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A child with giant juvenile xanthogranuloma: a case report and review of the literature

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Abstract— Juvenile xanthogranuloma (JXG) is a rare histiocytic disorder that typically affects children. The clinical presentation of this disease is characterized by single or, rarely, multiple yellow and brown skin nodules, most often found on the face and neck. Internal organ involvement has been sporadically observed in JXG and is associated with an increased risk of serious complications. We report a case with a giant form of JXG.

Keywords: Juvenile xanthogranuloma; non-Langerhans cell histiocytosis; giant type; systemic involvements & associations

Introduction:

Juvenile xanthogranuloma (JXG) is a rare, benign non-Langerhans cell histiocytosis [1]. It affects mainly individuals in early childhood, but adult presentations are possible. Cutaneous lesions are characterized by single or multiple asymptomatic red to yellowish small papules or nodules. However, Internal systemic localizations were also documented, causing rarely serious complications. Unlike the other xanthomatous affections, JXG is not associated with dyslipidemia or metabolic disturbances. JXG is presented as small to large nodular types, but unusual presentations have been observed [2,3]. Herein, we present a case of a child with a giant type of JXG.

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Case report:
A 20 months old male patient was brought to the dermatology clinic for a cutaneous lesion on the left scapular area (**Figure 1**). The lesion started at the age of 5 months as a small asymptomatic, firm, yellowish-brown nodule. The lesion gradually increased in size until it reached its current maximum size by nine months, measuring 25 mm X 30 mm, with occasional bleeding from the surface.

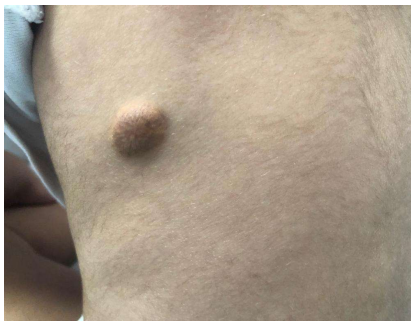
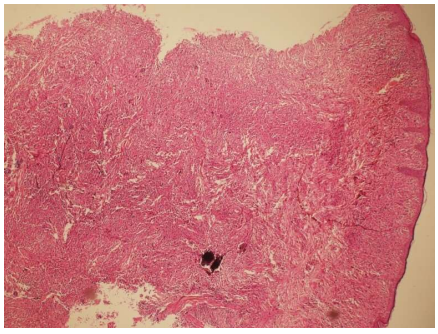


Figure 1.2.5 X 3 cm yellow-brownish colour nodule in the back, below the left scapula.

The child was born after the 39th week of pregnancy with insignificant perinatal history, no history of trauma, or specific medical or surgical history: no specific medical history or similar lesion in the family. The patient was thriving well, with no hepatosplenomegaly, or clinical signs of mucous membranes or ocular affection.
A skin biopsy was taken with a histopathologic image showing an intradermal collection of histiocytes mixed with multinucleated giant cells of the Touton type (**Figure 4(a), 4(b), 4(c)**).

4 (a)



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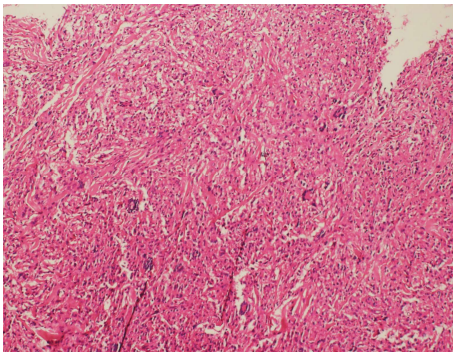

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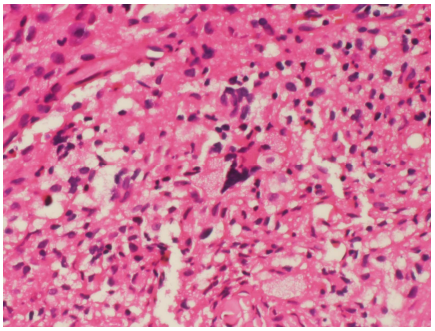

Figure 4(a). low power, H&E stain showing a dermal lesion with dense inflammatory infiltrate.

Figure 4(b).higher power, H&E stain shows multiple Touton giant cells, associated with multiple inflammatory cells. Touton cells have a wreath of nuclei within the cells.

Figure 4(c). higher power view, dermal histiocytic infiltrate mixed with lymphocytes and scattered Foamy cells.

During follow up after three months, the back lesion reduced in size up to 20 mm X 15 mm (**Figure 2**). The patient did not show up in the subsequent visit, and upon telephone contact with his parents, they have reported a quasi-complete remission of the lesion within ten months (**Figure 3**).

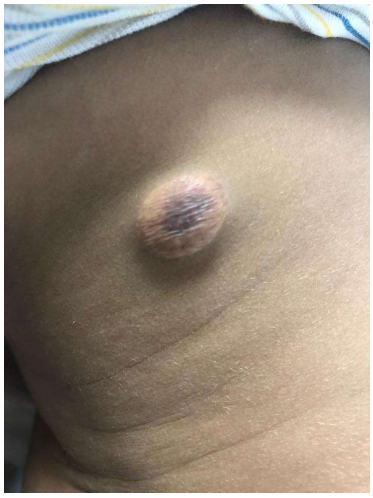

Figure 2. Regression in size of the nodule up to 2.0 X 1.5 cm after three months of follow-up.

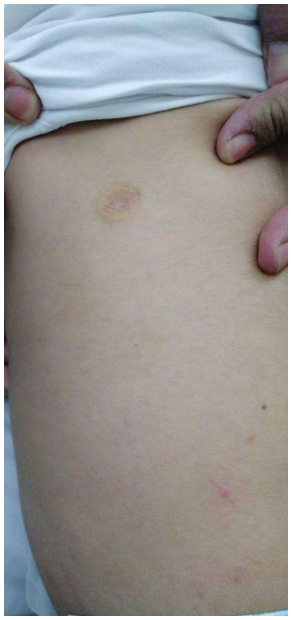

Figure 3. Quasi-complete regression of the lesion after ten months of follow-up.

DISCUSSION

Juvenile xanthogranuloma (JXG) is the most common type of non-Langerhans cell histiocytosis [3]. First, it was described in 1905 as *congenital xanthoma multiples* bay Adamson [4]. Mc Donaph had designated the disease as *nevoxanthoendothelioma* in 1912, and endothelial cells were considered the disease's origin [5]. Based on the histologic finding of giant cell and lipid-laden histiocytes, Helwig and Hackney proposed the name of Juvenile xanthogranuloma and demonstrated that the disease has no endothelial origin [6].

JXG affects the principally pediatric population in their early childhood. It develops in 40-70% of patients during the first year of life, with a median age of onset between 5 months to one year. However, in 5-17% of cases, the lesions are present at birth. Moreover, JXG has a male predominance estimated at 1.5:1. Adult-onset is rare, with no sex predilection [3,7,8,9]. The exact etiology of JXG is not well known. It is considered a reactional granulomatous process of histiocytes in response to an unknown stimulus, most probably physical or infectious [10,11]. Bergman et al. suggested that the synthesis and accumulation of cholesterol are enhanced in the monocyte-derived macrophages in the cutaneous lesion of the adult patients with JXG [12].

Clinically, JXG is presented as a well-demarcated, pinkish-yellowish round to oval dome-shaped papules or nodules, measuring 5-20 mm of diameter, with occasional development of telangiectasias on the surface. Ulceration and bleeding could also occur [3]. Rarely, JXG can take a plaque-like presentation [1], or take a linear or segmental distribution [13,14]. It is presented as a single lesion in 60-82% of patients. In both pediatric and adult forms, JXG affects any area of the body. Still, the head and neck are the main affected areas, followed by the trunk and extremities [3]. However, mucosal lesions of JXG are infrequent [7,15,16,17]. Gianotti has described the most frequent clinical types of JXG; a small nodular form with nodules measuring 2-5 mm, and large nodular form with nodules measuring 10–20 mm. However, both forms may coexist in the same patient [18]. Rare variants of JXG include the giant form with lesions measuring larger than 2 cm in size, as in our case. Like the classical JXG, the giant type could be acquired, cutaneous, or systemic. However, the congenital presentation is the most common picture of the giant variant [19]. Nevertheless, other clinical presentations include a facial type called *Cyrano type*, lichenoid type, subcutaneous and deep in soft tissue presentations [1,11,20,21].

Extracutaneous systemic involvement is rare and could affect 4% of JXG patients, involving lung, myocardium, spleen, liver, kidney, gonads, retroperitoneum, central nervous system, and bones, with different symptoms and possible complications [22-25]. Patients with visceral involvement of JXG always have a concomitant skin lesion [3], but isolated visceral localization of JXG was exceptionally reported [25-28]. Ocular localization is the most common systemic involvement and detected in 0.3-0.4% of patients with cutaneous lesions. Furthermore, it starts in most cases at the age of 2 years or younger, with an average age of onset of 8 months. The skin lesions associated with ocular involvement were always multiple, but isolated ocular lesions were also reported. The possible complications are hyphema, redness, irritation, uncontrolled glaucoma, photophobia, and uveitis [29]. However, in giant JXG, the extracutaneous is seldom, and the most common localization is intramuscular. And as in classic JXG, the most common cutaneous localization of the giant type was head and neck followed by trunk and extremities [19].

The Association of JXG to other affections is rarely possible. The occurrence of juvenile chronic myeloid leukemia (JCML) in patients with JXG is documented, starting in most patients by the end of the second year of life. JXG, in these cases, is typically multiple and can precede or appear concomitantly to JCML [30]. Nevertheless, the risk of development of JCML is 20-32 folds higher when the JXG is associated with café-au-lait spots and family history of neurofibromatosis type1

(NF1), than patients with NF1 but no JXG. Moreover, the triple association between JXG, NF1, and JCML is 30-40 folds higher than expected [31]. Additionally, one of the rarely documented associations is JXG, NF1, and juvenile myelomonocytic leukemia (JMML) [32]. The association of JXG to Langerhans cell histiocytosis (LCH) has also been described in the literature. However, both entities can coexist or overlap clinically and histopathologically. It is assumed that chemotherapy used to treat LCH or the associated inflammatory reaction can play a developmental role for JXG [13,33]. Limited reports have demonstrated an association of JXG to cytomegalovirus infection, Niemann-Pick disease, and urticaria pigmentosa [11,34,35]. Moreover, a mitogen-activated protein kinase (MAPK) mutation has been described in some JXG, especially extra-cutaneous cases [36,37]. And a revised classification recommend performing a molecular analysis of BRAF, NRAS, KRAS, or MAP2K1 in extra-cutaneous JXG [38].

The diagnosis of JXG is usually clinical, but due to its rarity or atypical presentations and the lack of knowledge about this disease among physicians, it occasionally requires some investigative tools to confirm the diagnosis. The clinical differential diagnoses include Spitz nevus, Langerhans cell histiocytosis, neurofibroma, mastocytoma, xanthoma, and molluscum contagiosum [39]. Histologically, a dense histiocytic infiltrate characterizes it in the dermis, giant cells, and Touton cells. The histiocytes in older lesions are characterized by foamy, vacuolated cytoplasm. At the same time, Touton cells are giant cells characterized by a central wreath of nuclei, surrounded by eosinophilic cytoplasm. These cells are observed in variable numbers in 85% of JXG cutaneous lesions; however, they are absent or present in a reduced number in the extracutaneous lesions. Eosinophil, lymphocytes, and plasma cells are often present in the dermal infiltrate. Immunohistochemical examination shows a positive immunoreactivity for CD68, vimentin, and factor XIIIa. However, JXG is always negative for CD1a and weakly reactive with some positive cases to protein S100 [1,3,40,41].

Moreover, Radiologic images are occasionally required, especially in the case of internal localization. The Doppler ultrasound gives an image of a well-defined, non-vascular, hypoechoic lesion [41].On the other hand, the computed tomography (CT) scan can give an image of a homogenous, solid soft-tissue mass. Additionally, Magnetic resonance imaging (MRI) is an excellent option to localize the lesion. However, its image ranges from hypointense to isointense on T2 and from isointense to hyperintense on T1 [42]. Moreover, in classic and giant JXG, dermoscopy could be used as an ancillary noninvasive diagnostic tool with a characteristic image of "setting sun sign" represented as a non-structured orange-yellow pattern surrounded by an erythematous border [43,44]. Reflectance confocal microscopy (RCM) can also be performed. The expected image is dilated papillae at the dermal-epidermal junction, containing large, rounded multinucleated structures representing Touton cells, in addition to discoid-shaped structures with bright peripheral ring representing foamy histiocytes [45].

The prognosis of cutaneous lesions is good, with expected self-healing within 1 to 6 years [3]. Occasional post-healing sequels are observed, including hyperpigmentation, slight atrophy, or anetoderma. For esthetic reasons or diagnostic purposes, the lesion is occasionally excised. Nevertheless, the lesion's excision is sometimes an adequate

treatment, especially in the adult form, where the spontaneous regression does not typically occur. However, post-excisional recurrence has been documented [45, 46].

The systemic form typically also has a benign course with spontaneous regression. However, therapeutic intervention is occasionally required, especially in significant morbidity due to vital threatening, as in the hepatic presentation. The risk of complication in the intraocular localization is high, and it requires, as well, a therapeutic initiation after the diagnosis with systemic or intralesional steroid or surgical excision. Other systemic involvement treatments include systemic corticosteroids, cyclosporine, methotrexate, chemotherapy, radiotherapy, or surgery [3, 20, 23, 47].

Conclusions

Juvenile xanthogranuloma is a rare cutaneous pediatric condition. Skin lesions, especially single ones, are frequently underdiagnosed. Nevertheless, because of the low but severe possible risk of internal organ involvement and systemic associations, it is crucial to know the nature and possible prognosis of this affection.

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