

## Case Report

# Tuberous Xanthomatosis as a Presentation of Familial Hypercholesterolemia

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Submitted: 17 August 2016

Accepted: 27 September 2016

Published: 29 September 2016

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ISSN: 2373-9819

OPEN ACCESS

**Keywords**

- Xanthomatosis
- Familial hypercholesterolemia
- Xanthomas
- Lipid disorders

**Abstract**

Xanthomas are localized lipid deposits within organs that may manifest as papules, plaques, or nodules in skin. The subtype of xanthoma provides a clue to the underlying lipid abnormality. Accurate diagnosis of xanthomas is important because it can lead to the identification and treatment of underlying disease. Xanthomas associated with familial hypercholesterolemia are an exception. In patients with this disorder they often begin to develop prior to the age of 10 years. Herein, we report a case of a 10-years-old who presented with a 2-year history of slow and multiple mass growths on the extensor surfaces of the upper and lower extremities laboratory findings advocated familial hypercholesterolemia. These lesions were surgically removed for cosmetic reasons. Clinicians should be aware of differential diagnosis when approaching cutaneous lesions related to lipid disorders.

**ABBREVIATIONS**

LP: Lipoprotein; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; VLDL: Very Low Density Lipoprotein; IDL: Intermediate Density Lipoprotein; ErYAG: Erbium-Doped Yttrium Aluminium Garnet; DM: Diabetes Mellitus; Apo: Apoprotein

**INTRODUCTION**

Xanthomas are localized lipid deposits within organs that may manifest as papules, plaques, or nodules in skin. The clinical variants of cutaneous xanthomas include a wide arrange of lesions such as cutaneous xanthomas that can be idiopathic or may present as a sign of an inherited abnormality of lipoprotein metabolism (primary dyslipidemia), hyperlipidemia secondary to systemic disease or medication, or hematologic disease. The subtype of xanthoma provides a clue to the underlying abnormality. Accurate diagnosis of xanthomas is important because it can lead to the identification and treatment of underlying disease. Epidemiologic data on cutaneous xanthomas are limited. Tuberous, tuberoeruptive, tendinous, and non-xanthelasma plane xanthomas typically occur in association with inherited or acquired dyslipidemia or hematologic disease [1,2]. Cutaneous xanthomas most often present in adulthood. Xanthomas associated with familial hypercholesterolemia are an exception. In patients with this disorder they often begin to develop prior to the age of 10 years and tend to occur in

both males and females and do not appear to be a clear sex predilection. The pathogenic mechanism that leads to cutaneous xanthomas are not fully understood and may differ based upon the etiology and type of xanthoma. For xanthomas occurring in association with hyperlipidemia, it is hypothesized that when serum levels of lipoproteins are substantially elevated, extravasations of lipoproteins through dermal capillary blood vessels with subsequent engulfment by macrophages leads to the lipid-laden cells found in xanthomas [3,4]. Primary or secondary hyperlipidemic states can lead to xanthoma formation. Primary hyperlipidemia results from genetic defects in receptors, receptor ligands, or enzymes involved in lipid metabolism. Causes of secondary hyperlipidemia include underlying disease states and medications. Examples of diseases and physiologic states associated with hyperlipidemia include obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, cholestasis, and pregnancy [5-10]. Examples of medications that may lead to hyperlipidemia (often hypertriglyceridemia) include estrogens, tamoxifen, prednisone, oral retinoids, cyclosporine, olanzapine, and protease inhibitors [11-14].

Immune complex formation between antibodies and lipoproteins leading to lipid accumulation within macrophages is a proposed mechanism for xanthoma formation in the setting of monoclonal gammopathy [15]. The clinical variants of cutaneous xanthoma include eruptive, tuberous, tuberoeruptive, tendinous,

plane (including xanthelasma), and verruciform xanthomas. Most xanthomas present as erythematous to yellow papules, plaques or nodules representative of lipid deposition in the skin. The characteristic histologic feature of cutaneous xanthomas is lipid-laden macrophages, also known as “foam cells.” The number of foam cells and the presence of associated findings, such as inflammatory cells, extracellular lipid deposition, and fibrosis vary with the type and age of the xanthoma. Eruptive xanthomas often have prominent extracellular lipid deposition, and tuberous and tendinous xanthomas often have large foam cells with associated fibrosis [1,16]. Tuberous xanthomas are yellow-orange or erythematous papules or nodules located over joints or extensor surfaces of the extremities, especially the elbows and knees and they may be solitary or grouped and they can reach sizes up to 3 cm and mainly occur in hypercholesterolemic states, such as with familial hypercholesterolemia (elevated low-density lipoprotein levels) or when intermediate density lipoprotein levels are high (familial dysbetalipoproteinemia), in which case the serum cholesterol and triglyceride levels may be similarly increased (eg, each is approximately 400 mg/dL) [17].

### CASE PRESENTATION

A 10-years-old boy presents as an outpatient in a rural hospital complaining of slow and multiple mass growth on extensor surface of right elbow and both knees since the age of 8 years old. He has no remarkable past medical history. On physical exam, the patient does not reveal any signs of distress, focused examination shows an arrange of small solitary masses of approximately 3x3 cm located at the extensor surfaces of right elbow (Figure 1), left and right knee. On palpation they present as a firm, mobile and non-painful nodules, smaller multiple lesions of approximately 5 mm were seen on the inferior and superior pole adjacent to the patellar region of the right and left knee respectively (Figure 2). Laboratory studies revealed a high low-density lipoprotein level measured at 623 mg/dL, a 12 lead EKG was found to have no apparent cardiac abnormalities. With biochemical results and a typical clinical presentation of tuberous xanthomas, a diagnosis of familial hypercholesterolemia was established. The patient was offered initial medical treatment with high dose statins, ezetimibe and elective surgical resection of xanthomas which occurred without any complication with surgical findings of one firm yellowish nodule located at the extensor surface of right elbow of 3x3 cm, one firm yellowish round nodule of 3x3 located on the anterolateral surface of the patella and two firm nodules at the left and inferior borders of the left patella of 3x3 cm and 2x2 cm respectively without any compromise of surrounding structures. After his surgical intervention the patient underwent an uneventful recovery and it was discharged after 16 hours of in hospital surveillance.

### DISCUSSION

The diagnosis of cutaneous xanthomas involves determining the type of xanthoma and the underlying cause through the patient history, physical examination, and relevant laboratory studies. Often, the classic yellow or yellow-red color and distribution of eruptive, tuberous, and plane xanthomas (eg, eyelids in xanthelasma) enables a presumptive diagnosis. Correlation of the clinical, biochemical and pathologic findings



Figure 1 Tuberous xanthoma on the extensor surface of the right elbow.

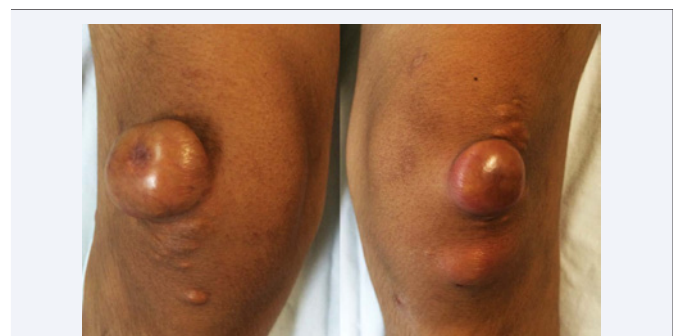
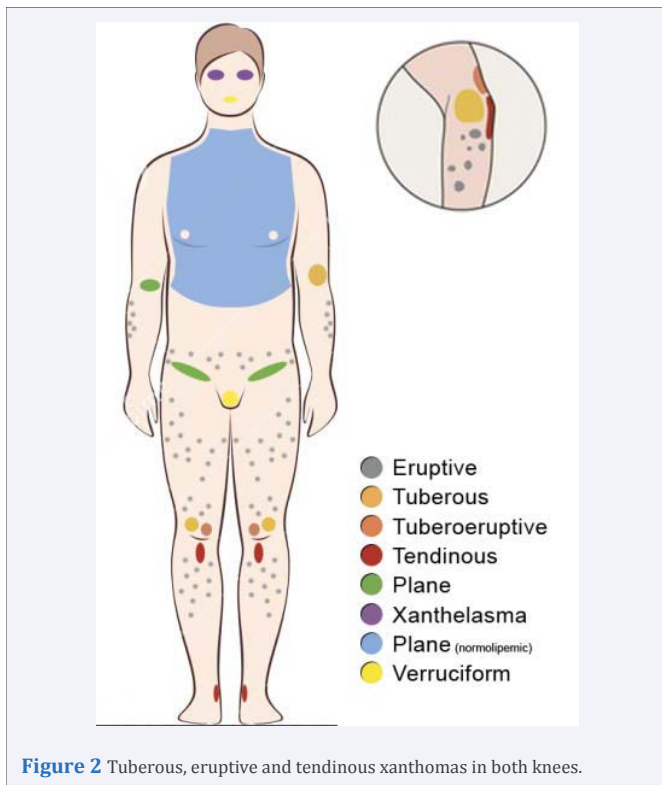


Figure 2 Tuberous, eruptive and tendinous xanthomas in both knees.

confirms the diagnosis. The patient history should include an assessment for risk factors for xanthoma development such as underlying diseases (eg, diabetes, thyroid disease, nephrotic syndrome, hematologic disease), medications that may cause hyperlipidemia (eg, estrogens, tamoxifen, prednisone, oral retinoids, cyclosporine, olanzapine, and protease inhibitors), family history of primary lipid disorders or diseases associated with hyperlipidemia. The physical examination should include an assessment of the morphology and location of the xanthomas. Physical findings that suggest particular variants include eruptive xanthomas (Multiple small, yellow to yellow-red papules on the buttocks or extensor extremities), tuberous xanthomas (Yellow-orange or erythematous papules or nodules on the extensor extremities or joints), tendinous xanthomas (skin-colored, mobile nodules over tendons or ligaments), plane xanthomas (yellow, thin plaques on the eyelids, neck, trunk, shoulders, or axillae (also known as xanthelasma), verruciform xanthomas (verrucous papules in the oral cavity or on anogenital skin) (Figure 3). A fasting lipid panel to evaluate for dyslipidemia should be performed in all patients with xanthomas, with the exception of patients with verruciform xanthomas. Verruciform xanthomas are not associated with hyperlipidemia. Patients with tendinous or tuberous xanthomas automatically should be evaluated for an inherited dyslipidemia. In the absence of dyslipidemia, a diagnosis of eruptive, tuberous, or tendinous xanthomas should be reconsidered, given the strong association of these subtypes with dyslipidemia. Tendinous and tuberous xanthomas may resemble other nodular eruptions with predilections for sites



**Figure 2** Tuberos, eruptive and tendinous xanthomas in both knees.

over joints or tendons. Examples include rheumatoid nodules, gouty tophi, subcutaneous granuloma annulare and erythema elevatum diutinum. Knowledge of underlying medical conditions is useful for narrowing the differential diagnosis. Verrucous xanthomas on the oral and genital mucosa may be clinically confused with condylomata, oral papillomas, verrucous carcinoma, and squamous cell carcinoma. Cutaneous xanthomas are not life-threatening and are usually asymptomatic. Therefore, treatment

specifically for cutaneous xanthomas is not mandatory, although it is often desired for cosmetic reasons. However, pharmacologic treatment of dyslipidemia is usually indicated and often leads to concomitant improvement in eruptive, tuberos, tendinous, and plane xanthomas caused by hyperlipidemia. Eruptive xanthomas typically resolve within several weeks when triglyceride levels are reduced. Tuberos and tendinous xanthomas are slower to regress during treatment of dyslipidemia. Different approaches are necessary for the treatment of xanthomas that are not associated with dyslipidemia. Normolipidemic patients with xanthelasma who desire treatment are primarily treated with surgical excision or destructive interventions. Traditionally, surgical excision has been used, with good cosmetic results [18]. Other effective treatment methods include destruction of xanthelasma with cryotherapy, 70 percent trichloroacetic acid chemical peels, and treatment with carbon dioxide or erbium-doped yttrium aluminium garnet (ErYAG) lasers [19-23]. Without treatment, xanthomas typically persist. Patients with hyperlipidemia-associated xanthomas require clinical follow up for morbidities associated with hyperlipidemia and underlying causes of hyperlipidemia (Table 1). In addition, patients with diffuse plane xanthomas who lack evidence for hematologic disease at the time of diagnosis require long-term follow up for the development of hematologic disease [17].

**CONCLUSION**

In conclusion, this case underscores the importance of proper identification of nodular lesions and a differential diagnosis of specific subtypes of xanthomas as a way to suspect dyslipidemic disorders. Resection of the lesion is the treatment of choice usually for cosmetic reasons. The size and location of this dermatologic illness should always be considered in the diagnosis and surgical approach. In spite of adequate treatment, high recurrence should always be expected. Therefore, proper identification and management of the underlying disorder should be achieved.

**Table 1:** Major types of hyperlipidemia [23].

Type	Laboratory findings	Clinical findings	
		Skin (types of xanthoma)	Systemic
Type I (Familial LP deficiency, familial hyperchylomicronemia)	Slow chylomicron clearance Reduced LDL and HDL levels Hypertriglyceridemia	Eruptive	No increased risk of coronary artery disease
Type II (Familial Hypercholesterolemia or Familial deficiency of apo B-100)	Reduced LDL clearance Hypercholesterolemia	Tendinous, tuberoeruptive, tuberos, plane, (xanthelasma, intertriginous areas, interdigital web spaces)	Atherosclerosis of peripheral and coronary arteries
Type III (Familial dysbetalipoproteinemia, broad beta disease, apo E deficiency)	Elevated levels of chylomicron remnants and IDLs Hypercholesterolemia Hypertriglyceridemia	Tuberoeruptive, tuberos, plane and tendinous	Atherosclerosis of peripheral and coronary arteries
Type IV (Endogenous familial Hypertriglyceridemia)	Increased VLDLs Hypertriglyceridemia	Eruptive	Frequently associated with type 2 DM, obesity and alcoholism
Type V	Decreased LDLs and HDLs Hypertriglyceridemia	Eruptive	DM

**Abbreviations:** LP: Lipoprotein; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; VLDL: Very Low Density Lipoprotein; IDL: Intermediate Density Lipoprotein; ErYAG: Erbium-Doped Yttrium Aluminium Garnet; DM: Diabetes Mellitus; Apo: Apoprotein

## ACKNOWLEDGEMENTS

Special greetings to the department of general surgery of the Hospital de Especialidades. Centro Médico Nacional la Raza in Mexico City.

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### Cite this article

Vargas-Flores E, Lourdes Estrada-Alpizar E, Arenas-Osuna J (2016) Tuberos Xanthomatosis as a Presentation of Familial Hypercholesterolemia. *JSM Clin Case Rep* 4(5): 1114.