Progressive tubero-eruptive xanthoma in familial hyperlipidaemia: A case report

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SUMMARY

Xanthoma is a unique clinical presentation in primary care that requires prompt suspicion of familial hyperlipidaemia (FH), urging immediate lipid tests and comprehensive clinical evaluation for a confirmed FH diagnosis. In atypical cases, further investigation is necessary to differentiate xanthoma from malignant skin tumours, which require distinct management strategies. This case report details a 33-year-old man who presented with multiple subcutaneous nodules spreading over 5 years. Laboratory investigations confirmed tubero-eruptive xanthoma associated with FH. This report emphasises the importance of early recognition and comprehensive management of xanthomas to mitigate cardiovascular risks and highlights the need for strict treatment adherence in FH.

INTRODUCTION

Xanthoma, characteristic manifestations of lipid deposition in skin tissues, serve as clinical indicators of certain lipid metabolism disorders, particularly in the context of familial hyperlipidaemia (FH) that encompasses a group of genetic conditions leading to elevated levels of cholesterol and other lipids in the blood. Recognising and understanding xanthoma is pivotal in diagnosing and managing lipid disorders within the spectrum of FH.[1] Tubero-eruptive xanthoma is a specific type of xanthoma commonly associated with severe hypertriglyceridemia and hypercholesterolemia in the context of FH and strongly associated with systemic atherosclerotic diseases, significantly contributing to morbidity and mortality.[1]

CASE PRESENTATION

A 33-year-old Malay man with underlying diabetes mellitus (DM), hypertension and hyperlipidaemia presented with progressive development of subcutaneous nodules that initially appeared at the extensor surfaces of the bilateral knee and ankle, then subsequently spreading across multiple body regions over 5 years. While some nodules displayed eruption, they were not painful or itchy, but significantly impeded joint mobility, causing discomfort. He had a strong family history of DM and hyperlipidaemia. The patient was obese, with a BMI of 32 kg/m². Skin evaluation showed clustered, reddish nodules with a central yellowish hue distributed bilaterally on elbows, anterior thighs, knees, Achilles tendons and other extremities (Figure 1 and 2). Nodules varied in size, with the largest measuring 3 × 4 cm characterised by a firm consistency and fusiform nodules were also identified bilaterally on the Achilles tendons (Figure 2).

The plasma lipid profile showed markedly elevated triglycerides (TG) of 22.61mmol/L (normal range: 0.68-1.88 mmol/L) and total cholesterol (TC) of 8.7 mmol/L (normal range 3.6-6.3 mmol/L). The patient had uncontrolled diabetes, with a fasting plasma glucose levels of 20 mmol/L and an elevated HbA1c value of 11.7% (NGSP). Liver and kidney function and uric acid levels were normal. Other tests, including an electrocardiogram and chest radiograph, showed no notable abnormalities. The patient declined a carotid ultrasound and genetic testing. A skin biopsy revealed presence of extracellular lipid accumulation in subcutaneous tissue with numerous lipid-laden histiocytes with lymphoplasmacytic cell infiltrates, which were characteristics of xanthoma (Figure 3). Based on the distributions and characteristics of the nodules, the patient was diagnosed with tubero-eruptive xanthoma and familial hyperlipidaemia (FH), supported by clinical history and laboratory findings.

The patient initially was prescribed atorvastatin 80 mg and ezetimibe 10 mg for hyperlipidaemia, along with lifestyle modifications advocating a low-cholesterol and low-saturated fat diet. For diabetes, he was treated with subcutaneous premixed analogue 28 units twice daily, extended-release Metformin 2 g daily and gliclazide MR 60 mg in the morning. For hypertension, he took perindopril 4 mg daily. In a recent follow-up, atorvastatin was switched to rosuvastatin 40 mg, with ezetimibe 10 mg maintained. Repatha (evolocumab) was considered if his lipid levels remained poorly controlled. On subsequent follow-up, his TG levels decreased to 11.30 mmol/L with TC to 7.4 mmol/L. The appearance of xanthomas flattened, and no new lesions were detected.

DISCUSSION

Xanthomas are distinct cutaneous lesions resulting from lipid accumulation in the skin and subcutaneous tissues. They can manifest as plaques, nodules or papules and often serve as crucial clinical markers of FH. FH is a group of inherited disorders characterised by abnormally high levels of fats

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Fig. 1: Extensive clustering of tubero-eruptive xanthomas on the elbow, showing numerous reddish-brown nodules of varying sizes.



Fig. 2: Pronounced tubero-eruptive xanthomas on the Achilles tendon, characterised by fusiform nodules and large nodular formations.

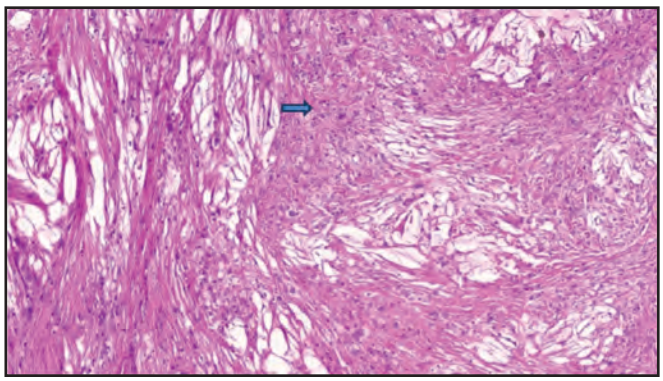


Fig. 3: Histopathological examination of biopsied xanthoma. Photomicrograph using hematoxylin and eosin (H&E) staining with arrow show numerous lipid-laden histiocytes which distinctive characteristic for xanthoma.

(lipids) in the blood, particularly cholesterol and triglycerides that result from genetic mutations affecting proteins involved in lipid metabolism, leading to impaired processing or clearance of lipids from the bloodstream. It is often hereditary and can manifest in various forms, including familial hypercholesterolemia and familial combined hyperlipidaemia. Genetic studies should be conducted when genetic cause-related hyperlipidaemia is suspected, however our patient was not keen for a genetic study due to financial issue.

Xanthomas are categorised as eruptive, tubero-eruptive, tuberous, tendinous and planar based on presentation and distribution. Eruptive xanthomas, characterised by multiple reddish-yellow papules arranged in crops, typically affect the extensor surfaces of limbs and buttocks. This manifestation is causally linked to severe hypertriglyceridaemia.[2] In contrast, tendon xanthomas appear as firm subcutaneous nodules localised over ligaments, fascia or extensor surface tendons of the hands, knees and elbows. Achilles tendons are commonly affected in this type of xanthoma, and these lesions are associated with conditions such as familial hypercholesterolaemia, familial dysbetalipoproteinaemia and phytosterolaemia.[3,4] Tuberous xanthomas manifest as nodules frequently found on the extensor surfaces of the elbows, knees, knuckles and buttocks, and they are linked to conditions such as familial hypercholesterolaemia, familial dysbetalipoproteinaemia, β-sitosterolaemia or cerebrotendinous xanthomatosis.[1] Other types of xanthomas include planar xanthomas, encompassing entities like xanthelasma palpebrarum/xanthelasma, xanthoma striatum palmare and intertriginous xanthoma. Xanthomas, while primarily known for their cutaneous manifestations, can also affect various organs and systems throughout the body, such as xanthomas that involve tendons and ligaments, oesophagus, orbit soft tissue, bone, oral and the brain.[5]

The unique appearance of xanthomas can sometimes resemble cutaneous tumours, leading to occasional diagnostic confusion with skin malignancies. We send this patient for a skin biopsy to rule out other skin malignancies. The reason is that xanthoma may be associated with malignancies of the reticuloendothelial system, such as myeloma, lymphoma and malignant histiocytosis that will change the treatment for the patient. Histopathological examination (HPE) findings of xanthoma typically reveal characteristic features, such as extracellular lipid accumulation, lipid-laden histiocytes, inflammatory infiltrate and fibrosis.[6] It is similar to the HPE findings of this patient that reported the presence of extracellular lipid accumulation within the subcutaneous tissue with numerous lipid-laden histiocytes were observed, often in association with lymphoplasmacytic cell infiltrates (Figure 3).

Tubero-eruptive xanthoma, a specific type of xanthomas characterised by the development of nodules with an eruption tendency, can lead to several complications, primarily due to their association with severe hyperlipidaemia and underlying metabolic disorders, specifically for this patient, he was diagnosed with FH. FH manifests as increased serum cholesterol level and/or increased TG, as shown by this patient. The abnormal increases in plasma lipids and TG present in patients with FH are prone to accelerated atherosclerosis formation, leading to a greater risk of cardiac events that eventually cause significant morbidity and mortality impacts.[7] Hypertriglyceridaemia associated with tubero-eruptive xanthoma in FH is associated with a higher incidence of acute pancreatitis and ocular complications such as lipemia retinalis that will impair vision.[8,9] The mortality risk is higher when associated with other comorbidities such as DM, obesity, hypothyroidism and liver disease.[10] Xanthomas in tendons and ligaments can impair joint function, and their rupture may lead to infection and pain. Tubero-eruptive xanthomas due to their size, distribution and tendency to erupt, can cause significant cosmetic concerns and affect self-esteem and quality of life. The visible appearance of these lesions may lead to social stigma and psychological distress.

Treatment aims to address lipid abnormalities and reduce xanthoma size and appearance. Statin therapy, the first-line treatment for FH, has been shown to effectively reduce xanthoma size.[11] Other options include fibric acid derivatives (fibrates), ezetimibe, bile acid sequestrants and PCSK-9 inhibitors. Intensive treatment combining statins, ezetimibe and PCSK-9 inhibitors has demonstrated significant xanthoma regression.[12] In cases resistant to medical treatment, plasma exchange has shown remarkable resolution of xanthomas and significant lipid profile improvement. While specific studies on exercise's direct impact on xanthoma reduction are lacking, incorporating regular physical activity into a comprehensive lifestyle approach for managing lipid abnormalities and cardiovascular health is widely recommended. This strategy includes exercise, dietary adjustments, medication and other lifestyle changes. The patient however, experiences limitations in engaging in aerobic exercise due to the inability to wear appropriate sports shoes. The size of the xanthomas on both feet hinders finding suitable footwear, leading to discomfort and pain when the xanthomas are compressed during exercise. For these reasons, this patient was planned to be referred for surgical excision to remove the larger lesions. Alternatively, laser therapy has been found to effectively treat xanthomas, though it may result in dyspigmentation and scarring. Other options such as chemical peeling, cryotherapy and electrosurgical techniques like radiofrequency ablation and plasma sublimation offer alternative approaches, each with its own considerations. Topical trichloroacetic acid (TCA) may be less invasive, but it still carries the risk of scarring and pigment changes. Careful consideration based on lesion characteristics and patient factors is essential, with discussions between patients and healthcare providers to determine the most suitable treatment approach.

Follow-up care is crucial to monitor complications and ensure optimal outcomes not only for the patient but also for his family members who require screening and long-term follow-up. In our patient, after intensifying lipid therapy with a high dose of statin and ezetimibe, along with suggested lifestyle modifications, the xanthomas flattened and no new lesions were observed during subsequent follow-ups, obviating the need for surgical or dermatologic intervention.

CONCLUSION

In conclusion, various types of xanthomas can serve as valuable indicators of underlying genetic disorders related to lipoprotein metabolism. Clinicians should remain vigilant regarding the cutaneous manifestations of metabolic disorders, as they necessitate prompt treatment due to the increased risk of cardiovascular events that contribute significantly to morbidity and mortality. The comprehensive evaluation and management of xanthomas are essential not only for cosmetic reasons but also for the prevention of severe systemic complications associated with underlying lipid metabolism disorders.

PATIENT CONSENT INFORMATION

The patient had given informed consent to publish his clinical details in this case report.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

FINANCIAL DISCLOSURE

The authors declared that this study has received no financial support.

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