# Juvenile Xanthogranuloma: Case Report and Review of the Literature

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Juvenile xanthogranuloma, the most common form of non–Langerhans cell histiocytosis, is a benign, self-limiting histiocytic disorder that most commonly occurs during infancy or early adolescence. Facial involvement is common, and, in some cases, multiple lesions may occur. This article presents a case of multiple facial juvenile xanthogranuloma lesions in an 8-month-old male infant. Discussion includes patient evaluation and a review of potential ocular and systemic associations.

Histiocytoses are divided into 3 classes: Langerhans cell histiocytosis (LCH) (class 1); non-LCH (class 2); and malignant histiocytosis (class 3). Juvenile xanthogranuloma (JXG) is a benign, self-limiting histiocytic disorder that occurs during infancy or early adolescence. JXG is the most common of the non-LCHs, which include other disorders such as papular xanthoma, benign cephalic histiocytosis, hemophagocytic histiocytosis, and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). We present a case of multiple JXG lesions on the face. JXG can be differentiated from LCH on the basis of histologic features and the presence or absence of various immunohistochemical markers. Unlike LCH lesions, JXG lesions do not contain Birbeck granules and are negative for CD1a and S-100 on immunostaining.

## CASE REPORT

An 8-month-old male infant presented to the office with multiple well-demarcated, firm, yellow to rust-brown, dome-shaped papules on the face (Figure). His past medical history was significant for a respiratory syncytial virus infection at the age of 3 months. The review of systems was negative. There was no history of any recent weight loss, night sweats, fevers, or chills.

Hematoxylin-eosin stained sections of a biopsy specimen revealed a granulomatous tissue reaction in the papillary dermis with Touton-type giant cells and histiocytes consistent with a diagnosis of JXG.

It was recommended to the parents that the child be seen periodically by the pediatrician for general follow-up and that an ophthalmology consult be completed. The family moved one month later to another state and was lost to follow-up.

## HISTORY OF JXG

JXG is the most common non-LCH and was originally reported in 1905 by Adamson.[1] McDonagh,[2,3] in 1912, introduced the term *nevoxanthoendothelioma*, as he considered the lesions to originate from the endothelium of the capillaries. Senear and Caro[4] coined the term *juvenile xanthoma* in 1936. The current designation, JXG, was proposed by Helwig and Hackney[5] in 1954.

## CLINICAL PRESENTATION

Clinically, JXG usually presents as a solitary firm, rubbery, smooth, domed papule that may have surface telangiectasias. The color can vary from reddish-yellow to brown. The most common site of involvement of cutaneous JXG reported in the literature is the head and neck region.[6,7] Multiple lesions, as seen in our case, can develop. Affected patients have normal lipid metabolism. A male predominance of 1.4:1 to 1.5:1 has been noted.[8,9]

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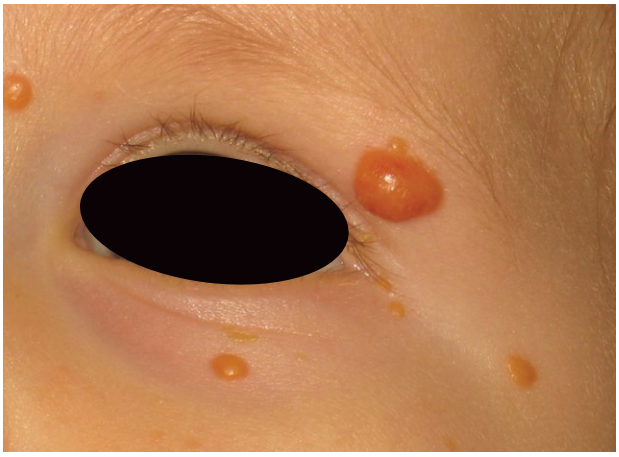

Multiple juvenile xanthogranulomas: numerous red-brown, smooth, dome-shaped papules located in the periocular region.

JXG occurs more commonly in infancy and adolescence, but there have been reports of occurrence in adulthood, with one report involving an 80-year-old patient.[6,10-13] Sonoda et al,[6] in a clinicopathologic analysis of 57 patients, noted infantile lesions to be present at birth in 17% of patients and in 70% within 1 year after birth.

Multiple forms of cutaneous JXG have been reported. Two variants have been reported, a small nodular or micronodular form and a large nodular form, which may coexist, based on the number and size of lesions.[14] The micronodular form is clinically seen as multiple, dome-shaped papules measuring from 2 to 5 mm in diameter, whereas the macronodular form is seen as few larger nodules measuring from 10 to 20 mm in diameter. A giant form, with lesions greater then 2 cm in diameter, is also described.[15,16] Imiela et al[16] reported the largest nodule, measuring 10×9 cm, occurring in a 9-month-old male infant over the inner, anterior, and posterior surfaces of the proximal thigh.

JXG involving the nail structure has been reported. It may present clinically as a hyperkeratotic cuticle with longitudinal depressions on the nail plate or a dystrophic nail plate.[17-19]

Solitary subcutaneous or soft tissue masses of 3 cm or less have been noted in 16% of patients.[7] Sánchez Yus et al[20] presented a case of a 1-month-old female infant with a 2-×3-cm congenital subcutaneous nodule in the right retroauricular area. The lesion was surgically excised and diagnosed as JXG by histology. No recurrence was noted after 2 years. Subcutaneous xanthogranulomas have also been reported in adult patients.[21]

## RESULTS OF CLINICOPATHOLOGIC STUDIES

Janssen and Harms[8] conducted a clinicopathologic study of 129 patients from the Kiel Pediatric Tumor Registry. The age at diagnosis ranged from 0 to 244 months, with a median of 5 months and a mean of 22.4 months. Seventy-one percent of patients developed JXG by the age of 1 year. A male to female ratio of 1.4:1 was noted. The most common site of involvement was the trunk (41.3%), followed by head and neck (40.5%), lower extremity (10.3%), and upper extremity (7.9%). Other sites of involvement included the penis, scrotum, perianal area, labia, finger, plantar surface, and auditory canal. The size of lesions ranged from 0.2 to 8 cm. Systemic JXG was noted in 5 patients (4%).

Dehner[7] conducted a clinicopathologic study of 174 patients and reported similar results. In 79% of patients, JXG was present before the age of 1 year, and a male to female ratio of 1.3:1 was noted. A solitary lesion was noted in 67% of patients, whereas 7% of patients had multiple lesions. Systemic JXG was noted in 8 patients (5%) and was fatal in 3 cases. Hepatic failure was determined to be the cause of death in 2 patients, and severe hypercalcemia was the cause in 1 patient. Forty-two percent of lesions were located on the head and neck, followed by the trunk (26%), lower extremity (16%), and upper extremity (15%).

## EXTRACUTANEOUS JXG

Systemic or extracutaneous JXG was first reported in 1937 by Lamb and Lain,[22] who described a case of a 3-month-old infant with pulmonary JXG, although no biopsies were done. Systemic JXG lesions have been reported to involve the genitourinary tract, central nervous system, eye/orbit, oropharynx, liver, pancreas, spleen, abdominal lymph nodes, bone marrow, muscle, and lung.[23-27] Systemic JXG may occur with or without cutaneous JXG. Isolated bone marrow involvement was recently reported by Kesserwan et al,[27] who described a 6-week-old male infant with isolated bone marrow involvement sparing skin and viscera. The most common reported site of systemic JXG is the eye, followed by the lung and then the liver.[26] Systemic JXG with fatal outcome is rare.[7,24,28] Hepatic failure has been reported, and it can present with direct hyperbilirubinemia, progressive hepatomegaly, and cholestasis.[24] Giant cell hepatitis was noted on autopsy of 2 patients.[7] Progressive central nervous system disease was seen in a fatal case reported by Flach et al.[29]

Ocular JXG is seen in approximately 10% of patients with JXG.[30] Ocular JXG was first described in 1949 in a 4-month-old infant who presented with an iris mass and secondary glaucoma.[30] Ocular JXG may involve the orbits, eyelid, conjunctiva, or iris and may present as uveitis, amblyopia, heterochromia, or posterior segment involvement.[30-35] Iris involvement may present as spontaneous hyphema.[31] Secondary glaucoma, seen in patients with JXG, can occur through many mechanisms. Histiocytic cells, shed into the aqueous medium of the eye, can

block the trabecular meshwork and cause an abrupt rise in the intraocular pressure. Anterior chamber hemorrhage, causing decreased aqueous outflow and elevated pressures, has also been suggested.[30]

Hemophagocytic lymphohistiocytosis (HLH)–like symptoms such as fever, pancytopenia, hepatosplenomegaly, and coagulopathy may precede JXG lesions.[36] Hara et al[36] presented a case of a 2-month-old infant who had HLH-like symptoms for 6 months preceding the proliferating skin nodules. Biopsy of the lesions revealed proliferation of fibroblasts and histiocytes that were positive for CD68 and XIIIa but negative for S-100 and CD56. Foamy cells and Touton giant cells were noted, establishing a diagnosis for JXG. The authors hypothesized that the cytopenia seen in their patient could be explained by the release of monokines, such as tumor necrosis factor-α, by HLH cells, or by direct invasive effects of JXG cells on the bone marrow.

JXG has been reported to develop after LCH.[37] Hoeger et al[37] reported 3 cases of patients who initially presented with LCH but developed JXG 3 to 6 years after initial presentation. The investigators hypothesized that the inflammatory reaction associated with LCH may be involved in precipitating JXG lesions. Patrizi et al[38] reported 2 cases of patients affected by LCH who developed JXG lesions while receiving chemotherapy.

JXG has been associated with other disease states such as neurofibromatosis 1 (NF1), Nieman-Pick disease, epilepsy, and childhood leukemia (xantholeukemia), most commonly juvenile chronic myelogenous leukemia (JCML), an aggressive myeloproliferative disorder. JCML accounts for 2% of childhood hematologic malignancies and may present as hepatosplenomegaly, lymphadenopathy, pallor, and skin eruption.[39] JXG has been observed with NF1 and also with JCML, but a triple association (JXG, NF1, and JCML) has also been reported.[9] Patients with NF1 have a higher occurrence of JXG than does the general population.[41] Zvulunov et al[9] conducted a world statistical analysis in 1995 and concluded that the frequency of the triple association was 30- to 40-fold higher than expected. The authors estimated that children with NF1 and JXG had a 20- to 32-fold higher risk for JCML than do patients with NF1 without JXG. However, these results were refuted by Gutmann et al,[41] who cited incorrect methods used in the analysis by Zvulunov et al.[9] Cambiaghi et al[42] followed 14 patients with JXG and NF1 over the first few years of their lives, and none of the patients developed any hematologic malignancies such as JCML.

## HISTOLOGY OF JXG

Histologically, in JXG, a dense, sheetlike histiocytic infiltrate is seen that primarily involves the papillary dermis but may involve both the papillary and the reticular dermis. Extension into the fascia, skeletal muscle, or subcutaneous tissue may occur in up to 38% of cases.[8,14] The epidermis is usually unaltered, but acanthosis, parakeratosis, hyperkeratosis, or hypergranulosis may be seen.[8] The lesion is relatively sharply delineated and nonencapsulated. The infiltrate is composed of histiocytes, giant cells, Touton giant cells, lymphocytes, and eosinophils. Charcot-Leyden crystals were seen in 2.7% of patients in the study done by Janssen et al.[8] The classic Touton giant cells, seen as a central wreath of nuclei surrounded by foamy cytoplasm, are characteristic but not specific for the diagnosis of JXG and may be absent. Early lesions of JXG are nonlipidized and usually devoid of Touton-type giant cells. The mononuclear and giant cells may have fine cytoplasmic vacuoles in the cytoplasm, which give the cells a xanthomatous or lipidized appearance.[7] Spindle cells, highlighted by immunoperoxidase stains for vimentin or factor XIIIa, were seen in 20% of patients by Dehner.[7]

## IMMUNOHISTOCHEMISTRY OF JXG

Immunohistochemically, most JXG lesions are positive for vimentin, CD68, and factor XIIIa. A strong granular cytoplasmic staining with the macrophage marker Ki-M1P was seen in 100% of patients by Janssen et al.[8] Ki-M1P recognizes a formalin-resistant epitope of lysosomal structures. CD4, expressed by histiocytes, may be seen. JXG lesions are nonreactive for CD1a and are usually negative for S-100, but weak focal positivity to S-100 may be noted.[7,8,14,28] Weak positivity to $\alpha_1$-antitrypsin and $\alpha_1$-chymotrypsin may be seen in the cytoplasm of some histiocytes.[20]

## MANAGEMENT

JXG usually is a self-limiting disorder, and no treatment is usually required. The lesions most often regress over a period of 6 months to 3 years. Anetoderma, hyperpigmentation, or atrophy may occur in up to half of the patients after lesions have resolved.[14,16,43] Klemke et al[44] have demonstrated the successful use of $CO_2$ lasers in the treatment of multiple JXG lesions. Importantly, as the histology is characterized by dermal involvement that is sometimes deeper into the reticular dermis, complete lesion removal may warrant surgical excision. Shave technique may serve for biopsy purposes but is not likely to completely excise many of these lesions. Regardless of the surgical approach to biopsy or lesion removal, scarring implications must be considered and discussed as part of informed consent.

Treatment of ocular JXG with secondary glaucoma requires close follow-up and aggressive treatment with topical and systemic pressure-lowering agents. Corticosteroid therapy or radiation treatment may be required to prevent recurrences of secondary glaucoma.[9,30,33]

Clinicians should be aware of the presenting features of JCML, so if patients with NF1 and JXG develop hepatosplenomegaly, lymphadenopathy, pallor, and cutaneous eruption, they should be promptly evaluated for JCML.

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