



Emperipolesis in a Juvenile Xanthogranuloma: Sentinel Case Report and Review of the Literature

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Abstract

This is the first reported case of a giant juvenile xanthogranuloma with multiple unusual features. The patient is an infant who presented with a rapidly growing 4.0 cm soft tissue mass on the back with necrosis and ulceration. MRI demonstrated the characteristic signaling of sebaceous cyst. Histology revealed a large and well-circumscribed dermal lesion that is composed predominately of histiocytes, lymphocytes, eosinophils, multinucleated giant cells, Touton giant cells and the extremely unique feature consisting of an extraordinarily high degree of emperipolesis. The diagnosis of juvenile xanthogranuloma is confirmed by positive immunostaining for CD68 and CD163, and negative immunostaining for CD1a, CD117 and S100 ruled out a Langerhans cell lesion. The final diagnosis is giant juvenile xanthogranuloma with emperipolesis simulating Rosai-Dorfman Disease, a lesion that has never been reported, and may represent a mixture of a dendritic cell related tumor and a macrophage related tumor according to the 1997 WHO classification of histiocytic lesions.

Keywords: Xanthogranuloma; Juvenile; Emperipolesis; Non-Langerhans cell histiocytosis

Introduction

Juvenile Xanthogranuloma (JXG) is a non-Langerhans histiocytic proliferative disorder most common in infancy or childhood although cases in adult and elderly patients have been reported [1,2]. JXG presents with one or more cutaneous or subcutaneous nodules often occurring in head and neck but also on trunk and extremities. Extra-cutaneous manifestations include the eye, testis, lung, kidney and retroperitoneum. Several authors have reported on the association between JXG, neurofibromatosis and juvenile chronic myelogenous leukemia [3-8]. Whether JXG is a reactive or neoplastic process is still unsettled.

There are multiple unusual features described in this case report:

1. Emperipolesis which has only been reported in a single series with 10 cases [9],
2. The large size of 4.0 cm in an infant,
3. Superficial necrosis and ulceration and,
4. The central tumor necrosis which gave the impression of sebaceous cyst on MRI.

Histological, JXG is a histiocytic infiltrate as well as lymphocytes, eosinophils, and plasma cells can be observed. Touton cells are typical but not diagnostic. Emperipolesis has only been reported in JXG in 10 cases and in only three of these cases did their co-exist emperipolesis that simulated RDD as in this case. The typical clinical appearance is that of red to yellow to orange 2 mm to 5 mm dome-shaped papules or 1 cm to 2 cm small nodules. Epidermal variants including atrophic plaques, lichenoid and those with features of a cutaneous horn [10-12]. The giant variety seen in this case is very rare [13]. JXG is generally asymptomatic and tend to resolve spontaneously in 6 to 36 months and the necrosis and superficial epidermal ulceration present in our case is highly unusual [14-16]. MRI imaging of JXG usually exhibit homogenous increased intensity of signal due to the lipid contents in the histiocytes and the unusual sebaceous signal pattern in our case is due to the centrally necrotic areas of the tumor [17].

In this article, we report a case of a Juvenile xanthogranuloma with unusual features including large size, ulceration, tumor necrosis and extraordinary high degree emperipolesis. The histological features and immunostaining results of this case are presented and differentiations with other histiocytic lesions such as Rosai-Dorfman diseases are discussed.

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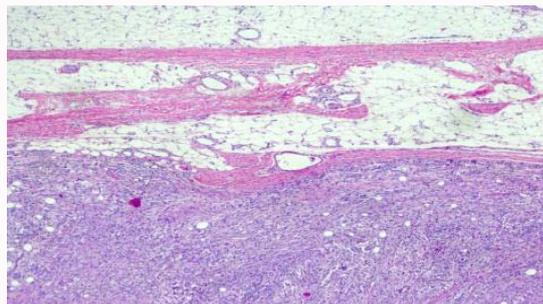


Figure 1: Well circumscribed lesion, 20X.

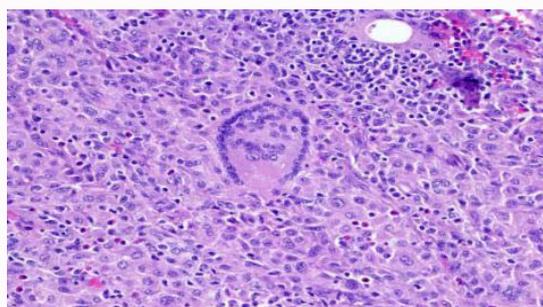


Figure 2: Touton giant cell, 40X.

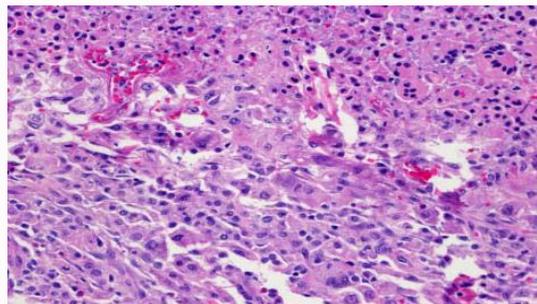


Figure 3: Tumor necrosis, top; viable tumor bottom, 40X.

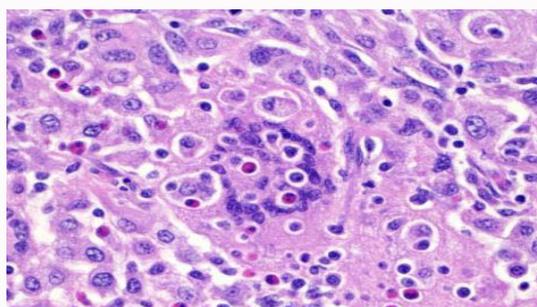


Figure 4: Touton giant cell with emperipolesis by eosinophils and lymphocytes, 200X.

Case Presentation

The patient is a six month old infant presenting with a soft tissue lesion on the right back. The mass appeared at 4 months old, grew rapidly for two months and ulcerated before admission. MRI revealed a large soft tissue mass in subcutaneous tissues without extension into the muscular planes. Signal characteristics indicated a sebaceous cyst. Patient was referred to surgery for removal and possible skin grafting.

At admission, patient had a fever of 101.2°F, a 4 cm back mass, a ten-point review of systems and physical examination were otherwise negative. Blood counts were normal. The mass was surgically removed with 1 mm margins. The gross examination the specimens' skin surface was dark tan to brown with 2 cm ulceration. The cut surface revealed a well circumscribed, tan to yellow, 4.0 cm × 3.5 cm × 2.5 cm mass with hemorrhagic and necrotic areas.

Histological, the sections showed a large and well-circumscribed dermal lesion (Figure 1) composed predominately of the many morphologic variants of macrophages with lymphocytes, eosinophils, multinucleated and Touton giant cells (Figure 2), tumor necrosis (Figure 3) and occasional mitosis are also noted. The multinucleated cells and touton giant cells demonstrated emperipolesis by the lymphocytes and eosinophils (Figure 4). The tumor cells are positive for CD68 (Figure 5) and CD163 indicating histiocytic origin, and negative for CD1a (Figure 6), CD117, and S100 which rules out LC derivation. There are scattered CD3 positive T-cells and CD20 positive B-cells in the lesion. Ki67 staining of the histiocytes is relatively increased. The final diagnosis is giant juvenile xanthogranuloma with emperipolesis and multiple unusual features which has never been previously reported.

Discussion

The histiocytoses are disorders characterized by the accumulation of members of the mononuclear phagocyte system that including

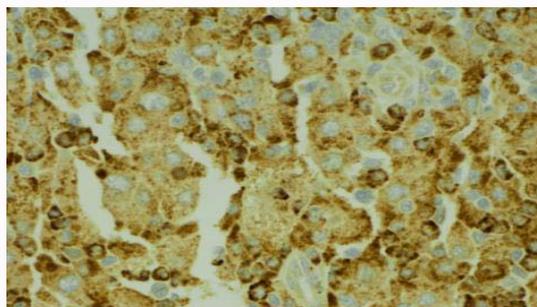


Figure 5: IHC for CD 68, 200X.

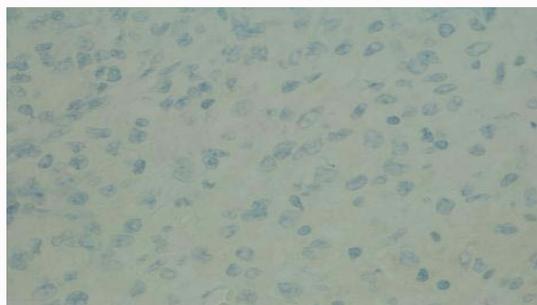


Figure 6: IHC for CD1a, 200X.

monocytes, macrophages and dendritic cells in various tissue and organ. More than 100 different subtypes have been described with a wide range of clinical features and histological presentations [18]. Their different microscopic features may partly result from effects of cytokines [19]. There are different classification systems that are mostly based on ontogeny, function, location and/or morphology of these histiocytes. Table 1 is a summary of the 1997 WHO classification

Table 1: A Contemporary Classification of Histiocytic Disorders Benign [36].

Macrophage-related
Hemophagocytic syndromes
Rosai-Dorfman disease (Sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Dendritic cell-related
Langerhans cell histiocytosis-epidermal dendrocytes
Juvenile xanthogranuloma and related disorders-dermal dendrocytes
Solitary histiocytomas of various dendritic cell phenotypes
Malignant
Monocyte-related
Leukemias (FAB and revised FAB classifications)
Chronic myelomonocytic leukemia
Extramedullary monocytic tumor or sarcoma
Dendritic cell-related histiocytic sarcoma
Macrophage-related histiocytic sarcoma

of Histiocytic/Reticulum disorders.

The histiocyte is the morphological term used to describe tissue resident macrophages. Although the term is outmoded, it has been used widely to label the disorders of other cells including Langerhans cells, indeterminate cells, interdigitating cells and other dendritic cells. For a long time these cells had been thought to be derived exclusively from blood monocytes. However, recent findings demonstrate that they are from one of three origins

1. Adult macrophages derived from precursors that arise during embryonic development.
2. Bone marrow derived monocytes that migrate to the tissue and can differentiate into any type of MPS depending on the different microenvironments.
3. Dendritic cells from bone marrow derived common DC precursors [20].

Macrophages and monocytes are distinguished as larger ovoid vacuolar cells that excel in the clearance of apoptotic cells, cellular debris and pathogens; however morphological analysis is sometimes equivocal, especially when complicated by inflammation [21]. They are believed to be derived from CD34 bone marrow precursors and stain positive for CD11, CD14, and CD68 and are negative for Langerhans cell markers CD1a, S100 and factor XIIIa. The Langerhans Cell (LC) is also derived from a CD34 bone marrow precursor but resides in the epidermis and is a specialized dendritic cell that takes up antigens in the epidermis, migrates through the dermis to lymphatic and lymph nodes and presents processed antigens in association with major histocompatibility complex molecules to T cells. LC's are negative for CD14 and CD68 (macrophage markers) and positive for CD45, S100 and CD1a. Dendritic cells reside in the dermis (not the epidermis where LC's cells reside) and are derived from dermal fibroblasts and in contrast to macrophages and LC's cells express Factor XIIIa, von Willebrand factor receptor and negative for S100 and CD1a. They are believed to be involved in tissue hemostasis and antigen processing. Table 2 for a synopsis of cell surface markers.

In 1997 the Histiocytic Society/WHO proposed a classification of benign and malignant disorders of histiocytes and (Table 1) lists some of the cutaneous diseases. The cause of JXG is unknown;

Table 2: Cell Surface Markers in Histiocytic Lesions.

	Positive Markers	Negative Markers
Macrophages	CD14, CD45, CD 68	S100, CD1a, Factor XIIIa
Langerhans cells	CD45, S100, CD1a	CD14, Factor XIIIa
Dermal dendrocytes	CD45, CD68, Factor XIIIa	S100, CD1a

Note: CD45 is a marker for hematopoietic cells, dendrocytes and fibroblasts.

Cytomegalovirus antigens are reported in some histiocytes from an oral lesion, suggesting an association with infection [22]. The cell of origin is controversial, most believe that the cellular origin is dermal dendrocyte (in contrast to the epidermal derived Langerhans cell lesions); although some conclude that there is a morphological and phenotypical overlap between the cells of JXG and plasmacytoid monocytes, which may explain the extracutaneous involvement [23]. Currently, JXG is classified as non-Langerhans cell histiocytosis. JXG may develop in patients with LCD [24,25]; This may represent a xanthogranulomatous response to the inflammation of LCD. Immunohistochemistry studies have shown that the histiocytes in JXG are regularly positive for vimentin, macrophages markers including CD14, CD68, lysozyme, HAM56 and negative for S-100, CD1a. Indeed, JXG can mimic, or be mimicked by diverse entities such as LCD, epithelioid melanocytic tumors, lipidized dermatofibroma, reticulohistiocytoma and mastocytoma [26]. In this article, the histology and immunochemical studies revealed typical features of JXG. However, there is significant high degree of emperipolesis, which raise the concern of Rosai-Dorfman Disease (RDD) and Erdheim-Chester Disease (ECD).

RDD histiocytes may have a foamy appearance and can be multinucleated and may be difficult to differentiate from JXG. There is a case report of a child with both RDD and JXG [27], however, the two lesions were in different locations at different time points. However, the connection between two is interesting [28]. RDD histiocytes are derived from sinus histiocytic macrophages which are positive for S100, fascin, CD68, CD14, CD163 and HLA-DR and negative for CD1a and CD207. In this case report the cells are negative for S100 and CD1a. ECD is not different from extracutaneous or disseminated JXG especially when in ECD without long bone involvement. A few S100 positive cells with emperipolesis may be presented in ECD [18,29]. Molecular analysis of gain of mutation of BRAF, NRAS, KARS or MAP2K1 is recommended for ECD and disseminated JXG [30,31]. In this case, both b-raf and V600e mutations are negative.

Indeed, emperipolesis is a condition that can be observed in many physiological and pathological conditions, where hematopoietic cells in living and intact state are seen in the cytoplasm of host cell without damage [32]. In RDD, the involved histiocytes exhibit emperipolesis of lymphocytes, plasma cells, neutrophils and red blood cells. In this reported JXG, emperipolesis of lymphocytes, plasma cells and eosinophils is observed. It is believed that occurrence of emperipolesis is correlated with cytokines released by lymphocytes. It is a mechanism to improve cell survival and help prevent apoptosis of cells as they travel within the host cells [33,34]. Some studies also suggest that emperipolesis is a pathway that mediate natural killer cell mediated tumor cell death [35].

This is the first reported case of JXG with significant emperipolesis and may represent a mixture of a dendritic cell related tumor and a macrophage related tumor according to the 1997 WHO classification of histiocytic lesions.

Additionally the tumor was very large with ulceration and central necrosis, features that are extremely rare in JXG's. In general, the diagnosis is a challenge that only can be resolved by the combination of clinical, radiographic, pathological, phenotypic and molecular findings.

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