

Disseminated juvenile xanthogranulomas with ocular involvement: A case report and literature review

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Abstract

Cutaneous juvenile xanthogranuloma is an uncommon disorder usually arising during infancy. Systemic involvement of juvenile xanthogranuloma remains rare, and there are no published guidelines to date on screening extracutaneous manifestations in these patients. Ocular involvement is the most common extracutaneous manifestation of juvenile xanthogranuloma. We present the case of an infant with disseminated juvenile xanthogranulomas and associated ocular involvement and present a review of literature, focusing on identifying risk factors for ocular and systemic involvement in disseminated cases.

Keywords

Intraocular juvenile xanthogranuloma, cutaneous juvenile xanthogranuloma, spontaneous hyphema, histiocytosis

Introduction

Juvenile xanthogranuloma (JXG) is a typically self-limited non-Langerhans cell histiocytosis characterized by well-defined yellow papules on the skin arising during infancy or early childhood.¹ Lesions are frequently solitary, asymptomatic and preferentially distributed on the head and neck region.² Systemic involvement of JXGs has been reported, but remains rare.^{1,2} Ocular involvement is the most common extracutaneous manifestation.¹ Early recognition is important in order to prevent vision loss.³ We present the case of an infant with disseminated JXGs and associated ocular involvement and present a review of literature, focusing on identifying risk factors for ocular and systemic involvement in disseminated cases.

Case report

A 2-month-old boy presented with new onset of more than 60 asymptomatic well-defined orange to yellow papules and micronodular lesions mostly located on the head and upper trunk. These papules and nodules were round, dome-shaped, firm, varying in size from 4 mm to 1 cm without epithelial disruption. His arms, legs and perianal region were also affected. The child was born by vaginal delivery and was otherwise healthy. Histopathology revealed sheets of histiocytes

mainly foamy with scattered lymphocytes and exceptional eosinophils. Characteristic Touton multinucleated giant cells were found. All histiocytes were positive for CD68 and were negative for CD1a and S100 (Figure 1). A clinicopathologic diagnosis of disseminated cutaneous JXGs was therefore established. The patient presented no cutaneous signs of concomitant neurofibromatosis type 1 (NF1) and had an initial normal eye examination. However, at the age of 15 months, he developed a spontaneous hyphema in the right eye with normal intraocular pressure and multiple subconjunctival lesions compatible with ocular JXG. Although no iris lesion

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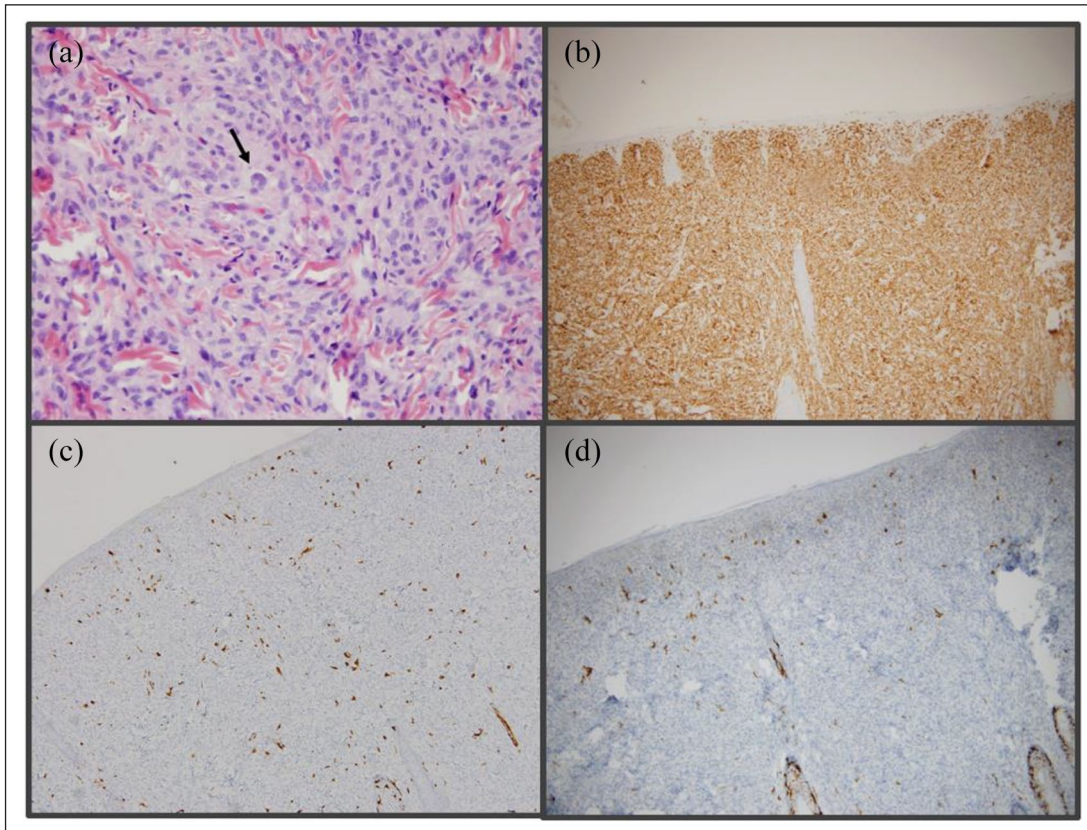


Figure 1. (a) Sheets of foamy histiocytes with scattered lymphocytes and exceptional eosinophils. Touton (arrow) multinucleated cell (HE $\times 40$). (b) Dense infiltrate of CD68 positive histiocytes (HE $\times 10$). (c) S100 negative with positive internal control (HE $\times 10$). (d) CD1a negative with positive internal control (HE $\times 10$).

was identified, this rare occurrence of a spontaneous hyphema was attributed to the disease. He was quickly treated with prednisolone and cycloplegic eye drops and had a favorable outcome. Because of his many skin lesions and eye findings, he was investigated for systemic involvement. Laboratory evaluation showed normal complete blood count (CBC), hepatic and kidney function. Abdominal and cardiac ultrasound did not show internal JXGs. He continued to develop new cutaneous JXGs upon follow-up. However, by the age of 4 years, most skin lesions had regressed leaving hyperpigmented macules and no new ocular lesion had appeared, while most conjunctival lesions had stabilized or regressed (Figure 2).

Discussion

There are currently no guidelines on screening for extracutaneous manifestations in patients with cutaneous JXGs. We reviewed the literature in order to identify risk factors for ocular and systemic involvement. Patients with cutaneous JXGs are typically classified as having solitary or multiple lesions as well as micronodular (measuring <1 cm) or macronodular lesions (measuring ≥ 1 cm).^{2,4} Patients most often present with solitary lesions that typically occur during

the first year of life.^{1,2} Multiple JXGs most commonly occur either as congenital lesions or within the first 6 months of life.^{1,5} There is no consensus on the number of lesions required to use the term disseminated or eruptive JXGs. Of note, a report from Selcen Kundak et al.² described patients with eruptive JXGs as having ≥ 6 lesions.⁶ A review of 338 children with cutaneous JXGs found that 26% of patients had multiple lesions (≥ 6).

Most cases of ocular JXGs present without cutaneous involvement.³ It is also the most common extracutaneous manifestation in a child with cutaneous JXGs, accounting for approximately 60% of extracutaneous involvement.¹ It was first recognized in 1949 by Blank et al.⁷ In Zimmerman's series of 53 patients with ocular JXGs, 85% presented before 1 year of age.^{8,9} Literature review of pediatric cutaneous JXGs series revealed that the incidence of ocular manifestations is 0.24% (7/2949) and the overall incidence of positive ocular screening in a cutaneous JXG patient is 0.17%.² Most ocular lesions are unilateral and range from iris lesions to spontaneous hyphema, conjunctival mass, uveitis, heterochromia and rarely, posterior segment involvement.^{2,7-13} Iris lesions can be subtle but are the most frequent intraocular manifestation (68%).³ They present as yellowish vascularized masses or as heterochromia, often leading to spontaneous



Figure 2. (a) Multiple yellow papules and nodules on the head and upper trunk of 12-month-old patient. (b) Patient continued to develop new lesions while others started to regress at 2 years old. (c) At the age of 4 years, most JXGs had completely regressed leaving hyperpigmented macules.

hyphema.³ Early recognition is crucial in order to prevent secondary glaucoma, vision loss and complications related to neovascularization since ocular lesions do not tend to resolve spontaneously.^{2,3,5-13} Risk factors for ocular involvement included multiple skin lesions, micronodular form of JXGs, newly diagnosed JXG and age 2 years or younger.^{2,4,11} In a recent review in *Pediatric Dermatology*, eye examination was recommended for patients with multiple JXG but unnecessary for those with single cutaneous JXG.¹ Given the absence of clear screening guidelines, we suggest that any patient presenting risk factors for ocular involvement be sent to ophthalmology, especially infants as they are unable to communicate symptoms. Management of iris JXG mainly involves the use of topical corticosteroids. Slow taper through months has been proven to cause tumor regression and prevent further complications.³ In the setting of hyphema, topical cycloplegics are added to stop the bleeding. Alternative treatments such as periocular or systemic corticosteroids can be required when compliance or treatment response is unsatisfactory.¹⁴ Conjunctival JXG tend to have a more benign course and can therefore be simply monitored even though topical corticosteroids have shown to be effective.^{3,7}

The likelihood of extraocular systemic involvement in patients with cutaneous JXG was found to be associated with increasing number of cutaneous lesions and younger age.² A

meta-analysis of 2949 JXG cases showed a 0.75% incidence of systemic manifestations.² The most commonly involved sites are liver, spleen and kidney.¹ Systemic involvement was associated with a mean of 17.4 cutaneous lesions per patient and a mean age of 23.1 months.¹ Most cases reported followed a benign course with spontaneous resolution.¹ Only six cases progressed to fatal complications including multi-organ failure, coagulopathy from severe liver failure, severe intracranial hypertension, sepsis and electrolyte disturbances.¹ There are no specific guidelines concerning the evaluation of systemic involvement. For children under 3 years of age or who have more than 10 lesions, an abdominal ultrasound could be performed.¹ Annual monitoring of asymptomatic systemic lesions is recommended until regression of the lesions. If visceral lesions are found, a case-by-case follow-up and management strategy should be elaborated following patient symptomatology, extent of disease and organs involved. Supportive measures as well as different chemotherapy regimens have been utilized in the past with variable success such as methotrexate, cyclophosphamide, etoposide, vinblastine, systemic corticosteroids, radiotherapy and immunoglobulins.¹

It has been reported that the presence of JXGs in patients with NF1 increases the risk of developing juvenile myelomonocytic leukemia (JMML); however, this association is

still unclear.^{2,15–19} A recent retrospective case–control study in 2017 concluded that JXGs are common in NF1 but not associated with greater risk of malignancy.¹⁸ To the extent of our knowledge, no such correlation was established for patients with multiple JXGs in the absence of NF1.¹⁹ Because of this controversial association, we regularly repeated CBC in our patient which remained normal until resolution of lesions.

Ocular involvement is the most common extracutaneous manifestation of JXG. Risk factors for ocular involvement include multiple skin lesions, micronodular form of JXGs, new diagnosis and age 2 years or younger. Early ophthalmology referral in patients with multiple JXGs is recommended in order to prevent long-term complications, including vision loss. Extraocular systemic involvement associated with JXG is a rare entity. Commonly reported involved sites are the liver, spleen and kidney. Most lesions follow a benign course and tend to spontaneously resolve. For JXG patients under 3 years of age or with 10 or more lesions, screening for systemic involvement with abdominal ultrasound should be considered.¹ To the extent of our knowledge, in the absence of NF1, no correlation was established for patients with multiple JXGs and the risk of developing JMML.

Declaration of conflicting interests

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Informed consent

The patient's caregiver provided informed and written consent for publication of the case report.

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