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TUBEROUS XANTHOMA WITH NORMAL LIPID PROFILE IN TWO SIBLINGS: A DIAGNOSTIC RARITY

Pathology

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ABSTRACT

Xanthomas are lesions characterised by accumulations of lipid laden macrophages within the dermis. Two siblings aged 21 year and 17 year respectively presented to our hospital with the lesions of multiple tuberous xanthomas all over the body. Routine investigations and systemic examination were normal. Lipid profile was within normal range. Histopathology from nodular lesions of both the siblings showed collection of foamy macrophages in the dermis. Tuberous xanthomas are particularly associated with hypercholesterolemia and increased level of LDL1. They can be associated with familial dysbetalipoproteinemia and familial hypercholesterolemia (Frederickson IIa and III hyperlipoproteinemias), and they may be present in some of the secondary hyperlipidemias. However, our patient did not show any type of hyperlipidemia. Normolipemic xanthomatosis have been reported in the literature, but this entity is uncommon. We present a case of normolipemic tuberous xanthomas in two siblings, which is an uncommon occurrence.

KEYWORDS

Tuberous, Xanthoma, Macrophages, Normolipemic

INTRODUCTION

The term Xanthoma was derived from a Greek word "Xanthos" meaning yellow and was generally used to describe lipid deposits in the subcutaneous plane. They do not represent a particular disease, but are cutaneous markers for dyslipidaemia or may even arise without any underlying metabolic defect. Tuberous xanthomas are located mainly over the extensor surface of the extremities and buttocks. They may be confused with lipomas. [1]

In children, they are mostly associated with abnormalities of cholesterol metabolism with hypercholesterolemia and high LDL cholesterol. [2]

It is a reactive histiocyte proliferation and is usually of great cosmetic concerns to the patient. It mostly develops in primary and secondary hyperlipoproteinemias. [3] Early diagnosis and treatment may help to prevent complications such as coronary artery disease, myocardial infarction and pancreatitis. [1]

Recently two siblings presented with multiple swellings varying from 2 to 4 cm all over the body. On histopathological examination, these were revealed to be tuberous xanthomas.

CASE REPORT

We present a case of two nonconsanguineous siblings - 21-year-old brother and his 17-year-old sister. They both came with complaints of multiple painless swellings over the body for 6-8 years. The swellings were present over the extensor aspects of elbows and knees and over the hands and feet and varied in size from 2 cm × 2 cm over dorsum of hands to 4 cm × 4 cm over knees. Family history was unremarkable. There was no history of diabetes, hypothyroidism or any other systemic disease in both the patients. They both were afebrile and all vitals were normal. Systemic examination was within normal limits. On physical examination of both, multiple yellowish, firm, non-tender cutaneous lesions were identified over the extensor aspect of bilateral elbow, ankle and knees, largest measuring 4 cm in size. X ray of the forearm of the elder sibling showed no bone/joint involvement with areas of dystrophic calcification. Hemogram of both revealed mild microcytic hypochromic anemia. Their biochemical investigations showed normal blood glucose levels, liver function tests, kidney function tests and electrolytes levels. The initial and repeat review of the patients' lipid profile was essentially within normal limits. The lipid profile of elder and younger sibling was as follows: total cholesterol: 190 and 181 mg/dL respectively; low-density lipoprotein (LDL): 99 and 110 mg/dL respectively; triglyceride (TG): 145 and 130 mg/dL respectively; high-density lipoprotein (HDL): 62 and 45 mg/dL respectively. Ultrasound of the right knee joint of the elder sibling was performed which revealed two round to oval exophytic soft tissue lesions measuring 3.4 x 1.4 x 3.3 cm and 2.9 x 1.4 x 2.2 cm respectively along with sonographic signs of inflammation. The findings were suggestive of benign subcutaneous exophytic soft tissue neoplasm ? fibroma . FNAC was performed from multiple sites of the elder sibling. One of the attempts yielded whitish aspirate while rest were blood mixed. Smears were sparsely cellular and showed predominantly foamy histiocytes in clusters and scattered singly, few benign mesenchymal cells and occasional inflammatory cells in a hemorrhagic background. Due to the mass effects and for cosmetic purposes they both were referred to surgery department to excise the masses which was reviewed by a pathologist.

Multiple swellings of both were excised with overlying skin and primary closure was done. The gross specimen revealed multiple firm, homogenous grey white masses smallest measuring 1.8 x 1.5 cm and largest measuring 4 x 3.8 cm. Cut section of all were grey white, solid and homogenous. Histopathological examination from the excised nodular lesions revealed infiltration of dermis by foamy histiocytes along with giant cells, fibrosis and cholesterol clefts indicating the diagnosis as normolipemic tuberous xanthomas.

Fig1 (a&b) -: Tuberous xanthomas on elbow and knee

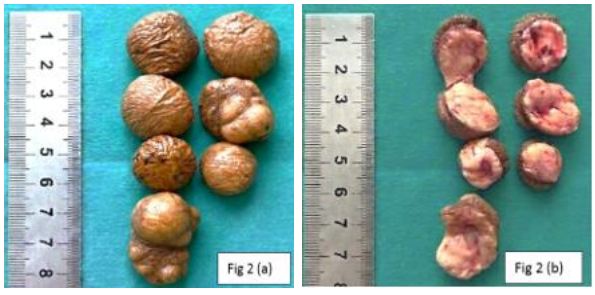
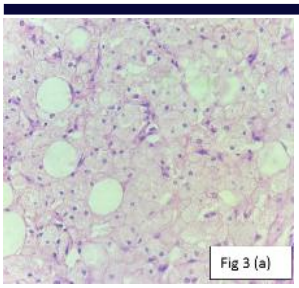
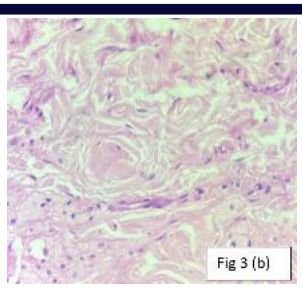


Fig2 (a&b) –: (Fresh unfixed sample) – Gross pictures of excised nodules of tuberous xanthoma. Cut section is solid, grey white





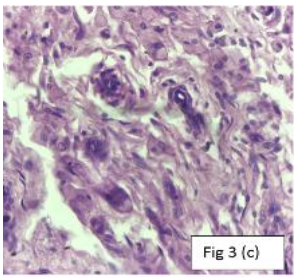


Fig3 (a,b & c)-: a)-dense infiltrate of foamy histiocytes involving whole of dermis.
b)-collection of foam cells, lipid laden macrophages, fibroblasts and histiocytes
c)- fibroblasts with giant cell (all photos- H&E x 40)

DISCUSSION

Xanthomas are tumors or infiltrates of the skin varying from yellow to brown-red colour, which are due to lipid-containing cells in the dermis. Xanthomas may be the symptoms of a general metabolic disease, a generalized histiocytosis, or a local fat phagocytosing storage process. [4]

Xanthomas are clinically classified as eruptive, tuberoeruptive or tuberous, tendinous or planar. Planar xanthomas include xanthelasma palpebrarum/xanthelasma, xanthoma striatum palmare, and intertriginous xanthomas. Eruptive xanthomata are multiple, reddish-yellow papules that appear suddenly and are arranged in crops on the extensor surface of the extremities and the buttocks. Tuberous xanthomata are nodules that are frequently localized to the extensor surfaces of the elbows, knees, knuckles and buttocks. Tendinous xanthomata are firm subcutaneous nodules found in fascia, ligaments, achilles tendons or extensor tendons of the hands, knees and elbows. [5] **Courtice** indicated that mechanical stress, similarly to the effect of mild heat injury to skin, also increases capillary permeability around the mechanical stress exposed areas, which may lead to the accumulation of LDL. This theory may explain why tuberous xanthomas are predominantly encountered in mechanical stress exposed regions. [6] They mostly manifest themselves in the skin over joints (elbows, knees, joints of hands and feet), or on the buttocks. [7]

The pathogenesis suggested in such lesions are that the lipid in these lesions is derived from blood. The serum lipoproteins leave the vascular compartment, traverse small vessels, and enter the macrophages of soft tissue. Once ingested by macrophages the lipoprotein is degraded to lipid, and the lipid is released to the extracellular space. The fibrosis characteristic of mature or longstanding xanthomas is believed to be related to the fibrogenic properties of extracellular cholesterol. [8]

Tuberous xanthomas are particularly associated with hypercholesterolemia and increased level of LDL1. They can be associated with familial dysbetalipoproteinemia and familial hypercholesterolemia (Frederickson IIa and III hyper-lipoproteinemias), and they may be present in some of the secondary hyperlipidemias. [9] However, our patient did not show any type of hyperlipidemia. Normolipemic xanthomatosis have been reported in the literature, but this entity is uncommon. [9][10]

Normolipemic xanthomatosis has been found to be associated with either a systemic disease/ malignancy/ serious hepatic disease/ hematological dyscrasias, especially multiple myeloma [9][10]. Our case showed multiple tuberous xanthomas but without any lipid disorder or associated systemic/ hematologic disease or malignancy. **Hu et al** reported unusual normolipemic cutaneous xanthomatosis with IgG gammopathy, hypernephroma, an unusual family cluster of leukemia. [11] **Glampiero et al** described a case of diffuse plane normolipemic xanthomatosis (DPNX) associated with Takayasu's disease and hyperhomocysteinemia. [12]

Gould et al reported a rare case of multitendon xanthomatosis occurring in a 38-year-old patient with normal standard lipid panel. [13] **Hoffman et al** reported a case of normolipemic plane xanthoma in a 9-year-old boy. [14]

Zhao et al also reported such a case in a 23-year old male having multiple large xanthomas with familial hypercholesteremia in which histopathological examination of excised lesion along with bio-chemical findings confirmed the diagnosis, however, they have not attempted the fine needle aspiration. [15]

Histopathology of tuberous xanthoma is characterized by large aggregates of foam cells, which are macrophages containing cholesterol and cholesterol esters along with focal mixed inflammatory infiltrate. [16] [17] They have also been found to contain primitive mesenchymal cells, elongated perivascular, and fibroblast-like cells, and lysosome filled macrophages, indicating possible stages in the evolution of dermal mesenchymal cells into mature, cholesterol-rich foam cells. [18]

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. 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. Without treatment, xanthomas typically persist. [19]

All patients with normolipemic plane xanthoma should have regular follow-ups with special emphasis on watching for the development of pathologic lipid counts and the occurrence of myeloproliferative disease. [14]

We must also keep in mind the possibility of tuberous xanthomas being a premalignant condition, and thus subject such cases to careful periodic histologic scrutiny and closer clinical follow-up to detect any malignancy at the earliest as it is a predisposing factor for cutaneous squamous cell carcinoma. [20]

It is advised in a study by Manucose et al to critically review normolipidemic xanthomatosis cases, since only after an extensive follow-up and sequential analyses of lipoprotein fractions is it possible to exclude the presence of time variables and complex lipoprotein abnormalities. [21]

This report emphasizes this disease entity in two patients with normal lipid profile and with no associated systemic disorders.

CONCLUSION

We present a rare case of tuberous xanthomas occurring in a young sibling aged 21 year and 17 year respectively with normal cholesterol levels and without a familial history. The clinicians should be prompt to perform a thorough investigation of the patient's metabolic panel and family history. Detection of xanthomas should raise suspicion for underlying hyperlipidemia and screening of parents and other siblings should be done. Early diagnosis and treatment can reduce the morbidity and mortality rate associated with the condition. Resection of the lesion is the treatment of choice usually for cosmetic reasons. Both patients were advised to be on follow up for few months and were asked to repeat lipid profile every month. Our case is unique as tuberous xanthoma has occurred in a normolipemic subject.

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