Xanthoma disseminatum with extensive koebnerization associated with familial hypertriglyceridemia

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INTRODUCTION

Xanthoma disseminatum (XD) is a rare subtype of non-Langerhan's cell histiocytosis (non-LCH). To date, just greater than 100 cases of XD have been reported; however, association with hyperlipidemia is extremely rare. We present a unique case of XD associated with familial hypertriglyceridemia (FHTG). Additionally, the patient had an extensive Köebner response.

CASE REPORT

A 37-year-old man, farmer by occupation, presented with numerous asymptomatic raised skin lesions of 2 months’ duration and hoarseness of voice for the past 2 weeks. He was otherwise healthy, and none of his family members had similar skin lesions. Physical examination found multiple discrete skin-colored and yellow dome-shaped firm papulonodules distributed symmetrically over the face, trunk, and extremities (Fig 1, A). An extensive Köebner response was seen over the chest and shoulder (Fig 1, A) at sites of contact with the shoulder straps of an insecticide sprayer tank fastened to his back. Skin lesions had a predilection for flexural and intertriginous areas (Fig 1, B). An indirect laryngoscopy found numerous yellow papulonodules in the larynx. Dermoscopy of skin lesions on chest is shown in Fig 2, C. Systemic examination was normal. Results of routine laboratory investigations, including a complete blood count, erythrocyte sedimentation rate, fasting blood sugar, blood urea and serum creatinine, and liver and thyroid function tests were normal. His total cholesterol was 138 mg/dL (normal <200); triglycerides, 205 mg/dL (normal <150); very low-density lipoprotein (VLDL), 41 mg/dL (normal <30); low-density lipoprotein (LDL) cholesterol, 80 mg/dL (normal <100); and high-density lipoprotein (HDL) cholesterol, 17 mg/dL (normal >40). His serum osmolarity and electrolytes were also normal, and magnetic resonance imaging of the brain did not find any abnormality. Serum protein electrophoresis did not show any M band. Urine examination was negative for Bence Jones proteins. Skeletal survey was also normal. Fasting lipid profile of his father found elevated triglycerides (348 mg/dL), high VLDL (69 mg/dL), low HDL (32 mg/dL), and normal levels of total cholesterol and LDL.

Histopathologic examination of a punch biopsy specimen obtained from a nodule on the back was consistent with xanthoma (Fig 2, A). Immunohistochemistry was positive for CD68 (Fig 2, B) but negative for S100 and CD1a. Based on his clinical, histologic and immunohistochemical features and lipid derangements in our patient and his father, a final diagnosis of xanthoma disseminatum.
with familial hypertriglyceridemia was made. He was admitted in the dermatology ward and started on oral thalidomide, 100 mg, to be taken every night. On the fourth day of admission, he complained of breathlessness that was relieved after the addition of a short course of oral prednisolone. Shortly thereafter, he had giddiness that warranted the discontinuation of thalidomide. We then started oral simvastatin, 10 mg/d, and fenofibrate, 200 mg/d, with the twin aim of correcting lipid abnormalities and improving mucocutaneous lesions. After 6 months of treatment on this combined regime, triglycerides and HDL levels showed significant improvement, progression of mucocutaneous lesions was arrested, and skin lesions began to flatten, soften, and turn brown in color.

**DISCUSSION**

XD is clinically characterized by multiple yellow-brownish papulonodules over the body with a predilection for the flexural and intertriginous areas and mucous membranes. Historically, XD was described to follow 1 of 3 clinical patterns: a common persistent form, a progressive form, and a rare spontaneously regressing form. Although cutaneous lesions are bothersome, involvement of mucosae and internal organs can result in significant morbidity and mortality. Systemic associations include central diabetes insipidus owing to involvement of pituitary stalk and paraproteinemias, such as multiple myeloma. Histopathologic examination of early lesions of XD shows a predominance of scalloped histiocytes, whereas more established lesions consist mainly of foamy histiocytes with few scalloped cells. In the most established or mature lesions, a mixture of scalloped cells, foam cells, lymphocytes, and Touton giant cells are seen.

The main differential diagnosis in our patient included eruptive xanthomas and other non-LCH disorders. Eruptive xanthomas are small yellowish papules with an erythematous halo distributed over the buttocks, shoulder, and extensor aspect of limbs; they commonly appear in crops and resolve spontaneously within a few weeks, although lesions may wax and wane with plasma triglyceride levels. In eruptive xanthomas, triglyceride levels are usually greater than 1000 mg/dL, and mucosae are uninvolved. Tuberous and tendon xanthomas are associated with raised total cholesterol and LDL levels. Other non-LCH disorders, such as generalized eruptive histiocytosis, progressive nodular histiocytosis, multicentric reticulohistiocytosis, and Erdheim-Chester disease can be differentiated from XD mainly based on the distribution of lesions, mucosal involvement and a predilection for the flexural and intertriginous areas would favor a diagnosis of XD. Erdheim-Chester disease is a multisystemic non-LCH characterized by involvement of bones, visceral organs, central nervous system, and skin xanthomas. In Erdheim-Chester disease, skeletal radiographs would show the characteristic features of symmetric sclerosis involving the distal portions of long bones. Recently, molecular genetic clonal markers have been identified in histiocytic disorders, such as generalized eruptive histiocytosis and Erdheim-Chester disease. Such markers would make the distinction among histiocytic disorders more accurate because the phenotypic markers (F13+/fascin/S100-) are less so. Our patient also presented with an extensive Köebner phenomenon. Earlier, Ghorpade described a patient with XD who had a Köebner response consisting of a few linear papules on the shaft of penis.

The association of lipid abnormalities with XD is exceedingly uncommon. FHTG is an autosomal dominant disorder of lipid metabolism that results from an overproduction of VLDL by the liver and impaired catabolism of triglyceride-rich lipoproteins. There are only 2 previous reports of hypertriglyceridemia in association with XD. Because the major class of lipoprotein elevated is VLDL, FHTG is also

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**Fig 1. A.** Xanthoma disseminatum shows numerous lesions on the chest and shoulder. Koebnerization is seen on sides of the chest and shoulder. **B.** Yellowish nodules grouped together in the left groin fold.
called Fredrickson’s type IV hyperlipoproteinemia. Diagnosis of FHTG is usually suspected by the triad of elevated plasma triglycerides, normal or mildly raised total cholesterol, and reduced plasma HDL cholesterol levels. Identification of a similar lipid abnormality in a first-degree relative confirms the diagnosis of FHTG. The exact molecular mechanisms underlying the plasma lipid abnormalities in XD are unknown. Interestingly in hemophagocytic lymphohistiocytosis, a histiocytic disorder resulting from overproduction and activation of histiocytes and T cells, plasma triglyceride levels are often elevated. Studies have found that tumor necrosis factor alpha inhibits the lipoprotein lipase—secreting activity of macrophages leading to hypertriglyceridemia. However, we were unable to concur whether such a mechanism was responsible for hypertriglyceridemia because our patient had FHTG.

Treatment of XD is challenging. Several medications including statins, fibrates, glitazones, azathioprine, cyclophosphamide, prednisolone, and thalidomide have been tried with variable results, but most success seems to be noted with 2-chlorodeoxyadenosine. The anti-inflammatory and lipid-lowering effects of statins and fibrates were used for the treatment of XD and familial hypertriglyceridemia in our patient.

**CONCLUSIONS**

Plasma lipid levels should be evaluated in all patients with xanthoma disseminatum, including their family members. We also suggest for the inclusion of xanthoma disseminatum in the differential diagnosis of dermatoses exhibiting the Köebner phenomenon.

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