

Discussion

ICH is an uncommon disorder defined by the presence of histiocytes with features of both Langerhans cells and macrophages. These cells are typically S-100 positive and may be CD1a negative or positive [8].

The so called “indeterminate” cells were described in 1963 [9], and the ICH was first defined by Wood et al. in 1985 [10]. According to the original definition the indeterminate histiocytes are positive for S-100 protein and CD1a, but do not contain Birbeck granules [11]. The definition of ICH differs from that proposed initially and they are identified as cells expressing macrophage markers, along with some Langerhans cell markers, showing an overlap between Langerhans cell histiocytosis and non-Langerhans cell histiocytosis [11–14].

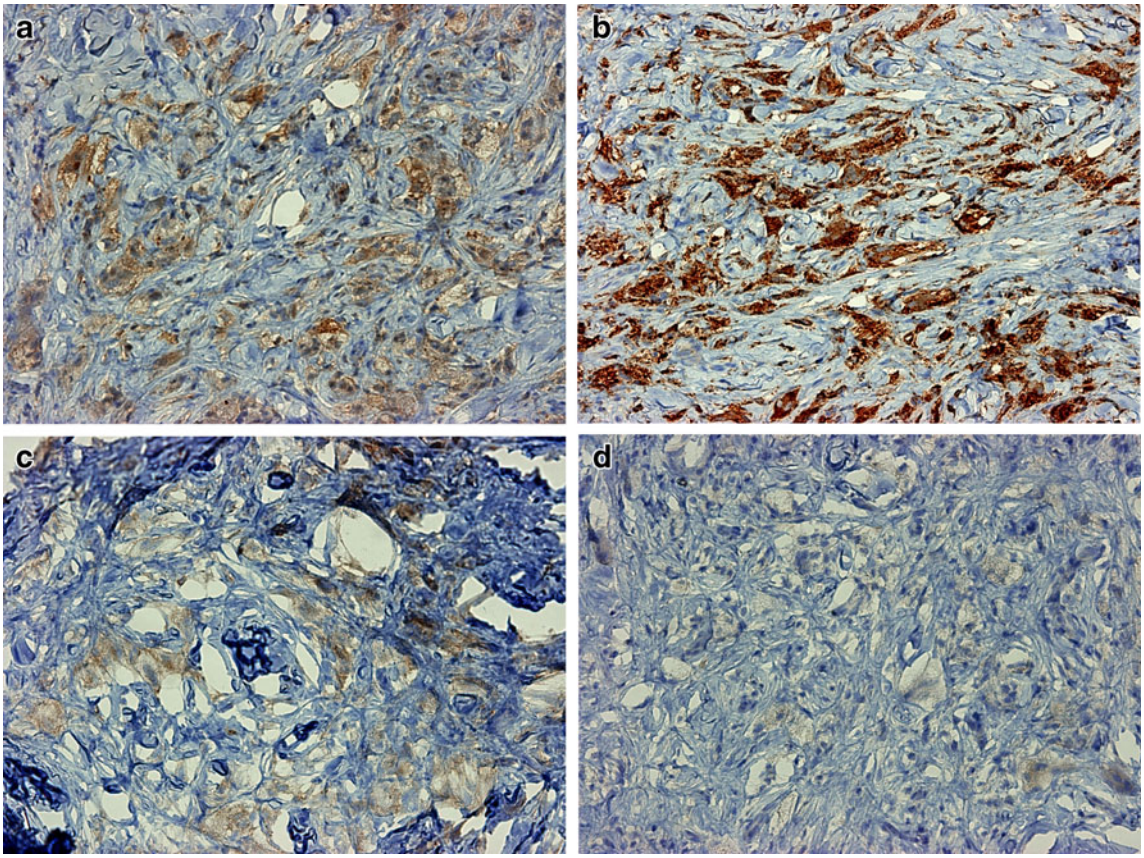

Fig. 3 **a**,**b**,**c**,**d** The "indeterminate" histiocytes are (**a**) S100 positive, (**b**) CD68 positive, (**c**) CD4 positive, (**d**) CD1a negative (original magnification ×400)

While the disease occurs mainly in adults without sex predilection, a congenital form and fewer than a dozen cases in children have been also reported [2, 7].

The pathogenesis is unknown.

Both isolated and generalized forms of ICH have been documented. The isolated variant is characterized by a few soft reddish cutaneous lesions, up to 1 cm or more in diameter. In the generalized form there are red to brown papules, less than 1 cm in diameter, later the lesions become brown to yellow and ulceration may occur. Our patient developed several 2–6 mm large, reddish-brown, partially yellowish compact papules on the trunk, upper and lower extremities and on the buttock.

The clinical course is usually benign, most patients experience partial or complete regression, although single cases of ocular or osseous involvement [15, 16] and ICH cases with leukaemia [12, 17–19] have been also described.

Histology generally reveals a monomorphous infiltrate of vacuolated, xanthomatized histiocytes throughout the entire dermis. The ICH cells display positive immunostaining for

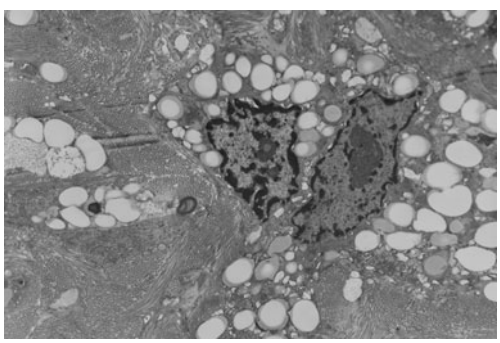

Fig. 4 Ultrastructure of the dermal foamy histiocytes with lipid bodies, intracytoplasmic lipid inclusions and few myeloid figures (original magnification ×24000)

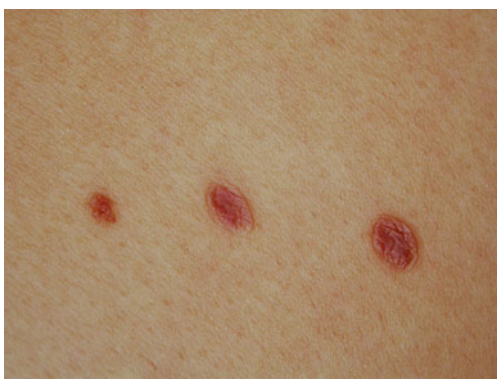

Fig. 5 Healing skin symptoms after a 2-month thalidomide treatment

S100, CD68 and in most cases CD1a, but lack Birbeck granules ultrastucturally. In our patient the dermal histiocytes were S100 and CD68 positive but CD1a negative, which is in contrast to some of the published ICH cases, while in a recent publication by Ratzinger et al. several out of the 18 adult patients were CD1a negative [11].

Most cases with ICH do not require treatment [11]. There are scattered case reports on surgery for the solitary lesions [13], on beneficial effects of topical coal tar or 5-fluorouracil application [7], psoralen–UVA treatment [20], or for extensive disease chemotherapy [10], or total skin electron beam therapy [21].

Thalidomide is an immunomodulatory and anti-inflammatory molecule with a significant anti-inflammatory cytokine modulation and inhibition of tumor necrosis factor-alpha, a key cytokine for Langerhans cell maturation, and interleukin-6 activation [19]. The efficacy of thalidomide might be also related to its antiangiogenic activity principally through the inhibition of the basic fibroblast growth factor-2 [22].

However thalidomide is far not an evidence based therapy of the disease: previously only Ventura et al. reported a 62-year-old man with ICH who had been successfully treated with this medication [23].

Although ICH is a usually benign disease, we decided to introduce a thalidomide treatment because the rapidly progressing skin symptoms on the face, ears and extremities seemed to endanger the boy's carrier. The treatment resulted in an immediate improvement and the disease healed with residual pigmentation within a few months. Since ICH can be rarely associated with haematological malignancies also the patient presented here should be regularly—now yearly—monitored for that.

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