Juvenile Xanthogranuloma (Nevoxanthoendothelioma)

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**Synonyms and related keywords:** nevoxanthoendothelioma, xanthoma multiplex, juvenile xanthoma, multiple xanthoma in infancy, congenital xanthoma tuberosum, xanthoma naviforme, juvenile giant cell granuloma

**INTRODUCTION**

**Background:** Juvenile xanthogranulomas (JXGs) are benign, usually asymptomatic,
papules and nodules composed of histiocytic cells that predominantly occur in infancy. Nodules occur in the skin, eyes, and viscera. JXG is the most common form of non–Langerhans cell histiocytosis.

Adamson first reported JXG in the English literature in 1905. He presented a child who had white papules on the body in the first 2 weeks of life. He named the entity congenital xanthoma multiplex.

In 1912, McDonagh presented the first case review and renamed the condition nevoxanthoendothelioma (although the condition is not associated with nevi or endothelial cells). In 1954, Helwig and Hackney again restated it juvenile xanthogranuloma, reflecting its histopathologic appearance. Laurb and Lain first reported JXG with visceral involvement in 1937. Blank et al first described ocular involvement in 1949.

**Pathophysiology:** The etiology of JXG is not known. The red-to-yellowish papules and nodules of JXG represent collections of differentiated non–Langerhans cell histiocytes. The consensus is that the dendrocytes. As postulated, JXG may be a granulomatous reaction of histiocytes to an as yet unidentified stimulus, possibly of either physical or infectious etiology. Recent evidence from Kraus et al, however, suggests a possible CD4+ plasmacytoid monocyte origin. Inhibition of cellular apoptosis appears to play a role in xanthogranulomas.

The appearance of giant cells and foamy lipid-laden histiocytes generally occurs late in the disease course, possibly in response to cytokine production by histiocytes. Serum lipid levels are usually normal and remain normal.

**Race:** JXG occurs in whites approximately 10 times more frequently than in African Americans.

**Sex:** In childhood, JXG occurs predominately in males (1.4:1). Equal incidence occurs in adults, with multiple cutaneous lesions occurring predominantly in males (12:1).

**Age:** Approximately 35% of cases of JXG occur at birth, with as many as 71% of cases presenting in the first year. The mean age at presentation is 22 months. Despite the term juvenile in the disease name, 10% of cases manifest in adulthood.

**History:** Patients usually present in infancy or early childhood with an asymptomatic, smooth, round, yellow papule or papules. Lesions are usually asymptomatic.

**Physical:**

- The most frequent site of occurrence is on the head and neck, followed by the trunk; however, JXG may occur anywhere on the skin.
- Up to 81% of cutaneous JXG cases manifest as a solitary lesion.
- Involvement is rare on mucous membranes, the tongue, palms, and soles.
- Both papular and nodular forms of JXG have been described.
The papular form consists of multiple, 2- to 5-mm, smooth, firm papules that quickly change to yellow.

The rarer nodular form consists of round, 0.5- to 2-cm, translucent, red-to-yellow, rubbery nodules with telangiectasias (nodules change to yellow-brown with time).

- Giant JXG refers to nodules and masses greater than 2 cm (largest reported mass was 10 X 5 cm).
- Rarer variants include a mixed form characterized by both papular and nodular lesions, in which grouped papules coalesce, and a subcutaneous form (approximately 5%), with a single deep nodule or mass.
- Extracutaneous JXG is rare (3.9%) and most commonly involves the eye (<1%). JXG most commonly manifests in the iris. Following in frequency are lung and liver manifestations.
- Rarely, lesions occur in the adrenal gland, appendix, bones, bone marrow, central nervous system, kidney, larynx, myocardium, pericardium, retroperitoneum, small and large intestines, spleen. Only 50% of systemic lesions are accompanied by cutaneous JXG, and these cutaneous lesions tend to appear as multiple papules or nodules. The size of a cutaneous lesion does not correlate with the presence or absence of systemic JXG.
- Café au lait macules occur in approximately 20% of patients with papular JXG.

**Causes:**

- Coexistence of café au lait macules has been associated with epilepsy.
- Niemann-Pick disease has been associated with JXG.
- Urticaria pigmentosa has been associated with JXG.
- Neurofibromatosis type 1 (NF1) has been associated with JXG. A retrospective study suggests that approximately 1 in 5 children with NF1 before age 3 years will develop JXG.
- Juvenile chronic myelogenous leukemia, now primarily referred to as juvenile myelomonocytic leukemia (JMML), has been observed in association with multiple JXGs, and the prevalence of patients with coexistent neurofibromatosis. Statistics regarding this triple association are controversial; estimates indicate that patients with NF1 and JXG have a 20- to 32-times increased risk of developing JMML than patients with NF1 alone. Patients have also been diagnosed with JMML and JXG, but without NF1.

**DIFFERENTIALS**

- Dermatofibroma
- Langerhans Cell Histiocytosis
- Mastocytosis
- Spitz Nevus
- Xanthomas

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Dermatofibroma  Langerhans Cell Histiocytosis  Mastocytosis  Spitz Nevus  Xanthomas
Other Problems to be Considered:

- Non–Langerhans cell histiocytosis
- Benign cephalic histiocytosis
- Generalized eruptive histiocytoma
- Self-healing reticulohistiocytoma
- Tuberous xanthoma
- Papular xanthoma
- Xanthoma disseminatum
- Mastocytosis (Urticaria Pigmentosa)

Procedures:

- A skin biopsy may be performed, both for diagnosis and cosmesis. The specimen papule or nodule.

Histologic Findings: Histological examination of JXG demonstrates a variety of findings. A time development of the characteristic histological features of JXG, which correlates with a dense monomorphous histiocytic infiltrate in the dermis. Extension into subcutaneous approximately one third of cases. Older lesions contain foam cells, Touton giant cells, infiltrate of neutrophils, lymphocytes, eosinophils, and (rarely) mast cells may be noted. A difference is reported between cutaneous and systemic JXG. Because of the difficulty presence of Touton giant cells in JXG lesions, these classic elements may not be present.

The histiocytes contain pleomorphic nuclei, with few or absent mitotic figures, and irregular bodies occasionally are observed on electron microscopy but are not specific. Use of Langerhans and non–Langerhans cell histiocytoses. In JXG, histiocytes are positive to KP1 (CD68), Ki-M1P, and Vimentin, and are generally negative to CD1a and S-100. N positivity, which has been used as evidence that plasmacytic monocytes may be the n instead of the dermal dendrocyte.

Medical Care: Anticipatory care, with patient reassurance, is appropriate because of the systemic lesions may respond to steroids or radiotherapy. Rare cases of severe systemic cases may require multiagent chemotherapy regimens.

Surgical Care: Lesions may be excised for diagnostic and cosmetic reasons. Ocular and systemic lesion excision usually is curative.

Consultations: A reasonable cost-effective recommendation is to refer the patient to an ophthalmologist. Patients younger than 2 years with multiple skin lesions comprise 92% of associated cases of ocular involvement. Refer these patients to an ophthalmologist.
Systemic steroids may be used for visceral lesions.

Drug Category: **Corticosteroids** -- Shrink visceral nodules. These agents have anti-varied metabolic effects. They modify the body's immune response to diverse stimuli.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Prednisone (Deltasone, Meticorten, Orasone) -- DOC for visceral lesions. May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.</th>
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<tbody>
<tr>
<td>Adult Dose</td>
<td>40-60 mg PO qd; taper over 2 wk as symptoms resolve</td>
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<tr>
<td>Pediatric Dose</td>
<td>0.14 mg/kg PO divided bid/qid or 4-6 mg/m²/d PO in d taper over 2 wk as symptoms resolve</td>
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<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; viral infection; peptic ulcer; hepatic dysfunction; connective-tissue disease; fungal skin infections; GI disease</td>
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<td>Coadministration with estrogens may decrease predni: concurrent use with digoxin may cause digitalis toxicity</td>
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Further Outpatient Care:

- Follow-up visits may be scheduled at regular intervals for reassurance and to monitor JXG and NF1, physicians should watch for signs and symptoms of JMML.

Complications:

- Complications are rare and are dependent on the site of involvement and associated conditions.
- Ocular involvement may progress to ocular hemorrhage, glaucoma, or retinal detachment. These complications are best prevented through early detection.
- CNS involvement is a very rare complication.
- Hepatic failure is a rare, but potentially fatal, complication of systemic JXG.

Prognosis:

- In the absence of therapeutic intervention, skin lesions flatten with time. Both cutaneous and extracutaneous lesions involute spontaneously within 3-6 years.
- Hyperpigmentation, mild atrophy, or anetoderma may persist.
- Lesions can recur after resection. The relapse rate is approximately 7%.
- In the absence of neurofibromatosis, no systemic health implications are involved.
- Vigilantly screen male patients with neurofibromatosis and JXG for leukemia.
- Ocular, neurologic, and hepatic disease are rare but may have serious long-term implications.

Patient Education:

- Reassure patients and their families.
Instruct patients concerning associations related to clinical situations (neurofibromatosis, ocular findings in diffuse JXG, JMML), and direct patient education toward these conditions.

**Medical/Legal Pitfalls:**

- Failure to screen for associated conditions once a diagnosis has been made. Patients with JXG and café au lait spots have a 20% risk of seizure disorders. Patients with multiple JXGs have increased risk of coexistent neurofibromatosis. Ocular hemorrhage, retinal detachment, and glaucoma are more likely to occur in patients younger than 2 years with multiple JXGs. Consider evaluating at-risk patients for JMML, epilepsy, and ocular findings.

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