

JUVENILE XANTHOGRANULOMA (JXG)

Carl Allen MD, PhD

Kenneth McClain MD, PhD

DEFINITION AND HISTORY

Juvenile Xanthogranuloma (JXG) is histiocytic disorder, derived from accumulation and/or proliferation of cells derived from the dermal dendrocyte, that affects the skin with multiple nodules in the head, neck and trunk primarily in children, although adults may also be affected (Dehner, 2003c). Rudolf Virchow may have been the first to describe a child with “cutaneous xanthomas in 1871 as noted in a 1954 report of this condition (Helwig and Hackney, 1954). Other early reports of JXG were published in 1905 by Adamson and 1912 by McDonagh (Adamson, 1905; McDonagh, 1912). Systemic involvement occurs in a few cases.

EPIDEMIOLOGY

Children are affected at a median age of 2 years with a male/female ratio of 1.5:1. However, children with multiple lesions tend to be younger with average age 5 months and a much higher rate of occurrence in boys with male: female ratio of 12:1. A review of JXG from the Kiel Pediatric Tumor Registry recorded 129 (0.52%) cases of JXG and 800 (3.25%) cases of LCH among 24,600 cases over a 36 year period. (Janssen and Harms, 2005f). However, a study to determine the true incidence and prevalence of JXG remains to be performed.

ETIOLOGY AND PATHOGENESIS

The etiology of JXG is not known. Patients with JXG and neurofibromatosis (NF) Types 1 and 2 as well as a triad with juvenile chronic myelogenous leukemia (JCML) have been reported. (Tan and Tay, 1998; Iyengar et al., 1998; van Leeuwen et al., 1996). These and other cases have led to discussion of apparent increased risk of the

leukemia in NF patients with JXG, but there is no rigorous proof for this (Gutmann et al., 1996).

CLINICAL FEATURES

The majority (80-90%) of patients are children less than two years of age who have solitary skin nodules on their head, neck, or trunk (Dehner, 2003b; Janssen and Harms, 2005e). The lesion is most often the same color as surrounding skin, but may be erythematous or yellowish. Rarely nodules may be in the subcutaneous fat, deep soft tissue or in skeletal muscle. Organ involvement is very rare and has been reported in the soft tissue, central nervous system, bone, lung, liver, spleen, pancreas, adrenal, intestines, kidneys, lymph nodes, marrow, orbit, and heart (Freyer et al., 1996b; Dehner, 2003a; Janssen and Harms, 2005d; Freyer et al., 1996a). Systemic symptoms and signs occur only if these organ systems are involved.

LABORATORY FEATURES

Immunohistochemical staining of biopsies is necessary to differentiate JXG from other histiocytic lesions. JXG lesions classically stain with macrophage markers including CD68 or Ki-M1P, anti-FXIIIa, vimentin, and often anti-CD4. They are distinguished from Langerhans Cell Histiocytosis lesions by being negative for S-100 and CD1a. There are three characteristic histologic patterns: early JXG (EJXG), classic JXG (CJXG), and transitional JXG (TJXG) (Janssen and Harms, 2005c). EJXG is characterized by small to intermediate-sized mononuclear histiocytes in a sheet-like infiltrate. The cells in this category have little lipid and Touton-type giant cells are absent. This type has relatively more mitoses than the others, but there is no cytologic atypia. CJXG exhibits abundant vacuolated, foamy histiocytes with Touton giant cells. The TJXG has a predominance of spindle-shaped cells resembling benign fibrous histiocytoma with foamy histiocytes and occasional giant cells. (Janssen and Harms,

2005b) Biopsies will also contain lymphocytes, eosinophils and occasionally Charcot-Leyden crystals.

If the marrow is involved patients may have cytopenias and liver infiltration may cause elevation of liver enzymes, hypoalbuminemia, and an elevated erythrocyte sedimentation rate. Pituitary involvement may lead to diabetes insipidus. Hypercalcemia has been reported.

DIFFERENTIAL DIAGNOSIS

LCH is the disease most often confused with JXG. (Janssen and Harms, 2005a) Others include fibrohistiocytic lesion NOS, reticulohistiocytoma, hemangioendothelioma, Spitz nevus, malignant fibrous histiocytoma, and rhabdomyosarcoma or other malignancies.

THERAPY

Patients with a single or only a few lesions need no therapy or an excisional biopsy if desired for cosmetic reasons. For the rare patients who have systemic disease and require treatment a wide variety of chemotherapy and radiotherapy regimens have been reported (Stover et al., 2008a; Freyer et al., 1996c). Inclusion of a vinca alkaloid and steroid is associated with better overall response rates. A child with CNS JXG who failed to respond to vinblastine was successfully treated with cladribine (Rajendra et al., 2009).

COURSE AND PROGNOSIS

Patients with only skin or soft tissue involvement all survive and the lesions spontaneously disappear over time in a majority of cases. Infants with large retroperitoneal masses, liver, bone marrow, or central nervous system involvement usually survive with chemotherapy treatment. Two of 17 patients with multisystem JXG reported in the literature died despite multiagent chemotherapy (Stover et al., 2008b).

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