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CASE REPORT

Surgical Treatment of Multiple Large Tuberous and Tendinous Xanthoma Secondary to Familial Hypercholesterolaemia: A Case Report

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Abstract: Xanthomas are well-circumscribed skin lesions that are commonly seen in patients with familial hypercholesterolemia (FH). The aim of this report is to present a rare case of multiple large tuberous and tendinous xanthomas. A 17-year-old female patient in this report presented with multiple asymptomatic and papulo-nodular masses in both sides of palms, elbows, buttocks, knees, and Achilles tendons. Surgical removal of the masses was carried out in combination with lipid-lowering therapy. A following up of 3 months showed all wounds were healing well, and no recurrence of masses was observed. Therefore, for patients with xanthomas related with familial hypercholesterolaemia, lipid-lowering therapy has reportedly reduced the size of masses, but surgical treatment may be essential for large xanthomas caused pain or limitation of daily activities.

Keywords: soft-tissue tumors, lipoprotein, atorvastatin, foam cells, lipid-lowering therapy

Introduction

Xanthomas are well-circumscribed exogenous masses, which mainly developed in soft tissue such as skin, tendons, joints, and fasciae. The clinical manifestations of xanthomas are variable, appear as yellow macules, papules, or large nodules. It is common to simply classify the xanthoma according to their location-skin or tendons. In the skin the xanthoma may take multiple forms: planar xanthomas, eruptive xanthoma, tubo-eruptive xanthoma, and tuberous xanthomata. In the tendons, the xanthomas called tendinous xanthomas.[1,2] Among these, tuberous xanthomas are usually presented as flat or elevated plaques less than 2 centimeters in diameter, often found in patients with lipoprotein metabolic disorders.[3,4] Here, we report a rare case of successful surgical treatment for multiple large tuberous and tendinous xanthomas secondary to familial hypercholesterolaemia (FH).

Case Report

A 17-year-old female patient presented to our hospital with complaints of multiple asymptomatic and papulo-nodular masses in different locations of the body, including palms, elbows, buttocks, knees, and Achilles tendons. The masses were of varying sizes, ranging from 0.3 cm to 8 cm (Figure 1). The patient complained of difficulty dressing and sitting due to unsightly and large masses. She reported a family history of hypercholesterolaemia and xanthoma for which his father also had two masses on both buttocks and received surgical removal at the age of 8. However, her mother had no history of xanthoma or hypercholesterolemia. Laboratory examinations showed marked abnormalities: serum cholesterol (Chl): 13.75 mmol/L (normal: <5.18 mmol/L); high-density lipoprotein cholesterol (HDL-C): 2.07 mmol/L (1.03–1.55 mmol/L); low-density lipoprotein cholesterol (LDL-C): 13.19 mmol/L (<3.37 mmol/l); small dense low-density lipoprotein cholesterol (sdLDL-C): 2.54 mmol/L (<0.9 mmol/L); apoprotein A1 (ApoA1): 1.03g/L (1.20–1.60 g/L);

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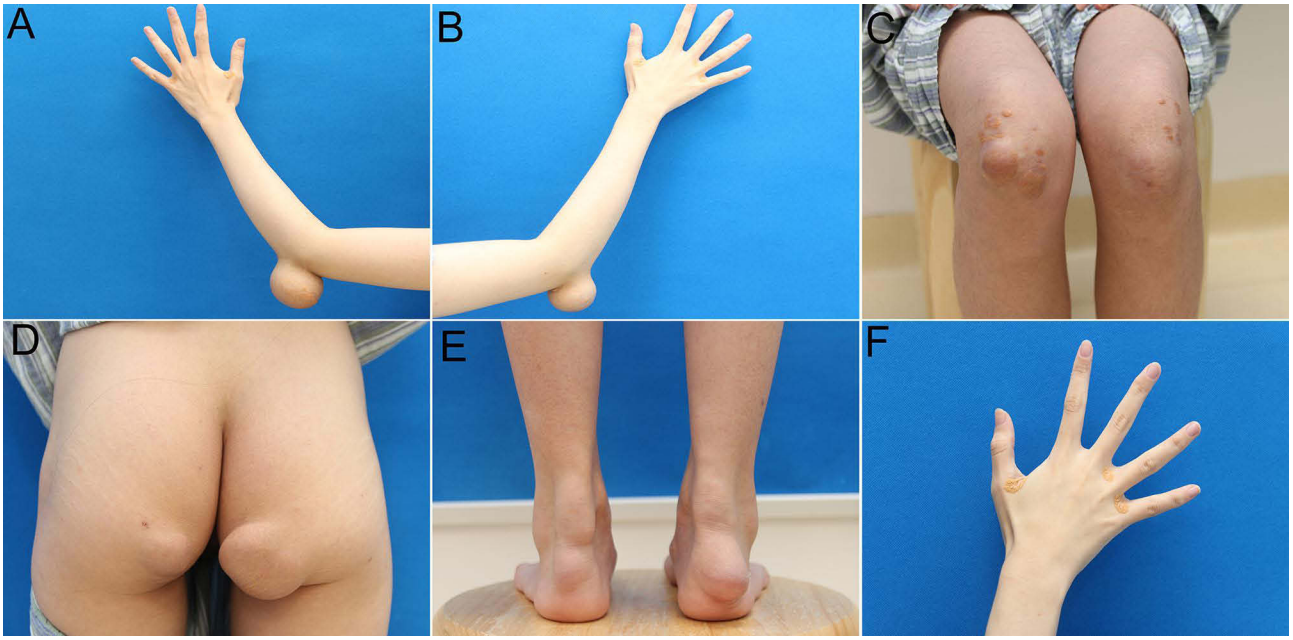

Figure 1 Multiple subcutaneous lesions over different locations. (**A** and **B**) lesions in both elbows. (**C**) lesions in both knees. (**D**) lesions in buttocks. (**E**) lesions in Achilles tendons. (**F**) lesions over proximal interphalangeal joints.

apoprotein B (ApoB): 2.61g/L (0.60–1.20 g/L); apoprotein A1/B (A1/B): 0.39 (1–2); apoprotein E (ApoE): 5.89 mg/mL (2.70–4.50 mg/mL); lipoprotein-associated phospholipaseA2 (Lp-PLA2): 1668U/L (≤535 U/L). The patient had no cardiac symptoms. The result of chest X-ray, electrocardiogram, echocardiogram, and abdominal ultrasound of the patient were normal. After admission, ultrasound produced inconclusive diagnosis and further MRI scan was applied. The masses revealed low signal intensity on T1-weighted images and low-high mixed signal intensity on T2-weighted images. (Figure 2). Based on the Simon Broome criteria, the patient was diagnosed with Familial hypercholesterolemia (FH). Unfortunately, the patient refused to receive genetic testing.

The patient then received surgical treatment to remove the masses. The masses on both elbows, buttocks, and knees were removed completely through W-shaped incisions. Masses on palms and Achilles tendons were not removed because these masses were small, and the patient had to walk to school in a few days. The surfaces of resected masses were normal skin. The cores of masses were yellowish-colored, relatively soft, no necrosis, and confined to the subcutaneous tissue without involving underlying muscle or joint capsule (Figure 3). Histopathology showed infiltration of foam cells and scattered giant cells with lipid-rich background (Figure 4). After removal, all incisions were sutured carefully (Figure 5). The patient was discharged at 5 days postoperatively, and all sutures were removed 14 days after operation without any complications. The patient had not been treated for this disease before, for the management of cholesterol, she received oral atorvastatin 40 mg once per day. A following up of 3 months showed all wounds were healing well, and no recurrence of masses was observed.

Discussion

Xanthomas are masses that are characterized by the clusters of foam cells, which are formed from lipid-filled macrophages within deep soft tissue.[2] The development of xanthoma begins with an increased permeation of lipids to the connective tissue interspace through the vascular wall. Macrophages accumulated there phagocytize the excessive low-density lipoprotein (LDL) particles. As a result, foam cells can be formed.

FH is an inherited autosomal dominant disorder with a raised LDL plasma level, so patients with FH have a high risk of xanthomas.[5] In this case, no obvious diseases affecting lipid metabolism such as liver and kidney diseases and diabetes were found by routine examination, and blood lipid tests showed significant increases in serum cholesterol, especially LDL level. In addition, the patient reported that her grandfather and father also had hypercholesterolemia. Furthermore,

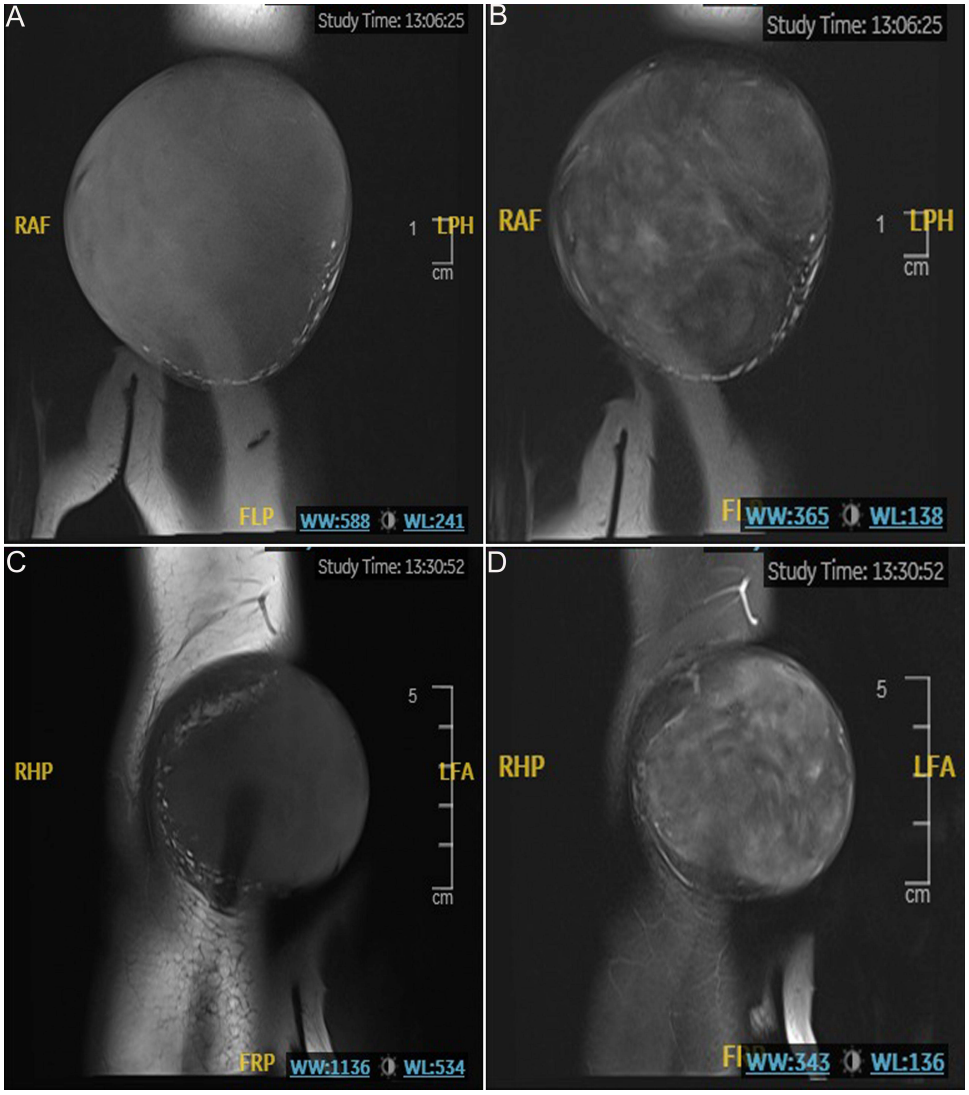

Figure 2 MRI imaging of xanthomas masses on left (**A** and **B**) and right (**C** and **D**) elbows. The masses revealed low signal intensity on T1-weighted images and low-high mixed signal intensity on T2-weighted images.

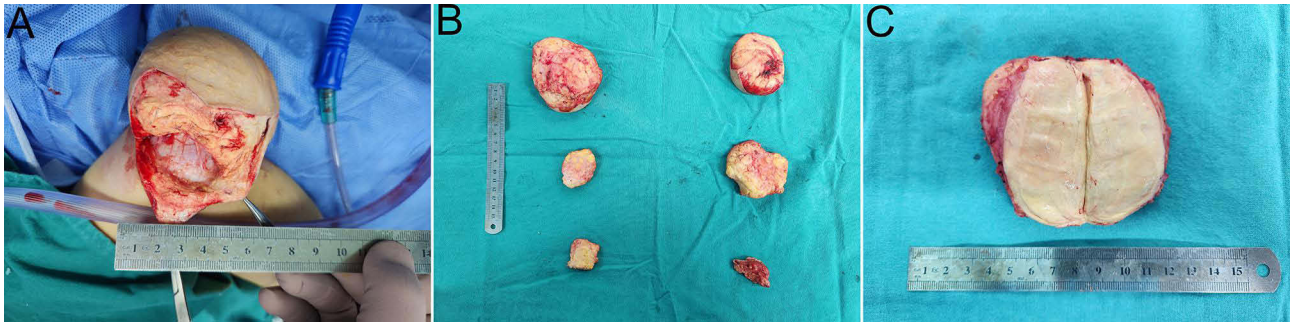

Figure 3 Intraoperative photograph of the lesions. (**A** and **B**) Resected xanthomas. (**C**) The sectional view of the xanthomas.

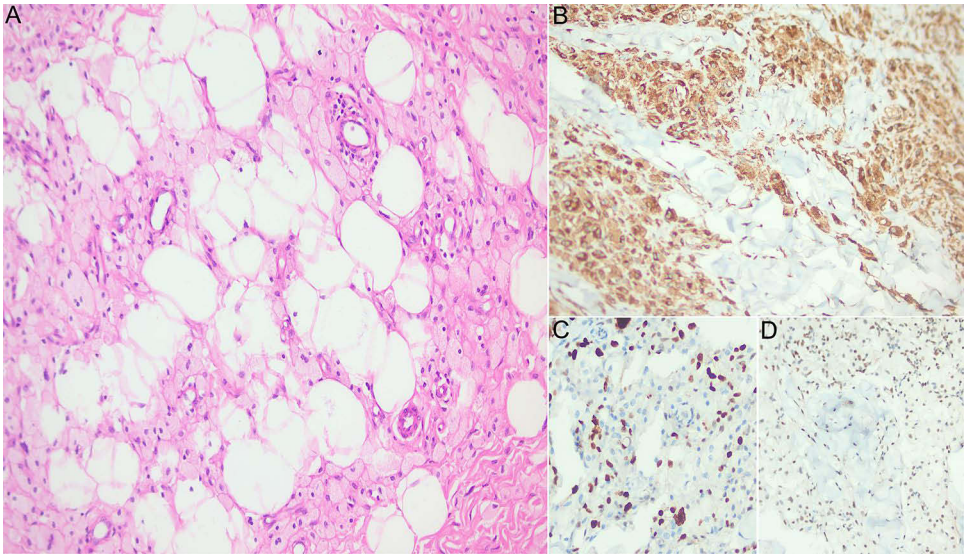

Figure 4 Pathological pictures of the lesion. (**A**) Hematoxylin/eosin analysis showed infiltration of foamy cells and scattered giant cells (x200). CD68-immunostaining (**B**), Ki67- immunostaining (**C**) and TFE3- immunostaining (**D**) of the xanthomas presented positive (x200).

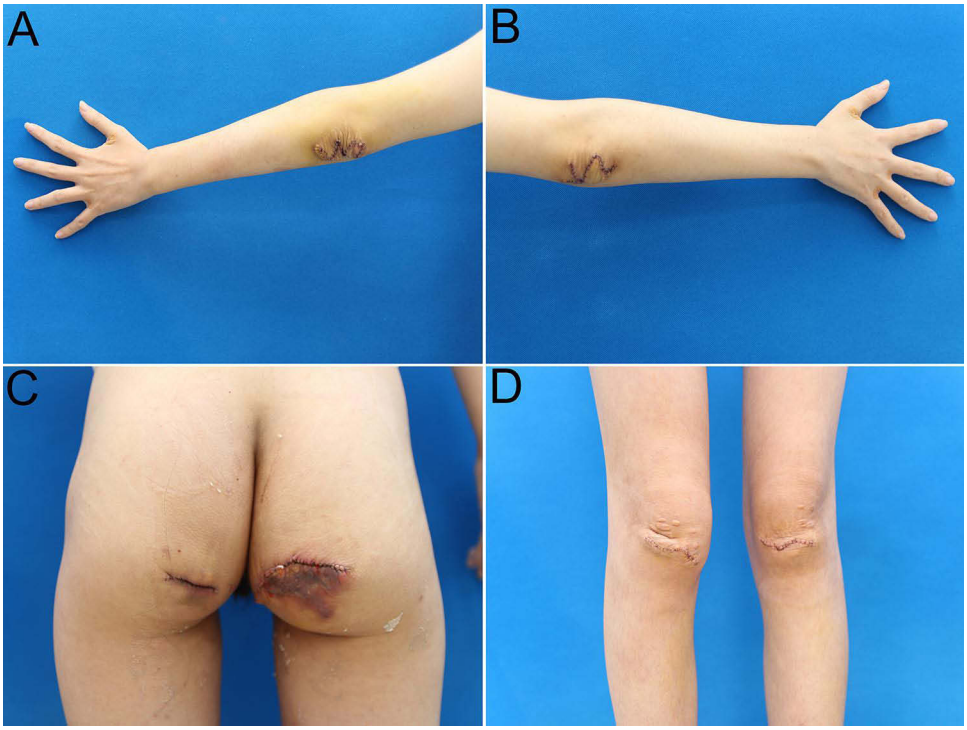

Figure 5 Status of the incisions two days after the operation. (**A** and **B**) elbows. (**C**) buttocks. (**D**) knees.

her father had two masses on both buttocks and received surgical removal at the age of 8. However, her mother had no history of xanthoma or hypercholesterolemia. According to the diagnostic criteria of Homozygous familial hypercholesterolaemia (HoFH),[6,7] a clinical diagnosis of HoFH rather than heterozygous familial hypercholesterolaemia (HeFH) for this patient can be made on the basis of skin or tendon xanthomas since infancy, and untreated LDL-C levels of 13.19 mmol/L(>500mg/dL), four times higher than normal levels.

As previously stated, xanthomas are typically less than 2 centimeters in diameter and occurred most frequently at extensor surfaces due to mechanical stresses, such as knuckles, elbows, knees, and buttocks.[8] Therefore, the occurrence

of our patient with multiple large xanthomas is rare. In our case, the masses grow to be large, entangled, and quite influence the patient's activities and life quality. This is the main reason for the patient to seek medical care.

For patients with xanthomas, lipid-lowering therapy is necessary for reducing the size of masses and decreasing cardiovascular complications.[9,10] In this case, the patient was started on atorvastatin 40mg/day immediately after admission. For large xanthomas caused pain or limitation of daily activities, surgical intervention is required. However, for use in the treatment of HoFH, additional therapy with PCSK9 Inhibitors also plays an important role. PCSK9 protein plays an important role in post-translational regulation of LDL- Receptor, and inhibition of pcsk9 protein can lead to upregulation of LDL- Receptor, resulting in greater LDL-C clearance. PCKS9 monoclonal antibodies such as evolocumab are effective in reducing LDL-C in patients with HoFH. PCSK9 inhibition can also be achieved with small interfering RNA therapy, and inclisiran is the first approved therapy of its kind.[11,12] Lowering LDL-C can also be achieved by using drugs such as lomitapide, which inhibits microsomal triglyceride transfer proteins, thereby reducing LDL synthesis.[13]

Similar to other tumor surgery, en bloc resection of the masses plays an important role clinically in preventing postoperative local recurrence. Meanwhile, as plastic surgeons, we are committed to achieving satisfying cosmetic effect. Appropriate skin flaps will be selected to repair the wound after resection, and all incisions are closed without tension. In this case, a following up of 3 months showed all wounds were healing well with slight scar or no scar formed, and no recurrence of masses was observed.

Conclusion

For patients with xanthomas related with familial hypercholesterolaemia, early diagnosis and treatment are of great importance, which will reduce the occurrence of cardiovascular complications. Surgical treatment is essential for large xanthomas caused pain or limitation of daily activities. However, for patients with FH, especially HoFH, initiation of aggressive LDL-C lowering as early as possible is essential for preventing their premature deaths.

Ethics Statement

No institutional approval is required for case reports, and the patient cannot be identified from the images.

Informed Consent Statement

Patient and her parents consented in writing for the publication of her case/photographs both online and in-print and understood that it will be publicly available and was sent a copy of the article to read.

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Disclosure

The authors report no conflicts of interest in this work.

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