Diffuse xanthomas in a patient with primary biliary cholangitis and lipoprotein X

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INTRODUCTION

Cutaneous xanthomas are common cutaneous lesions that arise from localized deposits of lipid in the dermis.[1] Their presence often represents an underlying disorder of lipid metabolism. The morphology of cutaneous xanthomas can suggest a particular lipid disorder. For example, the presence of tuberous, tendinous, and plane xanthomas can be associated with primary type II and III hyperlipidemia.[1]

Less commonly, xanthomas occur in the setting of secondary dyslipidemia, such as cholestasis in primary biliary cholangitis (PBC). PBC is an autoimmune disease of the biliary tree, which causes progressive destruction of the small intrahepatic bile ducts, resulting in cirrhosis. Dyslipidemia is seen in 75% of patients with PBC and arises in part due to accumulation of an abnormal lipoprotein called lipoprotein X, which carries large quantities of cholesterol in the blood.[2] As a result, patients may present with similar patterns of xanthomas as those seen in type II or III hyperlipidemia. Herein, we present a case of diffuse and multiple types of xanthomas arising in association with lipoprotein X in PBC. Our case demonstrates a constellation of xanthomas that can be seen in cases of lipoprotein X-associated dyslipidemia and reminds us to consider this unique pathophysiology in our workup for xanthomas.

Abbreviation used:

PBC: primary biliary cholangitis

CASE REPORT

A 33-year-old woman with a known history of PBC presented to our clinic with debilitating pruritus and numerous skin lesions on her face, trunk, and extremities. Physical examination revealed soft yellow-brown plaques in the periorbital areas. There were also innumerable soft yellow-brown papules distributed symmetrically on the trunk and extremities, coalescing into plaques in the intertriginous areas, on the extensor joints of the hands and feet, and in the palmar creases (Fig 1, *A* to *C*). Tuberous lesions were observed on the dorsal aspect of both hands, overlying the knuckles (Fig 1, *D*). A clinical diagnosis of xanthomas was made. Shave removals were performed for bothersome lesions, and histopathology confirmed the presence of a xanthomatous and xanthogranulomatous infiltrate.

A review of the patient's history revealed that she had first developed these lesions 2 years prior. Their presence prompted a lipid panel, showing the following parameters: cholesterol, 1300 mg/dL; triglycerides, 222 mg/dL; high-density lipoprotein cholesterol, 6 mg/dL; and low-density lipoprotein, 1249 mg/dL. Shortly thereafter, a liver biopsy was performed, demonstrating late-stage cirrhosis secondary to PBC, and additional bloodwork revealed the presence of lipoprotein X in her serum.

Prior to her visit to our clinic, the patient was treated with ursodeoxycholic acid, without any improvement of her dyslipidemia. She additionally underwent plasmapheresis, resulting in the temporary improvement of her cholesterol levels and xanthomas, but this was discontinued after a line infection. Her pruritus was refractory to hydroxyzine, naltrexone, escitalopram, and tramadol.

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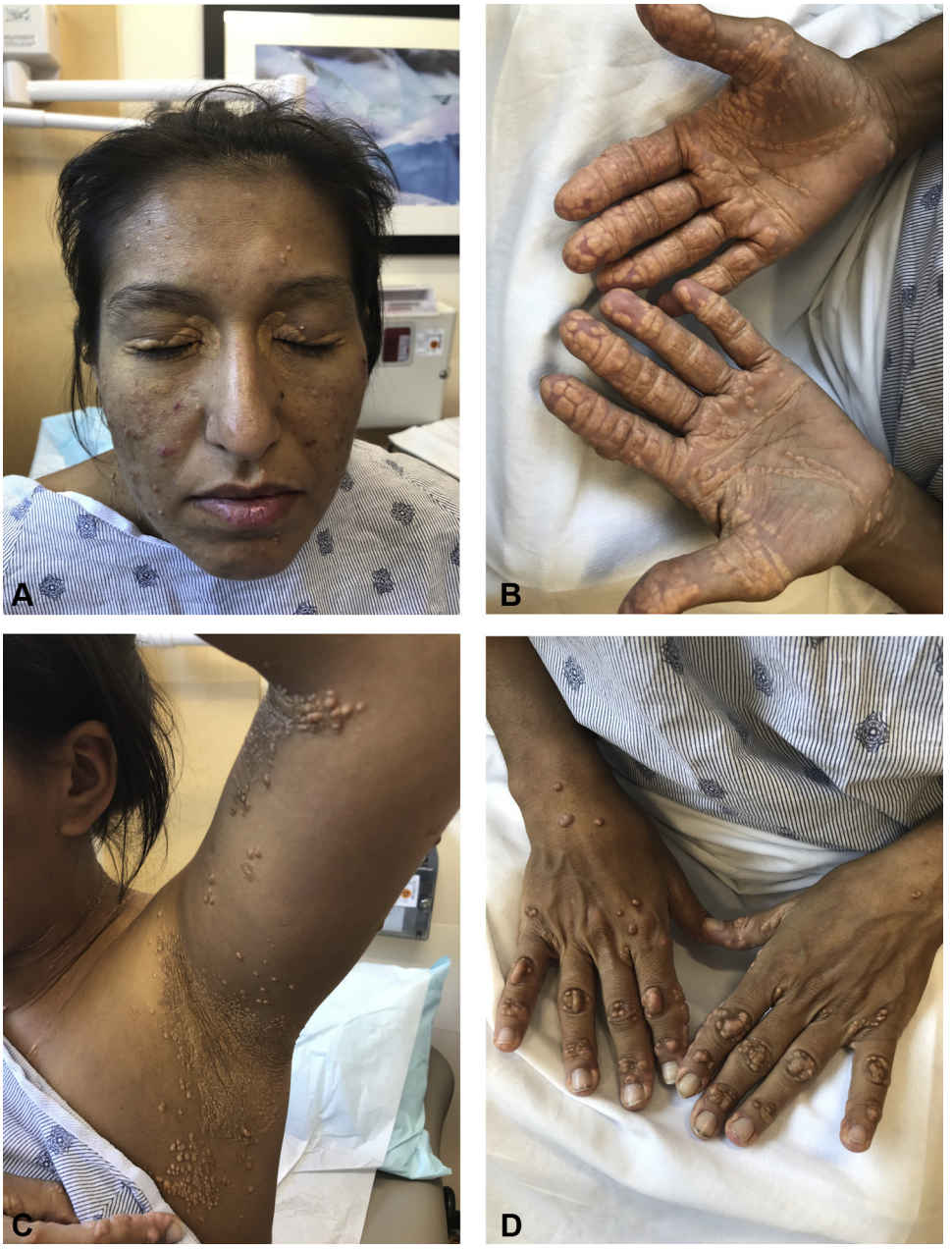

Fig 1. Numerous xanthomas in a patient with lipoprotein X in the setting of PBC. **A**, Xanthelasma: soft, yellow-brown plaques along the medial canthi and the upper eyelids. **B**, Xanthoma striatum palmare: multiple soft, yellow-brown papules coalescing into plaques across the palmar hands, favoring the palmar creases. **C**, Intertriginous xanthomas: soft, yellow-brown papules coalescing into plaques within the axilla. **D**, Tuberous xanthomas: multiple soft, yellow-brown papules and nodules symmetrically distributed along the dorsal aspect of the digits of the hand. *PBC*, Primary biliary cholangitis.

Fortunately, 4 months after her visit to our clinic, the patient received a liver transplant. The morning after her transplant, her pruritus completely resolved. Post-transplant lipid testing was significant for cholesterol (140 mg/dL), triglycerides (185 mg/dL), high-density lipoprotein cholesterol (34 mg/dL), and low-density lipoprotein (70 mg/dL). At the time of this writing, 5 months after the transplant, the patient reported a marked regression of her xanthomas.

DISCUSSION

Lipoprotein X is an atypical lipoprotein detected at increased levels in the serum of patients with severe cholestatic disease.[3-5] The accumulation of

lipoprotein X was previously considered to be due to the reflux of biliary lipoproteins into the systemic circulation. However, recent evidence suggests that lipoprotein X is generated in hepatocytes and secreted directly into the blood.[4,5] Lipoprotein X has a unique composition of apoproteins, including ApoA1, ApoE, and ApoC, which allows it to carry large quantities of phospholipids and free cholesterol in almost equal parts.[1,6] As a result, lipid profiles in patients with advanced cholestasis show striking elevations in the total cholesterol, high triglycerides, and low high-density lipoprotein levels. The patients are, therefore, susceptible to developing diffuse xanthomas. Indeed, an in vitro study in which lipoprotein X was incubated with human monocyte–derived macrophages demonstrated that lipoprotein X is directly responsible for foam-cell formation.[3]

As was seen in our patient, the clinical presentation of xanthomas is similar to what would be expected in type II and type III hyperlipidemia, with xanthelasma, tendinous xanthomas, xanthomas in the intertriginous areas, and xanthoma striatum palmare.[1,3,5,6] Though limited case reports have described similar patterns of cutaneous xanthomas in patients with lipoprotein X, none have reported a patient with such diffuse and simultaneous involvement of multiple xanthoma subtypes yet.

Overall, the pathogenesis of lipoprotein X-mediated dyslipidemia and xanthoma formation was clearly demonstrated in our patient. Prior to her diagnosis of PBC, the patient had normal lipid levels and was, therefore, unlikely to have familial hypercholesteremia. With the disease's onset, striking dyslipidemia associated with lipoprotein X developed, with xanthoma formation. The correction of her underlying disease by liver transplantation led to the restoration of normal lipid levels and regression of her xanthomas. For completion, ApoE genotyping was performed, particularly because of a strong association between xanthoma striatum palmare and type III hyperlipidemia,[7] and was negative. A monoclonal gammopathy screen was also without abnormalities.

The management of xanthomas in patients with lipoprotein X rests on addressing the underlying cause of cholestasis. Lipid-lowering agents can be used but often with limited success.[2] Therapeutic plasma exchange is the treatment of choice in patients who develop complications of hyperviscosity syndrome but leads only to partial xanthoma regression. For xanthelasma, destructive methods, such as 70% trichloroacetic acid chemical peels and carbon dioxide laser therapy, have been described, though the effects are temporary as long as dyslipidemia persists.[4,8] As in our patient, a liver transplant is often the only means to restore biliary drainage and lipid homeostasis and thereby improve the xanthomas.

In summary, we present a rare case of cutaneous xanthomas arising secondary to lipoprotein X in a patient with PBC. Our case demonstrates the diverse morphologies of xanthomas that can be observed in patients with lipoprotein X and brings attention to an underappreciated pathway, which should be considered in our approach to treating cutaneous xanthomas. Indeed, in our patient, the presence of the xanthomas was what first prompted diagnostic testing and led to her diagnosis of PBC. The consideration of this pathophysiology adds to our knowledge of the assessment of the cutaneous manifestations of this systemic disease.

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