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CLINICAL CASE

Giant and ulcerated juvenile xanthogranuloma: an atypical presentation in infants

Xantogranuloma juvenil gigante y ulcerado: una presentación atípica en lactantes

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What do we know about the subject matter of this study?

Juvenile xanthogranuloma (JXG) is the most frequent form of non-Langerhans cell histiocytosis. It typically presents in the pediatric population as a papular or nodular, smooth, and isolated lesion smaller than 20 mm. Its presentation as a nodule larger than 20 mm and/or ulcerated is infrequent.

What does this study contribute to what is already known?

The differential diagnosis of large, ulcerated tumors in infants includes pathologies of intermediate and malignant behavior, as well as benign pathologies with atypical presentations, such as JXG. It is important to recognize atypical presentations of JXG that may simulate pathologies with ominous prognoses but have a good prognosis.

Abstract

Giant Juvenile Xanthogranuloma (GJXG) corresponds to an infrequent variant of Juvenile Xanthogranuloma (JXG) and is characterized by a lesion larger than 2 cm in diameter. It usually presents as a plaque but infrequently, presents as an ulcerated nodule. **Objective:** To report two cases of atypical presentation of GJXG, highlighting the importance of considering them in the differential diagnosis of large, ulcerated tumors in infants. **Clinical Cases:** Case 1: A 4-month-old healthy male infant presented with a rapid and progressive growing left inguinal nodule, present since 2 months of age. At physical examination he presented with a 2.6 cm indurated erythematous nodule with central ulceration. Histological study of an incisional biopsy was compatible with JXG. Ophthalmologic involvement was ruled out. Because of functional impairment and parents worry complete surgical removal was performed. The patient had favorable evolution without local recurrence at 4 years of follow-up. Case 2: A 6-month-old healthy male infant presented with a 2.4 cm scapular crusted nodule of rapid and progressive growth, present since birth. Histological study of an incisional biopsy confirmed

Keywords:
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JXG. Ophthalmologic involvement was ruled out. After 18 months of periodic clinical follow-up, there was a progressive reduction in size of the lesion. **Conclusions:** The cases presented highlight the importance of considering JXG in the differential diagnosis of large, ulcerated tumors in infants. When encountered to atypical JXG presentations, histologic studies help to confirm the diagnosis. Given the favorable prognosis of this diagnosis, periodic clinical follow-up is advised; in exceptional cases, surgical or ablative treatments may be considered.

Introduction

Juvenile xanthogranuloma (JXG) is the most frequent form of non-Langerhans cell histiocytosis. According to the new classification proposed in 2016 by Emilie et al, JXG is within group C, specifically to the xanthogranulomatous lesion family of cutaneous non-Langerhans cell histiocytosis[1]. It usually appears as a single lesion in patients younger than two years, mainly in males[2,3]. It has been reported that 40-70% of cases occur during the first year of life[4], with 15% of all cases present at birth[5]. Regarding its etiology, although there is no consensus, it is postulated that hyperactivity in the MAP-kinase pathway is related to a greater susceptibility to the development of these lesions[6].

JXG presents clinically as an isolated, asymptomatic papule or nodule, with a smooth surface, firm consistency, and initially pink in color, later acquiring a yellowish-orange hue. There are atypical presentations, which can manifest as an infiltrative plaque, exophytic tumor, or ulcerated nodule[7]. Regarding their size, they are classified as small (2-5 mm), large (5-20 mm), and giant (> 20 mm), the latter being the least frequent[8]. Unlike what has been reported for small and large JXG, giant JXG are usually isolated lesions that may present symptoms such as pain and bleeding. The most frequent morphology they present is as a plaque, followed by as a nodule, while its infrequent presentation is as an ulcerated nodule. It has been described that sometimes they present satellite nodules and peripheral telangiectasias[9].

The importance of identifying JXG of atypical presentation lies in its differential diagnosis with other ulcerated tumors in infants, which include pathologies of ominous prognosis, whether of vascular etiology (malformations or tumors e.g. hemangioma), soft tissue (myofibromas, fibrosarcomas, hamartomas, or teratomas), and cutaneous infiltrations by hematopoietic cells (cutaneous lymphocytoma, histiocytosis, and mastocytosis)[10,11].

The objective of this publication is to report the clinical case of two infants with atypical presentations of JXG as fast-growing nodules, of large size, and central ulceration, in which additional studies allowed to confirm the diagnosis. Atypical forms of JXG should be considered in the differential diagnosis of large, ulcerated tumors in infants. In addition, a review of the main aspects to consider when facing this diagnosis is presented.

Clinical Cases

Clinical Case 1

A 4-month-old male infant, previously healthy, consulted due to a 2-month left inguinal lesion, of sudden onset and rapid growth. Physical examination showed a rounded shiny erythematous nodule of 2.6 cm in maximum diameter, with well-defined borders and central ulceration (Figure 1). On palpation, it was rubbery in consistency and painless.

Initial differential diagnoses included vascular malformation or tumor (e.g. infantile hemangioma), soft tissue tumor (e.g. myofibromatosis, fibrosarcoma), isolated mastocytoma, and histiocytosis. The patient was initially studied with Doppler ultrasound, which showed a solid dermo-hypodermic nodule of heterogeneous echogenicity, 23 mm in diameter with discrete posterior enhancement. Color Doppler showed the presence of scarce central and peripheral vascular structures of low resistance. A pathology of vascular origin was ruled out; however, it was concluded that the ultrasound findings required histological correlation for greater diagnostic accuracy. An incisional biopsy was performed and the histologic evaluation described a diffuse tumor infiltrate in the dermis and hypodermis, composed predominantly of histiocytes, with some multinucleated Touton giant cells and numerous eosinophilic granulocytes. Immunohistochemical staining was positive for CD-68 and CD-4 and negative for S-100, confirming the diagnosis of JXG (Figure 2).

In the context of a giant JXG, an ophthalmology evaluation was requested, ruling out ocular involvement.

Once the diagnosis of cutaneous JXG without extracutaneous extension was confirmed, clinical follow-up was suggested, but given the location of the lesion in a rubbing area, its rapid growth rate, and the concern of the caregivers, a complete surgical excision of the lesion was performed. The patient presented a

favorable evolution, with no recurrence after 4 years of follow-up.

Clinical Case 2

A 6-month-old male infant, with no history of morbidity, consulted due to a rapidly growing mass in the right scapular area, present since one month of life. Physical examination revealed an erythematous indurated nodule of 2.4 cm in maximum diameter, with erosion, desquamation, and central crusting (Figure 3a). Dermatoscopy revealed a pinkish-orange background, a central hyperkeratotic area with a hematic crust, and a pseudo-pigmented network in the periphery (Figure 3b). On palpation, it was firm in consistency and painless.

Myofibroma, mastocytoma, or histiocytosis was initially suspected. As an initial approach, a Doppler ultrasound was performed, which showed a 22 mm, solid-appearing, hypoechogenic, dermal lesion with a subepidermal low-echogenic band. Color Doppler showed minimal peripheral vascularization. Ultrasonography ruled out a tumor of vascular origin and pointed towards a JXG, however, the atypical clinical features made diagnostic confirmation difficult, so an incisional biopsy was performed. Histologically, a complete dermal occupation by histiocytes and numerous Touton cells was described, confirming the diagnosis of JXG. The patient was subsequently evaluated by ophthalmology, ruling out ocular involvement.

Expectant management with periodic clinical follow-up was decided. The patient evolved with a progressive decrease in the size of the lesion after 18 months of follow-up.

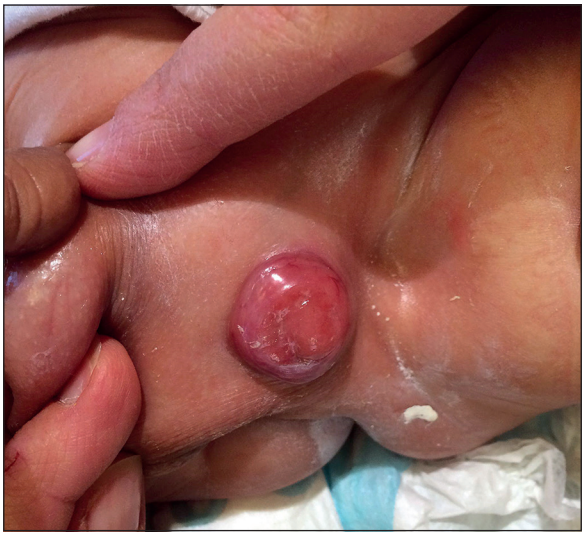

Figure 1. Round indurated erythematous nodule with central ulceration that measures 26 mm in the left inguinal fold.

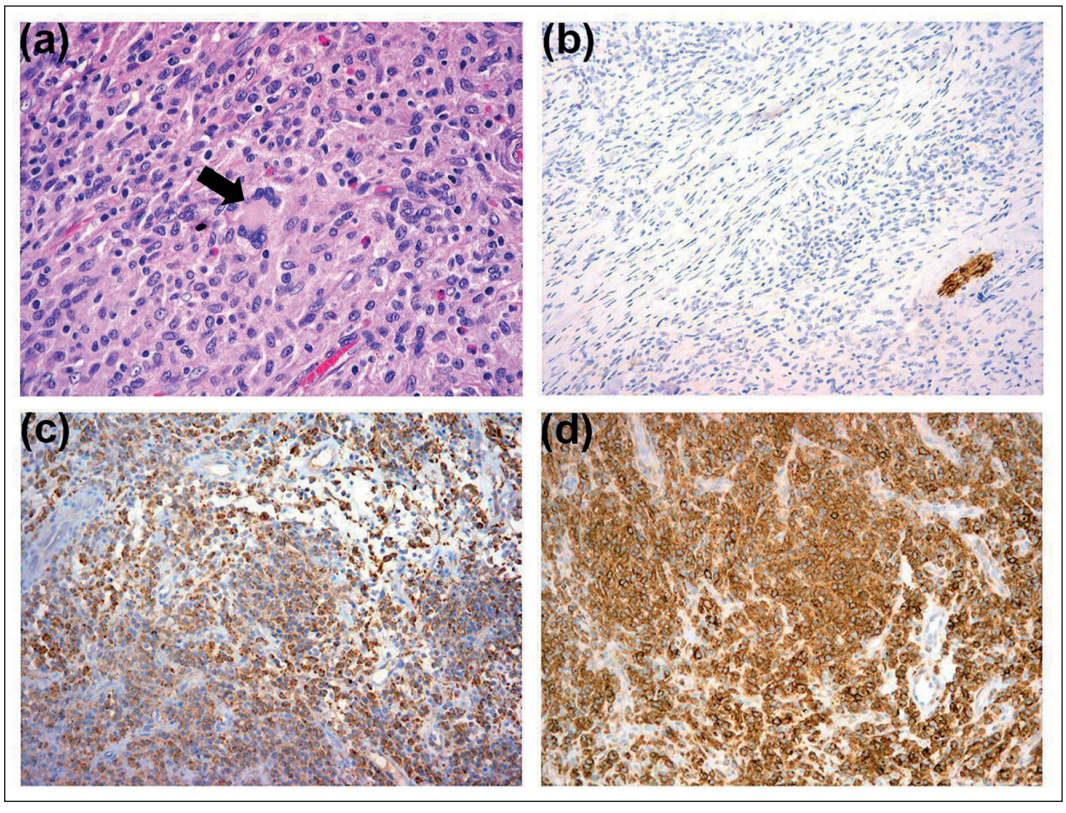

Figure 2. Dense dermal infiltration composed predominantly of histiocytes; in the central area a multinucleated Touton-type giant cell is observed-arrow (**a**). Immunohistochemistry negative for S100 (**b**) and positive for CD68 (**c**) and CD4 (**d**).

Discussion

The initial approach to large, ulcerated skin tumors in infants includes an exhaustive anamnesis and a complete physical examination, with special attention to the morphological characteristics of the lesion such as its color, shape, texture, and consistency[10]. In dermatological practice, non-invasive tools are also used to improve the visualization of lesions, such as observation with magnification through dermatoscopy, which allows observation of structural and pigmentary patterns that improve diagnostic accuracy[12].

When JXG presents typical clinical features, a physical examination confirms the diagnosis[13]. Dermatoscopic identification supports the diagnosis, where a "setting sun" pattern stands out, characterized by a central yellow-orange area surrounded by a peripheral erythematous halo[12].

In the presence of atypical presentations of JXG, the exclusively clinical diagnosis becomes difficult and dermatoscopy loses precision. Therefore, it is necessary to rely on complementary tests, such as Doppler ultrasound, biopsy, and histological study to confirm the diagnosis[8]. In the ultrasound, the JXG of typical presentation is visualized as a hypoechogenic nodule, well delimited, located in the dermis and/or hypodermis. No posterior enhancement or lateral shadowing is described. Doppler study can show low-flow vessels in its periphery, but absence of central vascularization[14]. Ultrasound can rule out an important differential diagnosis, such as infantile hemangioma[15]. However, currently, there is no consensus on specific diagnostic ultrasound criteria for JXG.

In the histology of JXG, dense histiocytic infiltrates are classically described, well-demarcated in the dermis and/or subcutaneous tissue, with intact epidermis. As a characteristic feature, multinucleated Touton giant cells can be observed, which correspond to histiocytes with large intracytoplasmic lipid accumulation; however, these cells are absent in up to 15% of cases[7]. Giant JXG may present extension towards underlying striated muscle fibers[9,16]. The immunohistochemical study allows differentiation of JXG from other histiocytoses, with CD68 and factor XIIIa expression being characteristically positive in JXG. Unlike Langerhans cell histiocytosis, in JXG the expression of langerin (CD207) and CD1a are negative[17].

Extracutaneous involvement of JXG is unusual, with ocular involvement being the most frequent, reported in 0.24% to 0.5% of cases[9,18,19]. Ocular involvement occurs most frequently in patients younger than 2 years with multiple skin lesions and the iris is the most affected structure. It presents most frequently as unilateral red eye, followed by iris or conjunctival tumor. Ocular lesions do not regress spontaneously and can lead to mass-effect complications such as glaucoma, hyphema, and even blindness[20,21]. Currently, the literature suggests that it is not necessary to perform an ocular involvement study in asymptomatic patients[18].

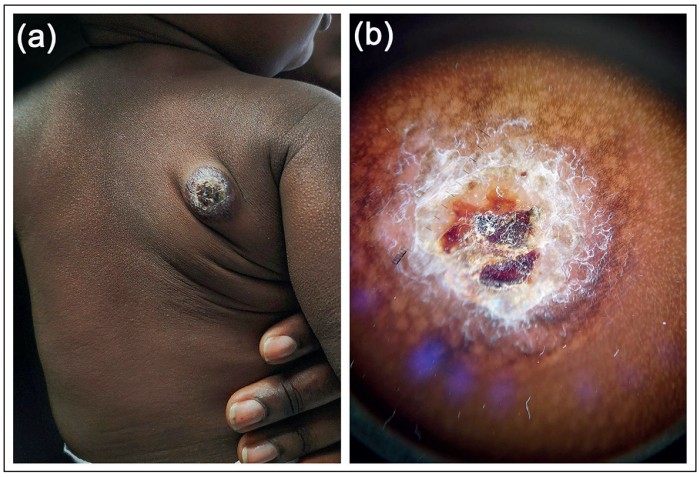

Figure 3. Oval erythematous nodule in the right scapular area that measures 24 mm (**a**). Dermatoscopy shows an orange erythematous background, a central sero-hematic crust, and peripheral pseudo-pigmentary network (**b**).

Systemic involvement of JXG affecting two or more visceral organs[13] is also infrequent, with a reported incidence of 0.3-0.8%[2,22]. The most commonly affected organs are the liver, spleen, lungs, and central nervous system[18]. Patients with systemic JXG usually present extensive cutaneous involvement, which generally precedes systemic involvement with a latency of years to months[13]. The appearance of cutaneous JXG at an early age is associated with an increased risk of systemic involvement[23]. There is no consensus on screening for extracutaneous involvement in asymptomatic patients; some authors suggest that it should be studied case by case, considering the patient's age, number of lesions, and presence of systemic symptoms[11,13].

The incidence of extracutaneous involvement and, therefore, study recommendations in giant JXG, are similar to that previously described for other forms of JXG.

In both cases reported in this publication, a study of systemic involvement was not performed; however, since the patients were younger than 2 years old, an ophthalmology evaluation was requested, ruling out ocular involvement.

Regarding their evolution, JXG represents benign lesions, with spontaneous regression within 3 to 6 years[18]. Hyperpigmentation, mild atrophy, and anetoderma are described as sequelae[9]. Parental education and clinical follow-up are recommended as the main management strategy, waiting for spontaneous regression of the lesion. In exceptional cases, such as functional alteration or psychological tension of the

caregivers, surgical excision or destructive methods such as CO2 laser can be used[24]. In the first clinical case reported, the ulcerated lesion was located in the diaper area and, due to the constant rubbing generated discomfort in the infant, with episodes of bleeding causing concern in the caregivers, it was decided to perform surgical excision of the lesion. On the contrary, in the second case reported, it was decided to perform serial clinical follow-up where spontaneous regression of the lesion was evidenced.

Conclusions

Cutaneous JXG shows a great diversity of clinical presentations. In the reported cases, the clinical presentation was atypical, as ulcerated nodules larger than 2 cm. We should include this type of lesion in the differential diagnosis of ulcerated cutaneous tumors in infants. In cases of typical clinical presentation, the diagnosis is clinical and can be reinforced by dermatoscopic findings. In cases of atypical clinical presentation, the study can be complemented with Doppler ultrasound; however, due to the absence of standardized ultrasound diagnostic criteria, histologic study with immunohistochemistry is currently the confirmatory diagnostic tool. Due to the spontaneous regression of these lesions, periodic clinical follow-up is suggested and, in exceptional cases, surgical or ablative treatments may be an option.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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References

1. Emile J-F, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127:2672-81. doi: 10.1182/blood-2016-01-690636.
2. Dehner LP. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. Am J Surg Pathol. 2003;27:579-93. doi: 10.1097/00000478-200305000-00003.
3. Cichewicz A, Białecka A, Męcińska-Jundziłł K, et al. Congenital multiple juvenile xanthogranuloma. Postepy Dermatol Alergol. 2019;36:365-8. doi: 10.5114/ada.2019.85643.
4. Cohen BA, Hood A. Xanthogranuloma: report on clinical and histologic findings in 64 patients. Pediatr Dermatol. 1989;6:262-6. doi: 10.1111/j.1525-1470.1989.tb00909.x.
5. Sonoda T, Hashimoto H, Enjoji M. Juvenile xanthogranuloma. Clinicopathologic analysis and immunohistochemical study of 57 patients. Cancer. 1985;56:2280-6. doi: 10.1002/1097-0142(19851101)56:9<2280::aid-cncr2820560923>3.0.co;2-l.
6. Collin M, Bigley V, McClain KL, Allen CE. Cell(s) of Origin of Langerhans Cell Histiocytosis. Hematol Oncol Clin North Am. 2015;29:825-38. doi: 10.1016/j.hoc.2015.06.003.
7. Lazarte L, Stefano PC, Bocian M, Solernou V, Pierini AM, Cervini AB. Solitary and congenital juvenile xanthogranuloma: case report. Arch Argent Pediatr. 2017;115:e9-e12. doi: 10.5546/aap.2017.e9.
8. Caputo R, Grimalt R, Gelmetti C, Cottoni F. Unusual aspects of juvenile xanthogranuloma. J Am Acad Dermatol. 1993;29:868-70. doi: 10.1016/0190-9622(93)70259-v.
9. Ladha MA, Haber RM. Giant Juvenile Xanthogranuloma: Case Report, Literature Review, and Algorithm for Classification. J Cutan Med Surg. 2018;22:488-94. doi: 10.1177/1203475418777734.
10. Levin LE, Kinariwalla N, Behr GG, Morel KD, Lauren CT, Garzon MC. Lumps and bumps: What not to miss. Pediatr Dermatol. 2022;39:679-88. doi: 10.1111/pde.15084.
11. Hernández-San Martín MJ, Vargas-Mora P, Aranibar L. Xantogranuloma juvenil: una entidad con amplio espectro clínico. Actas Dermosifiliogr. 2020;111(9):725-33. doi: 10.1016/j.ad.2020.07.004.
12. Palmer A, Bowling J. Dermoscopic appearance of juvenile xanthogranuloma. Dermatology. 2007;215:256-9. doi: 10.1159/000106586.
13. So N, Liu R, Hogeling M. Juvenile xanthogranulomas: Examining single, multiple, and extracutaneous presentations. Pediatr Dermatol. 2020;37:637-44. doi: 10.1111/pde.14174.
14. Niklitschek S, Niklitschek I, González S, Wortsman X. Color Doppler Sonography of Cutaneous Juvenile Xanthogranuloma With Clinical and Histologic Correlations. J Ultrasound Med. 2016;35:212-3. doi: 10.7863/ultra.15.04007.
15. Martínez-Morán C, Echeverría-García B, Tardío JC, Borbujo J. Ultrasound Appearance of Juvenile Xanthogranuloma. Actas Dermosifiliogr. 2017;108:683-5. doi: 10.1016/j.ad.2016.11.021.
16. Margulis A, Melin-Aldana H, auer BS. Juvenile xanthogranuloma invading the muscles in the head and neck: clinicopathological case report. Ann Plast Surg. 2003;50:425-8. doi: 10.1097/01.SAP.0000029628.20606.05.
17. Sangüeza OP, Salmon JK, White CR Jr, Beckstead JH. Juvenile xanthogranuloma: a clinical, histopathologic and immunohistochemical study. J Cutan Pathol. 1995;22:327-35. doi: 10.1111/j.1600-0560.1995.tb01415.x.
18. Samuelov L, Kinori M, Chamlin SL, et al. Risk of intraocular and other extracutaneous involvement in patients with cutaneous juvenile xanthogranuloma. Pediatr Dermatol. 2018;35:329-335. doi: 10.1111/pde.13437.
19. Ayechu Díaz A, Navarro González D, Virto Ruiz MT. Giant juvenile xanthogranuloma. An Pediatr. 2012;76:300-301. doi: 10.1016/j.anpedi.2011.07.008.
20. Samara WA, Khoo CTL, Say EAT, et al. Juvenile Xanthogranuloma Involving the Eye and Ocular Adnexa: Tumor Control, Visual Outcomes, and Globe Salvage in 30 Patients. Ophthalmology. 2015;122:2130-2138. doi: 10.1016/j.ophtha.2015.06.009.
21. Meyer P, Graeff E, Kohler C, Munier F, Bruder E. Juvenile xanthogranuloma involving concurrent iris and skin: Clinical, pathological and molecular pathological evaluations. Am J Ophthalmol Case Rep. 2018;9:10-13. doi: 10.1016/j.ajoc.2017.09.004.
22. Chang MW, Frieden IJ, Good W. The risk of intraocular juvenile xanthogranuloma: Survey of current practices and assessment of risk. J Am Acad Dermatol. 1996;34:445-9. doi: 10.1016/s0190-9622(96)90437-5.
23. Zou T, Wei A, Ma H, et al. Systemic juvenile xanthogranuloma: A systematic review. Pediatr Blood Cancer. 2023;70:e30232. doi: 10.1002/pbc.30232.
24. Itin K, Häusermann P, Itin P, Fosse N. Symmetrical Facial Giant Plaque-Type Juvenile Xanthogranuloma: Case Report and Review of the Literature. Case Rep Dermatol. 2021;13:399-406. doi: 10.1159/000515151.