

Case Report

Juvenile xanthogranuloma developing after treatment of Langerhans cell histiocytosis: case report and literature review

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Received July 23 2012, Accepted August 4 2012, Epub September 5, 2012; Published September 15, 2012

Abstract: The synchronous or metachronous development of Langerhans cell histiocytosis and non-Langerhans cell histiocytosis in the same patient is rare. To date, only seven cases of xanthogranulomas developing in young patients with a history of Langerhans cell histiocytosis and systemic therapy have been reported in the literature. As of yet, the pathogenesis and the clinical significance of this phenomenon are unclear. We report the case of a 3 year old boy who developed juvenile Xanthogranulomas on the forehead and right upper eye lid 1.5 years after systemic therapy for monosystemic Langerhans cell histiocytosis of the bone and complete disease remission.

Keywords: Langerhans cell histiocytosis, juvenile xanthogranuloma, synchronous, metachronous, coincidence

Introduction

The term "histiocytosis" denotes various benign and malignant diseases, which are characterized by the proliferation of epithelioid ("histiocytic") cells. In general, these disorders are divided into Langerhans cell histiocytosis (LCH), non-Langerhans-cell histiocytoses (non-LCH) and malignant histiocytoses [1-3]. It is supposed that most histiocytoses develop from a CD34+ stem cell which can differentiate along different pathways depending on the cellular microenvironment[4].

LCH and non-LCH (juvenile xanthogranuloma/JXG, benign cephalic histiocytosis, papular xanthoma and others) are considered separate disease entities as reflected by their different prognosis and different treatment modalities. However, the distinction between LCH and non-LCH is not always well defined [5];. In the Histiocyte Society's Classification published in 1997, both JXG and LCH are assigned to the same group, namely the group of histiocytoses related to dendritic cells with variable biologic behavior [6].

In recent years, several reports have documented a synchronous or metachronous devel-

opment of LCH and JXG in the same patient. In particular, seven cases of young children with a history of LCH and chemotherapy who subsequently developed JXG have been reported [7-10]. This rare but well documented phenomenon has raised various questions as to the relatedness of LCH and JXG and to the pathogenesis of JXG.

Case history

The patient is a 3 year old boy with a history of monosystemic LCH diagnosed 1.5 years ago, in August 2008. At that time, radiologic imaging showed a multilocal involvement of the skeletal system with multiple osteolytic lesions in the skull and both femoral bones. There was no evidence of involvement of the skin, the inner organs or the soft tissues. A biopsy was taken from one of the osteolytic lesion in the right femur. Histology showed a dense infiltrate of CD1a and S100 positive epithelioid cells (**Figure 1A** and **1B**). On the basis of the clinical and the histological picture, a diagnosis of LCH was rendered. Subsequently, a systemic therapy with prednisone and vinblastin was carried out over several months. Clinical examination after completion of the therapy in March 2009

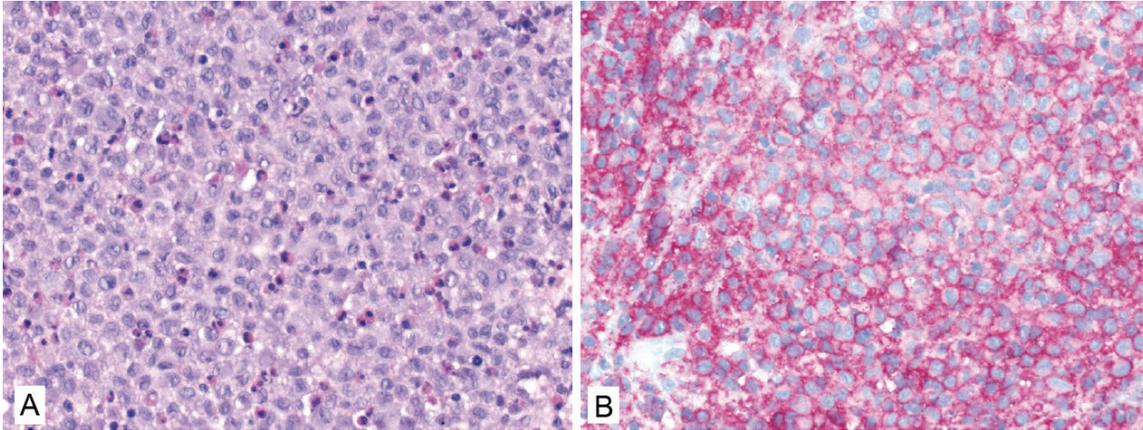


Figure 1. Biopsy taken from the osteolytic lesion of the right femur. A. Polymorphous infiltrate of LCH cells and eosinophils. Some of the LCH cells display the characteristic reniform, grooved nuclei (Hematoxylin-Eosin, x400). B. CD1a immunohistochemistry showed a strong membranous positivity (x400).

showed complete remission. 1.5 years after the termination of therapy, the mother of the boy noticed growing lesions on the right-sided forehead and on the right upper eyelid. Clinical examination showed a subcutaneous, non-movable, firm nodule of 2 cm on the right-sided forehead. There were no signs of inflammation. The overlying skin was normal. On the right upper eyelid an “appendage” of 0.3 cm was detected. This lesion was clinically interpreted as molluscum contagiosum. Both lesions were surgically excised.

Histological findings

Histologically both lesions displayed a solid tumefactive infiltrate, made up of mononuclear cells, which in part showed a xanthomatous morphology (**Figure 2A** and **2B**). In some areas a spindle cell morphology with storiform growth pattern could be demonstrated. Scattered multinucleated giant cells with a Touton-like morphology were observed (**Figure 2C**). The nodules were sharply delineated against the surrounding tissue. The tumor cells stained positive for CD68 (**Figure 2D**), but were negative for protein S100, CD1a (**Figure 2E**) and CD207 (Langerin). There was a patchy positivity for Factor XIIIa. Due to the histomorphological picture and the immunohistochemical results, a diagnosis of JXG was made. 2 years after the resection of the lesions the patient is doing well, with no evidence of recurrent LCH or JXG.

Discussion

LCH and JXG show a clinical as well as a histopathological overlap, especially in children [11] (**Table 1**). Both LCH and JXG follow a chronic course and have a predilection for the skin, but both diseases may also present with systemic involvement of the internal organs, soft tissues and bone. Although most affected patients are children and young adults, the disorders may occur at virtually any age. Spontaneous regression is possible in both diseases, but it occurs significantly more often in JXG [7].

The etiology of both LCH and JXG is still unclear. Specifically regarding LCH, the question whether the LCH lesions are neoplastic or reactive in nature is still a matter of controversy. Numerous characteristics of LCH, like the clonality of all non-pulmonary LCHs, recurrent genetic abnormalities of LCH cells and even, in rare cases, familial clustering of LCH are points in favour of the neoplastic theory. On the other hand, the benign cytology of LCH cells, the indolent clinical course of most LCH cases as well as the lack of clonality in pulmonary LCH may be considered arguments for a reactive nature of LCH [12]. These observations point to a heterogeneous etiology of LCH. In contrast, JXG is generally considered a reactive lesion derived from the monocyte/macrophage line [3, 13, 14].

The metachronous development of JXG in patients with a history of LCH and chemothera-

Juvenile xanthogranuloma after LCH

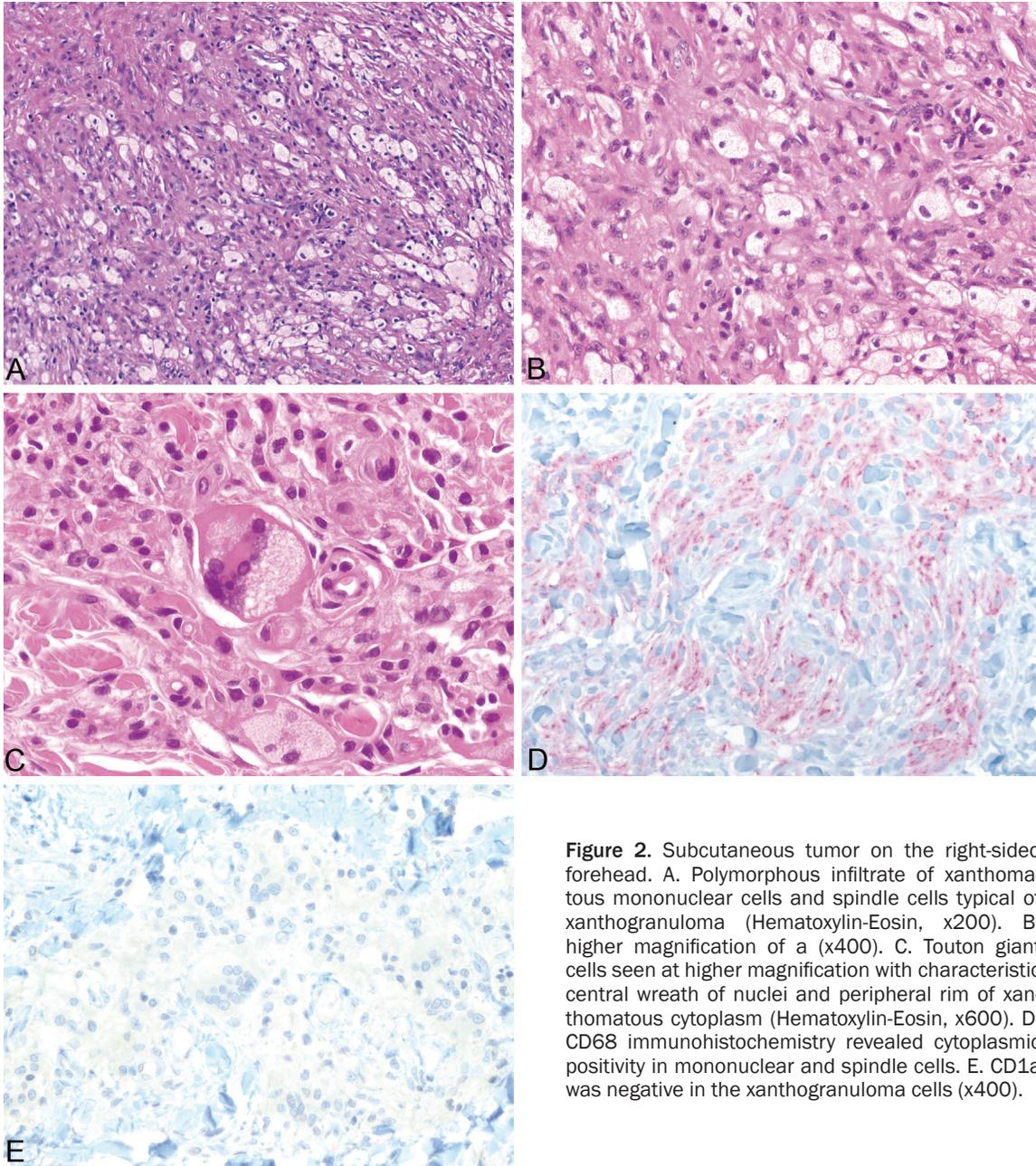


Figure 2. Subcutaneous tumor on the right-sided forehead. A. Polymorphous infiltrate of xanthomatous mononuclear cells and spindle cells typical of xanthogranuloma (Hematoxylin-Eosin, x200). B. higher magnification of a (x400). C. Touton giant cells seen at higher magnification with characteristic central wreath of nuclei and peripheral rim of xanthomatous cytoplasm (Hematoxylin-Eosin, x600). D. CD68 immunohistochemistry revealed cytoplasmic positivity in mononuclear and spindle cells. E. CD1a was negative in the xanthogranuloma cells (x400).

py is a relatively rare phenomenon, which has evoked many questions regarding the pathogenesis and biology of LCH and non-LCH and their interrelationship. Up to now, 7 children and neonates who developed JXG following LCH and systemic therapy have been reported in four previous studies (**Table 2**). The time span between the diagnosis of LCH and the occurrence of JXG ranged from months to years. JXG arose either in anatomic sites previously involved by the LCH or at new sites previously

unaffected by the LCH. All of the JXG were limited to the skin [7-10].

In addition, two cases of synchronous JXG and LCH have also been reported. Shani-Adir et al described a two year old boy who presented with both benign cutaneous histiocytosis (a subcategory of JXG) and LCH with multilocular bone involvement [5]. Yu et al. reported the case of a several weeks old baby with a mixed histiocytosis of the skin with hybrid features of

Juvenile xanthogranuloma after LCH

Table 1. Histomorphological, immunohistochemical and ultrastructural characteristics of LCH and JXG

| | Langerhans cell Histiocytosis | Juvenile Xanthogranuloma |
|--|--|--|
| Main lesional cell(s) | LCH cell. | Varying amounts of mononuclear cells, multinucleated cells with or without Touton features and spindle cells. |
| Accompanying inflammatory infiltrate | Pronounced. Made up of eosinophils, neutrophils, histiocytes, lymphocytes and plasma cells. The eosinophilic infiltrate may be very prominent, even dominating the histologic presentation. | Mostly sparse. Lesions may contain scattered eosinophils, lymphocytes and plasma cells. However, „younger“ lesions can present with a prominent eosinophilic infiltrate even reminiscent of LCH. |
| Cytology of main lesional cell(s) | LCH cells often have an elongated, reniform, vesicular nucleus which sometimes shows a groove parallel to its long axis (“nuclear fold”). | Mononuclear cells display a rounded to elongated, sometimes reniform nucleus. Mononuclear and multinucleated cells may contain fine cytoplasmic vacuoles leading to a xanthomatous appearance. |
| Touton cells | Touton-like multinucleated giant cells can be demonstrated in rare instances and do not preclude the diagnosis of LCH! | Classic Touton cells with a central wreath of nuclei and a peripheral rim of eosinophilic to vacuolated cytoplasm can be demonstrated in most of the cases. Absence of Touton cells however does not preclude diagnosis of JXG |
| Immunohistochemistry | CD1a:+ S100:+ CD207(Langerin):+ CD68:variable, usually negative Factor XIIIa: variable, usually negative | CD1a:- S100:- CD207(Langerin):- CD68:+ Factor XIIIa: variable, usually positive |
| Electron microscopy of main lesional cell(s) | Birbeck granules | No Birbeck granules |

Table 2. Reported cases of JXG following LCH and systemic therapy.

| No | Author/reference | Sex/Age at diagnosis of LCH | Localization LCH | Localization JXG | Time span between LCH and JXG |
|----|-------------------|-----------------------------|------------------------------|--------------------------|-------------------------------|
| 1 | Hoeger et al. | Male, 17 months | Scalp, skin, pituitary gland | Eye lids, axilla | 5 years |
| 2 | Hoeger et al. | Female, 2 years | skin | Eye lids, throat | 2.5 years |
| 3 | Hoeger et al. | Female, 11 months | Skin, bone, pituitary gland | Eye lids, throat, thighs | 3 years |
| 4 | Patrizi et al. | Female, 15 months | Skin, bones, lymph nodes | Trunk, thighs, perianal | 3.5 months |
| 5 | Patrizi et al. | Male, 14 months | Skin, bone | Trunk, extremities | 1.5 years |
| 6 | Perez-Gala et al. | Female, 2.5 months | Skin, bone, liver, eye | Cheek | 9.5 months |
| 7 | Bains et al. | Male, neonate | Skin | External auditory canal | 2 years |
| 8 | Current case | Male, 3 years | Bone | Eye lid, Forehead | 1.5 years |

JXG and LCH [4]. Furthermore, Tran et al described the case of a young woman with a history of JXG at the age of 20. She did not receive any systemic therapy. Three years later the patient developed diabetes insipidus as well as a pelvic mass lesion. A biopsy of the pelvic mass yielded a diagnosis of LCH [15].

These rare examples of JXG preceding, concomitant to or following a diagnosis of LCH underscore the close relationship between these clinically and biologically distinct disorders. On an experimental basis, studies have shown that the cells of LCH and JXG are derived from the same cell line, namely a colony forming type of dendritic cells/monocytes [16]. In-vitro experiments have demonstrated that variations in the local cytokine environment may activate macrophages and modulate their phenotype [3]. Even changes in lineage differentiation could be observed. On the basis of these observations, Patrizi et al hypothesized that JXG appearing subsequent to LCH may represent a further conversion or, rather, a form of "maturation" of the LCH cells under the influence of chemotherapy [7, 8]. However, the theory of a differentiation switch from LCH cell to JXG cell under chemotherapy remains purely speculative up to now.

Another theory regarding the occurrence of JXG in patients with LCH is based on the assumption that JXG may be triggered either by the LCH lesions themselves or by the effects of chemotherapy. Several disease entities have been described which seem to be able to promote or trigger the development of non-LCHs e.g. atopic dermatitis [17] and childhood leukemia [13]. These clinical observations have given rise to the hypothesis that JXG may be triggered or modulated by cytokines [3]. It is well known that LCH lesions produce abundant amounts of different cytokines, a phenomenon referred to as "cytokine storm" [18]. Chemotherapy itself is also liable to cause changes in the cytokine microenvironment. However, the current literature yields no conclusive data as to which specific cytokine or molecule might be responsible for the development of JXG.

In conclusion, we described a further case of JXG following treated LCH in a child and reviewed the literature on this topic. This rare occurrence underlines the relationship and overlap between LCH and non-LCH. However,

the significance of the synchronous or metachronous occurrence of JXG in patients with LCH remains still poorly understood. Two interesting theories exist which are aimed at explaining this phenomenon, but both lack scientific validation, especially on an in vivo level. Further studies are needed to further elucidate the etiology and interrelationship of LCH and JXG.

Acknowledgements

The authors would like to thank Ivor Leuschner, MD, Kiel, Germany, for performing the Langerin stain.

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Juvenile xanthogranuloma after LCH

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