Case Report

Tuberous xanthoma with cardiac failure in a child

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Abstract

A 14-year-old girl presented with gradually progressive breathlessness for 3 weeks. On evaluation, it was found that she had left ventricular hypertrophy and nonprogressive R wave in ECG. An echocardiogram revealed aortic stenosis and severe left ventricular dysfunction.Computed Tomography (CT) imaging showed aortic annulus calcifications causing aortic stenosis. Over three years she had gradually developed asymptomatic cutaneous swellings over the small and large joints of the extremities suggestive of tuberous xanthomas. Skin biopsy revealed scattered foamy macrophages in the upper dermis and cholesterol clefts. Her lipid profile showed raised total cholesterol and low-density lipoprotein levels. With the above clinical, histological, and laboratory findings she was diagnosed as a case of familial homozygous hypercholesterolemia with tuberous xanthomas and cardiac failure. She was started on statins, ezetimibe, and other anti-failure measures. We present this case for its rarity. Early diagnosis of this condition based on skin findings, could have prevented cardiac failure by initiating early appropriate treatment.

Keywords: Cardiac failure, foamy macrophages, tuberous xanthoma, xanthomas

Introduction

Genetic disorders of lipid metabolism such as hyperlipoproteinemia can be associated with clinical manifestations like premature atherosclerosis, cardiovascular involvements, cutaneous xanthomas, and pancreatitis.[1,2] Frederickson classified these disorders based on the electrophoretic mobility of plasma lipoprotein fractions into five classes.[3] Xanthomas in the skin arise from the deposition of qualitatively altered plasma lipoproteins and free fatty acids in the form of foam cells. Herein, we report a case study on a teenage girl with tuberous xanthomas who acutely presented to us with heart failure. This case emphasizes the importance of diagnosing any underlying familial hypercholesterolemia in the early stage, thereby preventing the chance of developing cardiovascular disease which should be kept in mind by primary care physicians when approaching a patient with xanthomas.

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Received: 16-07-2021 **Revised:** 12-12-2021
Accepted: 16-12-2021 **Published:** 30-06-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1416_21

Case Report

A 14-year-old girl presented with a 3-week history of gradually progressive breathlessness and raised skin lesions over hands, elbows, and ankles, which were gradually increasing in size for the past 3 years. On evaluation, her pulse rate was 92/min, BP-120/70 mm Hg. On auscultation, an ejection systolic murmur was heard in the high basal areas. Electrocardiography (ECG) showed left ventricular hypertrophy and non-progression of R wave in V1-V4. Echocardiogram (ECHO) showed features of severe left ventricular failure and severe aortic stenosis.. Coronal [Figure 1a] and axial plain CT images [Figure 1b] showed aortic annulus calcifications causing aortic stenosis. Axial CT coronary angiography showed wall irregularity with eccentric non-calcified plaques in ascending thoracic aorta [Figure 1c], arch, and descending thoracic aorta [Figure 1d]. The skin lesions initially started over the right elbow and later involved the dorsum

How to cite this article: Narasimhan M, Muthu P, Ramakrishnan R, Sriram V. Tuberous xanthoma with cardiac failure in a child. J Family Med Prim Care 2022;11:3290-2.

of the right hand and both feet. The lesions were skin colored with a slight yellowish hue, but without any symptoms like pain, itching, or discharge. They were firm non-tender nodules of size approximately 1 cm × 1 cm, over the dorsolateral aspect of both feet [Figure 2a] and the right elbow [Figure 2b] dorsum of the right hand [Figure 2c]. Hyperpigmented patches were noted over the web spaces of the right hand [Figure 1c]. As per the patient's history, these were sites of healed nodular lesions. The patient did not give any history of headache, vertigo, hearing loss, seizures, blurring of vision, or learning disability. With a clinical suspicion of tuberous xanthomas associated with cardiac involvement and underlying lipid abnormality, we proceeded with further investigations. Her fasting lipid profile revealed elevated total cholesterol (690 mg/dl), low-density lipoprotein (LDL) levels (510 mg/dl) and triglyceride levels (350 mg/dl). Serum urea 19 mg/dl, serum creatinine 0.4 mg/dl, albumin 3.9 g/dl, alanine transaminase (ALT) 30 U/L, aspartate aminotransferase (AST) 15 U/L, Alkaline phosphatase (ALP) 85 U/L, and total bilirubin 0.9 mg/dl. Skin biopsy from the nodular lesion revealed scattered foamy macrophages in the upper dermis and cholesterol clefts [Figure 3]. With the clinical, biochemical, and pathological findings, a diagnosis of familial homozygous hypercholesterolemia with tuberous xanthomas and cardiac failure was made. Cholesterol levels were normal in her first- and second-degree relatives with no history of myocardial infarction in her relatives. Genetic analysis for Apo B and LDL receptors could not be done. She was managed with statins, ezetimibe, diuretics, beta-blockers, and aspirin. With treatment, her cholesterol levels decreased and her cardiac status improved.

Discussion

Patients with elevated lipid levels may develop xanthoma as a cutaneous manifestation. Though xanthomas can manifest at any age, they are usually noted in the second decade of life especially in patients with disorders of lipoprotein metabolism.[4]

Xanthomas are clinically classified as tubero-eruptive, eruptive, tendinous, planar, and tuberous xanthomas. Tendinous xanthomas are slowly enlarging subcutaneous nodules or papules attached to tendons. Plane xanthomas are orange-yellow macules or minimally raised plaques present over large areas. Eruptive xanthomas present as yellow-colored papules on an erythematous base most commonly over the flexor aspect of arms, buttocks, thighs, shoulders, knees, axillary, and inguinal folds. Tuberous xanthomas are present as reddish-yellow firm, nodules, usually asymptomatic.[5] They occur over pressure sites like the extensor aspect of elbows, knees, and buttocks. Underlying dyslipidemia (raised LDL and cholesterol levels) is usually noted in these patients.

Among children, type 1 and type II hyperlipoproteinemia are common. In type II A [familial hypercholesterolemia] and type III [familial dysbetalipoproteinemia] hyperlipidemia, tuberous xanthomas are often noted. Familial hypercholesterolemia is autosomal dominant in inheritance, characterized by increased serum LDL levels due to elevated synthesis and decreased absorption of LDL. Heterozygotes have 50% of LDL receptors and homozygotes possess about one-fourth of these receptors.[6] Alterations in the function of vascular endothelium, elevated serum total cholesterol, and LDL cholesterol levels usually lead to atherosclerosis and ischemic heart disease.

Histologically, xanthomas are characterized by the presence of foam cells (lipid laden macrophages), along with focal mixed inflammatory infiltrate. Other findings include cholesterol clefts and fibrosis.

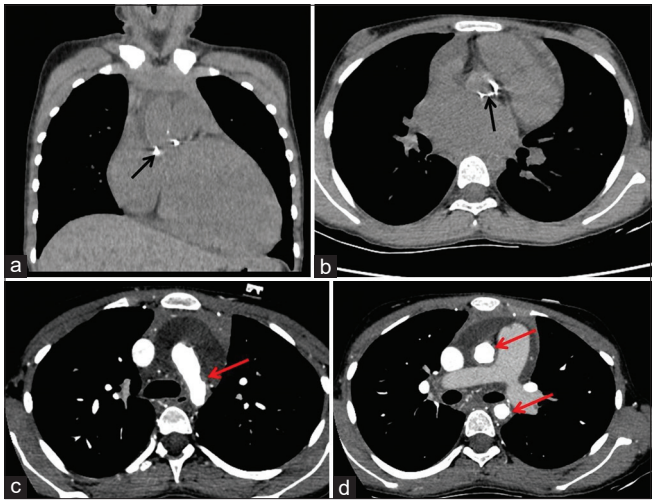

Figure 1: (a) Coronal CT image showing aortic annulus calcifications (black arrow) causing aortic stenosis, (b) Axial Plain CT image showing aortic annulus calcifications (black arrow) causing aortic stenosis, (c) Axial CT coronary angiography image showing wall irregularity with eccentric noncalcified plaques in ascending thoracic aorta (red arrow), (d): Axial CT coronary angiography image showing wall irregularity with eccentric noncalcified plaques arch and descending thoracic aorta (red arrows)

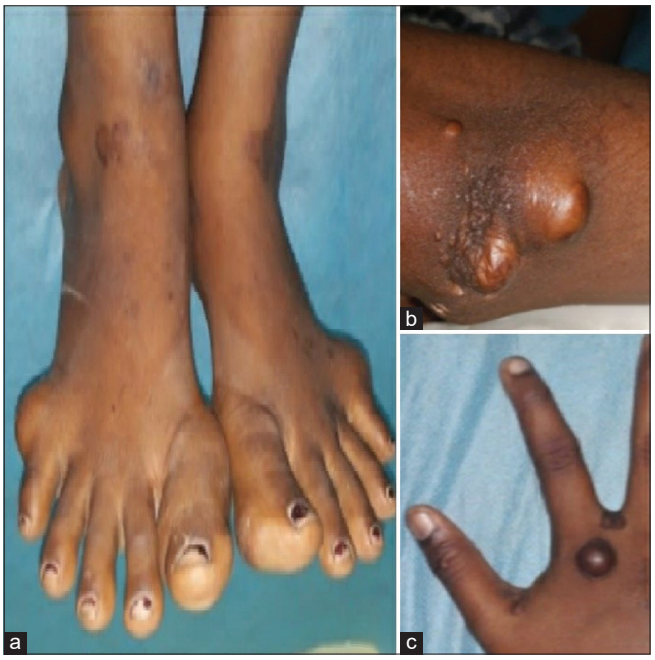

Figure 2: (a) Soft to firm, non-tender yellow to skin coloured nodules over both feet and (b) right elbow. (c) Soft to firm, non-tender hyperpigmented nodule over dorsum of right hand and hyperpigmented patches in the webspace of the right hand

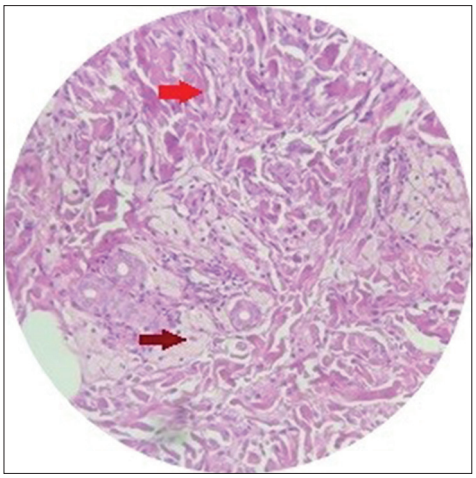

Figure 3: Skin biopsy revealing cholesterol clefts (indicated by ➡) and foamy macrophages (indicated by ➡) (H and E, ×100)

The prognosis of patients with xanthomas depends on the underlying systemic disease. Familial hypercholesterolemia may lead to premature coronary artery disease, resulting in early death in childhood and adolescent age group.[7] As per recent guidelines, the total calorie intake of these patients should be restricted, with a total fat intake of less than or equal to 3% of the total dietary intake.[8] Management includes lifestyle modifications, diet restriction, pharmacologic therapies, invasive practices like permanent lipid apheresis, and lastly, liver transplantation.[9] Universally used therapy includes statin, alongwith a cholesterol absorption inhibitor like ezetimibe.[10] Highly potent statins like atorvastatin, rosuvastatin, pitavastatin, or simvastatin reduce the LDL level by 50%.[11] Statins can cause myalgia, rhabdomyolysis, necrotizing, and autoimmune myopathy and hence should be used with caution and regular follow up.[12] Bile acid sequestrants can be added. Xanthomas can be managed by treating underlying lipid derangements along with surgical excision, where necessary. Newer treatments for familial hypercholesterolemia include monoclonal antibodies directed against proprotein convertase subtilisin/kexin type 9 gene.[13]

In children with a family history of high cholesterol levels or premature coronary heart disease, lipid profile screening should be performed starting at the age of 2 years. Similarly, immediate screening for dyslipidemia has to be performed for patients presenting with cutaneous xanthomas, irrespective of their age. This case has been presented to emphasize the importance of prompt initiation of screening for lipid profile derangements and cardiovascular manifestations in children presented with cutaneous xanthomas. This would help in preventing severe cardiovascular complications occurring early in life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the informant has given her consent for the patient's images and other clinical information to be reported in the journal. The informant understands that patient's name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Acknowledgements

I would like to thank our Radiology department for providing CT angiogram images of this patient.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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