Cutaneous Disseminated Xanthogranuloma in an Adult: Case Report and Review of the Literature

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RELEASE DATE: May 2009
TERMINATION DATE: May 2010
The estimated time to complete this activity is 1 hour.

GOAL

To understand xanthogranuloma (XG) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Describe the clinical, histologic, and immunohistochemical characteristics of XG.
2. Distinguish XG from other xanthomatous disorders.
3. Summarize pathogenic mechanisms of XG.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test and Instructions on page 263.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: April 2009.

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Mr. Asarch and Drs. Ashby-Richardson and Norden report no conflict of interest. Dr. Thiele is a consultant for Colgate-Palmolive Company. This relationship is not relevant to this article. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest. The staff of CCME of Albert Einstein College of Medicine and *Cutis*® have no conflicts of interest with commercial interest related directly or indirectly to this educational activity.

Accepted for publication May 23, 2008.

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This case was presented in part at a meeting of the New England Dermatological Society; December 1, 2007; Boston, Massachusetts.

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Xanthogranuloma (XG) is a rare, non–Langerhans cell histiocytosis (LCH) that most commonly presents in infancy or early childhood. The condition is typified by the formation of reddish to yellow papules and nodules that are usually solitary. Xanthogranuloma rarely occurs in adults with immunohistochemical features similar to those seen in juvenile XG. Lesions in the adult form also are typically solitary. We describe a 70-year-old white man who presented with widespread

flat-topped, reddish to yellow papules and nodules with histologic and immunohistochemical findings consistent with XG. We explore the pathogenesis, differential diagnosis, prognosis, and treatment of this rare eruption. Comparison of adult and juvenile XG will facilitate a better understanding of the disease. Although rare, XG is an important disease to consider in the differential diagnosis of xanthomatous disease in adults.

Cutis. 2009;83:243-249.

Xanthogranuloma (XG) is a rare, non–Langerhans cell histiocytosis (LCH) characterized by a proliferation of foamy histiocytes and multinucleate Touton giant cells. The condition is commonly called juvenile XG because it typically presents in infancy or early childhood. However, the condition occasionally occurs in young adults, particularly in the third or fourth decade of life. The condition rarely occurs above this age range. The etiology of XG disease remains elusive but may involve abnormal histiocyte proliferation in response to tissue injury. In both the juvenile and adult variants of XG, patients present with cutaneous, discrete, well-demarcated, reddish to yellow, dome-shaped papules and nodules that often are asymptomatic. Patients in both age groups typically develop solitary lesions without widespread cutaneous distribution or systemic involvement.[1-4] In reported cases of multiple XGs in adults, the development of lesions numbering in double digits is rare.[4,5] We report a case of 60 to 80 cutaneous disseminated XGs in an elderly man.

Case Report

A 70-year-old white man with a history of coronary artery disease and hypercholesterolemia presented with an eruption of multiple, reddish to yellow, asymptomatic lesions on his arms, face, and trunk. Remarkably, the lesions developed approximately 3 to 4 months after receiving a coronary artery bypass graft and had persisted for 2 years when the patient first presented to our clinic. The patient denied polyuria, polydipsia, or other systemic symptoms.

On physical examination, the patient had a cutaneous eruption of 60 to 80 discrete, reddish to yellow, dome-shaped and flat-topped, 0.5- to 1-cm papules and nodules on his face, chest, abdomen, back, and upper extremities, and one 0.9-cm papule on the thigh (Figure 1). Lipid studies and serum protein immunoelectrophoresis were normal. Other hematologic studies were within reference range and there was no evidence of an underlying myeloproliferative disorder. Moreover, there was no ocular or mucous membrane involvement, or other systemic disease. The remainder of the examination was unremarkable.

Four shave biopsy specimens of representative lesions demonstrated a dermal spindle cell proliferation with foamy histiocytes and rare Touton giant cells (Figure 2). On immunohistochemistry, the cells were negative for CD1a, CD10, S100 protein, and Melan-A/MART1, and focally positive for CD68. The characteristic histologic and immunohistochemical findings confirmed the diagnosis of XG. Lesions were persistent after 1 year of follow-up. Treatment consisted of excision of inflamed and cosmetically distressing lesions.

Comment

Juvenile XG was first described as a distinct form of histiocytosis in 1905 by Adamson[6] and in 1912 by McDonagh[7] using the names *congenital xanthoma multiplex* and *nevoxanthoendothelioma*, respectively. The name *juvenile* XG was introduced by Helwig and Hackney[8] in 1954. The adult variant of XG was first described in 1963 by Gartmann and Tritsch.[9] Xanthogranuloma is typified by the formation of benign,

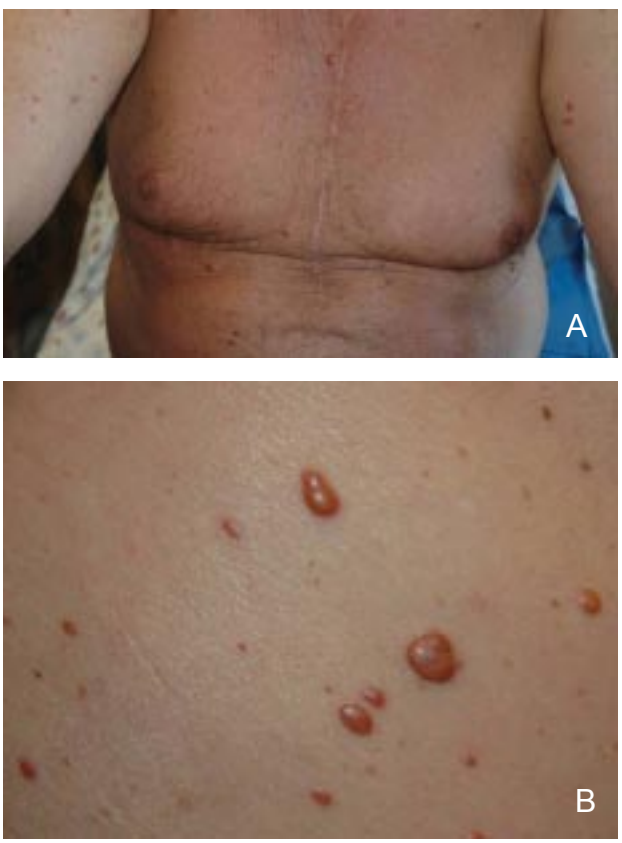

Figure 1. A 70-year-old white man with multiple, disseminated, well-circumscribed, reddish to yellow, dome-shaped, 0.5- to 1-cm papules on the chest, abdomen, and upper extremities (A). Close-up of reddish to yellow, dome-shaped, flat-topped papules and nodules (B).

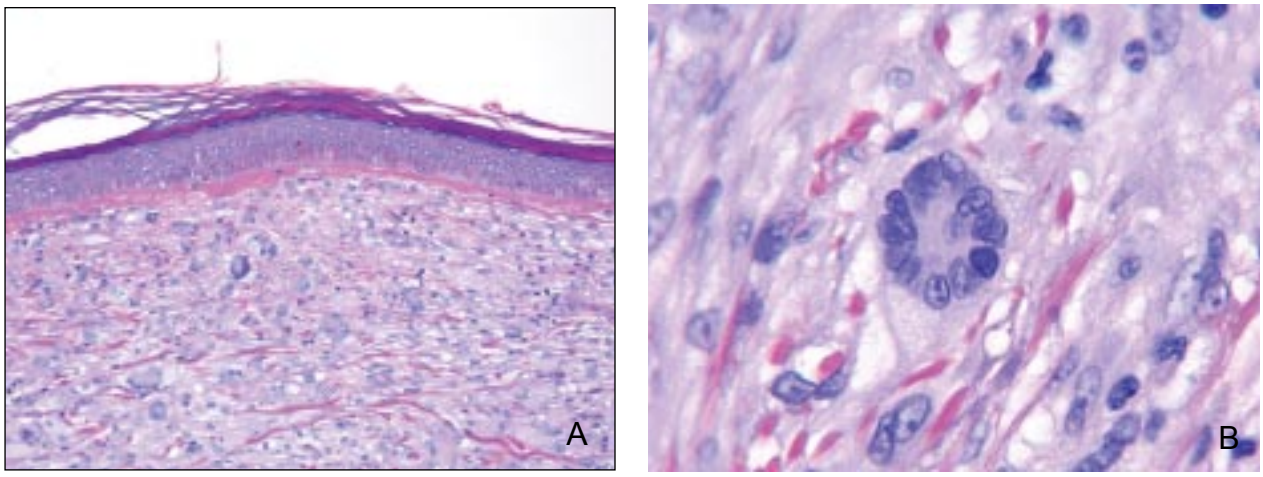

Figure 2. Dermal infiltrate of histiocytes with foamy macrophages and Touton giant cells (A)(H&E, original magnification ×10). Close-up of Touton giant cell with wreathed nuclei surrounded by foamy histiocytes (B)(H&E, original magnification ×40).

erythematous to yellow, rubbery, nodular cutaneous lesions. The lesions often are solitary on the scalp, face, neck, trunk, and upper extremities, but also can be multiple or disseminated in nature.[3] Juvenile XG can manifest with ocular and periocular lesions, mucous membrane lesions, and diffuse organ involvement. Rarely, juvenile XG is characterized by systemic dissemination that includes sites such as the central nervous system, liver, spleen, lungs, lymphatics, and musculoskeletal system.[1-3,10] Extracutaneous organ involvement is uncommon and typically follows a benign course in juveniles.[2] Ocular lesions also have been reported in the adult variant, but widespread visceral lesions have not been noted. Thus, extensive diagnostic testing is largely unnecessary.[3,4] Unlike other cutaneous xanthomatous conditions, hyperlipidemia, paraproteinemia, diabetes insipidus, or other metabolic changes are absent in both juvenile and adult XG.[2]

The recent expansion of diagnostic techniques allows for a thorough immunohistochemical, histologic, and electron microscopic examination of associative lesions in XG. In early phases, XG lesions consist of a dermal collection of monomorphous histiocytes that may extend into the subcutaneous and deeper fascial layers. In later stages, biopsy specimens demonstrate spindle-shaped mononuclear cells; foamy histiocytes; lymphocytes; eosinophils; multinucleate foreign body giant cells; and characteristic Touton giant cells, which are cells with a circular arrangement of nuclei surrounding an eosinophilic cytoplasm core. On immunohistochemistry, non-LCH histiocytes are positive for CD68 and sometimes factor XIIIa, and negative for CD1a and S100 protein. Histiocytes found in LCH are positive for CD1a and S100 protein. Electron microscopy, which demonstrates an absence of the distinct Birbeck granules commonly seen in LCH, provides another avenue for characterizing XG.[1,2,10,11]

In an effort to simplify the difficult process of dividing histiocytic disorders into distinct categories, the Histiocyte Society developed a 3-class system: class I, LCH; class II, non-LCH; class III, malignant histiocytosis.[12] Langerhans cell histiocytosis involves the abnormal proliferation of antigen-presenting Langerhans dendritic cells, while non-LCH involves the uncontrolled proliferation of monocytes and macrophages. Class II non-LCH disorders include XG (both juvenile and adult forms), necrobiotic xanthogranuloma, xanthoma disseminatum, papular xanthoma, generalized eruptive histiocytoma, and progressive nodular histiocytoma. In both histiocytic classes, antigen-presenting cells likely interact with helper T cells to initiate an immune reaction.[10,12] Of note, the Histiocyte Society has recently renamed the 3 major groups to dendritic cell-related disorders, macrophage-related disorders, and malignant disorders.[13]

Xanthogranuloma can resemble a number of xanthomatous disorders, but multiple clinical and histologic clues help rule out other conditions and make a definitive diagnosis of XG (Table). Eruptive xanthoma lesions may be confused with XG, but lesions in this condition are smaller, more papular in nature, and commonly found in crops on the buttocks, shoulders, and extensor aspects of the extremities. Unlike XG, the condition is associated with diabetes mellitus and hyperlipidemia, with a specific elevation in triglycerides and chylomicrons.[3,4] Necrobiotic xanthogranuloma, another distinct histiocytic disorder, characteristically presents with indurated and ulcerated plaques and nodules in a periorbital

Differential Diagnosis for Xanthogranuloma

Xanthomatous Disorder	Clinical Appearance of Lesions	Clinical Number and Distribution of Lesions	Mucous Membrane Involvement	Associated Abnormalities	Histology	Immunohistochemistry
Xanthogranuloma[3,4,11]	Discrete, well-demarcated, reddish to yellow, dome-shaped papules and nodules	Typically solitary on scalp, face, neck, trunk, and extremities, but also can be multiple or disseminated in nature	Rare	None	Spindle-shaped mononuclear cells, foamy histiocytes, lymphocytes, eosinophils, multinucleate foreign body giant cells, Touton giant cells	Positive for CD68 and sometimes factor XIIIa; negative for CD1a and S100 protein
Eruptive xanthoma[3,4,11]	Yellowish papules with erythematous base, commonly in crops	Multiple on buttocks, shoulders, and extensor aspects of extremities	No	Diabetes mellitus, hyperlipidemia	Foamy histiocytes, lymphocytes, or neutrophils	Not applicable
Necrobiotic xanthogranuloma[14,15]	Erythematous, yellow-brown plaques and nodules with associated induration and ulceration	Solitary or multiple on face (typically periorbital), less common on trunk and proximal extremities	Possible, typically ocular	Paraproteinemia	Plasma cells, cholesterol clefts, necrobiosis, fibrosis, multinucleate foreign body giant cells, lymphocytes, foamy histiocytes	Positive for CD15 and CD4; negative for CD1a and S100 protein

Xanthomatous Disorder	Clinical Appearance of Lesions	Clinical Number and Distribution of Lesions	Mucous Membrane Involvement	Associated Abnormalities	Histology	Immunohistochemistry
Xanthoma disseminatum[3,4]	Erythematous, yellow-brown papules with a characteristic coalescent pattern	Multiple on oral mucous membranes and flexural surfaces	Possible, typically oral	Diabetes insipidus	Histiocytes, foamy histiocytes, lymphocytes, Touton giant cells	Positive for CD68 and factor XIIIa; negative for CD1a and S100 protein
Papular xanthoma[3,4,16]	Yellowish papules and nodules	Solitary or multiple on extremities, trunk, and face	Possible, typically oral	None	Histiocytes, foamy histiocytes with limited inflammatory infiltrate	Positive for CD68; negative for CD1a and S100 protein
Generalized eruptive histiocytoma[3,4,11]	Red papules	Multiple, disseminated	Rare	None	Histiocytic infiltrate	Positive for CD68 and MAC387; negative for CD1a and S100 protein
Progressive nodular histiocytoma[17]	Reddish to yellow papules and nodules, can coalesce to form large disfiguring plaques that can resemble leonine facies	Multiple, disseminated, often progressive	Possible	None	Foamy histiocytes, multinucleate foreign body giant cells, Touton giant cells, lymphocytes	Positive for CD68 and sometimes factor XIIIa; negative for CD1a and S100 protein

distribution. Unlike XG, this condition is associated with paraproteinemia. The histopathology is distinct from XG and demonstrates plasma cells, cholesterol clefts, necrobiosis, and fibrosis.[14,15] Lesions in xanthoma disseminatum often are erythematous, yellow-brown papules confined to the oral mucous membranes and flexural surfaces and present with a characteristic coalescent pattern. This condition commonly is associated with diabetes insipidus. Papular xanthoma also might mimic XG, but lesions in this condition typically lack a reddish color and are less inflammatory in nature on biopsy.[3,4,16] In contrast, generalized eruptive histiocytoma presents with multiple, disseminated, red papules that lack both a yellowish color clinically and xanthomization on biopsy.[3,4]

The distinction between progressive nodular histiocytoma and XG is subtle and the conditions may represent spectrums of the same disease. Progressive nodular histiocytoma, which was first described in 1985, affects adolescents and adults.[18] Similar to XG, patients with progressive nodular histiocytoma present with multiple, disseminated, reddish to yellow papules and nodules that are typically asymptomatic.[17] Histology demonstrates lymphocytes and foamy histiocytes with a variable number of multinucleate foreign body giant cells and Touton giant cells. Cells are negative for CD1a and S100 protein and positive for CD68 and sometimes factor XIIIa on immunohistochemistry. Other laboratory findings are within reference range. However, unlike reported cases of XG, lesions in progressive nodular histiocytoma can coalesce to form large disfiguring plaques. Furthermore, as its name suggests, lesions can be progressive.[17] Nonetheless, the similarities between these 2 disease states are striking and worthy of further exploration.

The exact pathogenesis of XG has not been fully elucidated, but physical, infectious, and neoplastic processes all have been implicated.[2,19] In our patient, the temporal proximity of the disseminated eruption to surgery suggests a possible causal relationship. A release of cytokines and other inflammatory mediators by proliferating histiocytes may facilitate the development of XG disease, which is supported by the characteristic histologic evolution of XG lesions over time. While early lesions are composed of sparsely lipidized histiocytes with scattered inflammatory cells, older lesions contain foamy histiocytes, Touton giant cells, and foreign body giant cells with a more prominent inflammatory infiltrate.[1,2,5] This proposed mechanism is intriguing in light of systemic inflammation that is known to occur after cardiac surgery.[20]

In juvenile XG, local lesions tend to resolve spontaneously, making intervention unnecessary unless ocular or other systemic involvement is present. Solitary lesions in adults typically are excised, making spontaneous involution patterns difficult to pinpoint. However, when multiple cutaneous lesions are present in adults, spontaneous resolution appears to occur in approximately 50% of cases.[3] Surgical excision is the mainstay of treatment for inflamed or cosmetically distressing lesions, but observation and reassurance often are sufficient.[2] Because of the risks associated with surgically excising ocular proliferations, these lesions often require treatment with topical steroids, steroid injections, or radiotherapy. Systemic juvenile XG is a benign manifestation and aggressive treatment is largely unnecessary in these cases. In the past, systemic disease has been treated with systemic steroids, chemotherapy, and cyclosporine, but these treatments typically are unwarranted.[2] Adults do not appear to present with systemic disease and the use of these treatments is unnecessary in older patients.[3,4]

Our case represents an unusual variant of XG. The age of the patient and widespread nature of the eruption are both rare. Although lesions can cause distress for patients, they do not appear to be harmful in adults. While lesions may stem from inflammation, further research is required to uncover the etiology of the condition. Fortunately, lesions seem to clear spontaneously in approximately half of adults and aggressive treatment is not required.

Acknowledgment—We thank Daniel Wasserman, MD, Boston, Massachusetts, for all of his assistance.

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