CASE REPORT

Multiple xanthomas in a patient with hypothyroidism: A case report and review of literature

Lubna Khondker[1], MD, Farhana Huda[2], MBBS

[1]Associate Professor, Department of Dermatology and Venereology
[2]DDV student, Department of Dermatology and Venereology
Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

ABSTRACT

Xanthoma is a symptom rather than a disease, clinically manifesting as soft to firm papules, plaques or nodules at various sites of skin. 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. Cutaneous xanthomas most often present in adulthood. Xanthomas with familial hypercholesterolemia are an exception. 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. 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. Examples of medications that may lead to hyperlipidemia (often hypertriglyceridemia) include estrogens, tamoxifen, prednisone, oral retinoids, cyclosporine, olanzapine, and protease inhibitors. Primary hypothyroidism is typically associated with the increased level of triglycerides. To date, there have been only a few case reports of hypothyroidism patients associated with xanthomas. We report here on a case of a 56 years old male patient who was diagnosed with multiple xanthomas and associated with primary hypothyroidism. As xanthomas are seldom larger, this case is reported because of its atypically larger clinical presentation and patient represented different types of xanthomas at the same time as well..

KEY WORDS: Xanthoma, lipid disorder, foam cells, hypercholesterolemia

INTRODUCTION

Xanthomas are deposits of lipids in the skin and sometimes of the subcutaneous tissue that are expressed clinically as yellowish to erythematous papules and plaques.[1] The lipid deposits in xanthomas are thought to be derived from circulating plasma lipoproteins.[2] In many cases, this condition is secondary to a metabolic condition, such as hyperlipidemia, but not in all cases. It is important to determine if there is an underlying hyperlipidemia, as this can lead to atherosclerotic disease attributing to severe morbidity and mortality. It is also important to assess the cause of the hyperlipidemia, as

Correspondence: *Dr Lubna Khondker, Associate Professor, Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Email: lubnaderma@gmail.com*

it may be a manifestation of other systemic diseases. Some common conditions that can lead to hyperlipidemia include diabetes, obstructive liver disease, thyroid disease, renal disease, and pancreatitis. If recognized and treated early enough, progression to atherosclerotic disease and/or pancreatitis may be prevented, as well as resolution of the xanthomas.[3] Eruptive xanthomas are often the result of elevated serum triglyceride levels. They present in a disseminated manner, with predilection for the buttocks, extensor surfaces of the thighs and arms, knees, intertriginous areas, and oral mucosa. Pruritus is variable, but is often severe and the presenting complaint of the outbreak.[4] Hypertriglyceridemia levels associated with eruptive xanthoma often exceed levels of 3,000-4,000 mg/dL.[5] In addition to hyperlipidemia, certain medications have been shown to cause eruptive xanthomas. The most common inciting medications to cause eruptive xanthomas include systemic estrogens, systemic corticosteroids, systemic retinoids, and olanzapine.[4,6] Other forms of xanthomas include, tuberous/tuberoeruptive xanthomas, tendinous xanthomas, plane xanthomas, and verruciform xanthomas. Tuberous/tuberoeruptive xanthomas are described as being pink-yellow papules or nodules, most commonly found on the extensor surfaces, most notably on the elbows and knees. These lesions are usually seen in individuals with elevated serum cholesterol.[5] Tendinous xanthomas are described as being firm, smooth deposits of lipid that effect the Achilles tendon, as well as extensor tendons of the hand, knees or elbows.[5] Plane xanthomas are described as being orange-yellow macules, papules, patches, and plaques. Plane xanthoma location is often predictive of underlying disease.[5,7] Xanthalasma (xanthelasma palpebrarum) are plane xanthomas of the eyelids. While about half of these patients have an underlying hyperlipidemia, the presence of these lesions is not pathognomonic for such conditions. Plane xanthomas in the setting of a normolipemic individual raises the concern of an underlying monoclonal gammopathy, including multiple myeloma, B-cell lymphoma or Castleman's disease.[5] Verruciform xanthomas are typically solitary lesions that average 1-2 cm in diameter. These lesions usually arise in and around the mouth or in the anogenital region. Unlike the other forms of xanthomas, verruciform xanthomas are not associated with underlying hyperlipemic states. Verrucform xanthomas are often found in the presence of other disease states, such as lymphedema, epidermolysis bullosa, graft-verse-host disease, and CHILD syndrome.[5] Treatment of eruptive xanthomas is directed at lowering the serum triglyceride levels. An overview of the patient's medication list will show if an offending agent is being used, and if so it should be stopped or switched to an alternative medication that is not known to trigger eruptive xanthomas. Balanced diet and exercise is the cornerstone for lipid lowering techniques; however, in most cases this is not enough to normalize the extremely elevated triglyceride levels that are associated with eruptive xanthomas. The best medications for lowering serum triglycerides specifically are the fibric acid derivatives (fibrates) and omega-3 fatty acids. The fibrates decrease VLDL synthesis and increase lipoprotein lipase LPL which aid in lowering serum triglyceride levels. Omega-3 fatty acids increase triglyceride catabolism, which also aids in lowering serum

triglyceride levels.[8] Failure to treat the extremely elevated serum triglyceride levels that are associated with eruptive xanthomas can lead to more serious sequel, including pancreatitis and atherosclerosis. Once serum triglyceride levels approach reasonable levels, not only does the risk of pancreatitis and atherosclerosis decease, but the cutaneous lesions also will resolve over several days to weeks.[5] In addition to oral medications, other treatment modalities have been described for lesions resistant to contemporary medical treatment options. Surgery, lasers, and cryotherapy are the most commonly used of these alternative treatment options.[9]

CASE REPORT

A male patient, 56 years old teacher, hailing from Rajshahi, visited Bangabandhu Sheikh Mujib Medical University (BSMMU) on 27 December 2016 with the complaints of multiple asymptomatic papules, plaques, nodules and tumour like masses involving different parts of the body for 25 years. Initially he developed yellowish papule over right cheek, gradually increased in size and number which coalesced to form plaque involving both periorbital areas. After that he developed multiple, firm, painless, yellowish-brown papules of various sizes and shapes, distributed over the forehead, around the nostrils, around the mouth, both ear lobules, both elbows and knees and upper back. Lesions over the forehead, elbows and knees gradually increased in size, turning out as nodules and tumour like masses which were mild tender on pressure. With these complaints he visited Rajshahi Medical College 18 years back and nodule over the right elbow was excised. After that he was on homeopathic medication but the lesions were increasing both in number and size day by day without any spontaneous resolution. He also gave history of occasional palpitation, both heat and cold intolerance, gradual weight gain, increased frequency of micturition and occasional loose motion. He has no history of fever, joint pain and any mucosal site involvement. He has 3 brothers & 6 sisters and all are in good health. One of his sister has got Xanthelasma palpebrarum. Regarding drug history, he gave the history of Tab: Tolterodine 2mg and Tab: Clonazepam 0.5mg for 2 months, Tab. Atorvastatin 10mg for 3 months and he is on Tab. Escitalopram 5mg. On general physical examination, his appearance was normal, body build: average and he was co-operative and no abnormality was detected on anaemia, jaundice, cyanosis, clubbing, koilonychia, leukonychia, edema, dehydration, JVP, lymph nodes, thyroid gland and neck vein. His pulse was 70 beats/min, blood pressure: 110/70 mm of Hg, respiratory rate: 16 breaths /min, temperature: 98° F and body weight was 72 kg. On integumentary system examination, multiple, bilaterally symmetrical, well-defined, yellowish, nontender, firm, papules, plaques, nodules and non-adherent tumour like masses of various sizes and shapes over the face, both ears, upper back, right arm, left shoulder, extensor aspect of left elbow and knees, with sparing of the flexures, hands & feet. There is no loss of sensation over the lesions, no regional nerve thickening & no "button holing" sign is noted. Nails & hair distribution is normal. Other systemic examination reveals no abnormality. Regarding laboratory investigation on 28 december 2016, Hb was

13.9 g/dl, ESR-18 mm in 1st hour, WBC-10000/cu mm, Neutrophil-70%, Lymphocyte-25%, Monocyte-3%, Eosinophil-2%, Basophil-0%, RBC-4.98 million/cu mm, Platelet -2.2 lac/cu mm, PCV-43.7%, MCV-87.8%, MCH-27.9%, MCHC-31.8%. Lipid profile finding on 21 december 2016 was Total cholesterol 227 mg/dl, HDL-28 mg/dl, LDL-161 mg/dl, Triglyceride - 190 mg/dl. Lipid profile finding was on 28 december 2016, Total cholesterol-137 mg/dl, HDL-22 mg/dl, LDL-78 mg/dl, Triglyceride-185 mg/dl. Investigation findings on 28 december 2016 was SGPT 22 u/l, S. Creatinine 1.35 mg/dl, TIBC 313 micro gram/dl, S. Iron 60 micro gram/dl, S. Ferritin 93.32 micro gram/l, USG of whole abdomen showed Hepatomegaly with fatty change in liver, ICT for Kala-azar Negative, FT4 0.59 ng/dl, TSH 44.19 micro IU/mL, Chest-X-ray and Urine R/E showed normal findings. Skin Biopsy for histopathlogical examination done with stain: H & E, PAS, Fite Faraco and Toluidine blue and specimen was skin from left upper cheek and chin. Microscopic Examination revealed that the epidermis is thin. The dermis reveals many foamy histiocytes, fibroblasts and small number of lymphocytes and no AFB is seen in Fite Faraco stain. Their findings represented xanthoma. OGTT was done on 2 January 2017. Fasting Plasma Glucose 5 mmol/l, 1.5 hrs after 75gm glucose 6.9mmol/l, 2 hrs after 75gm glucose was 8.3mmol/l, HbA1c 6.5%, S. Calcium 9.2mg/dl, S. Inorganic phosphate 3.5mg/dl, S. Albumin 43gm/l, Anti-Thyroglobulin Ab >1000IU/ml and Anti-Thyroid peroxidase Ab >1000IU/ml. This patient was treated by cryotherapy, antithyroid drugs, lipid lowering drugs and excision was done for the larger lesions.

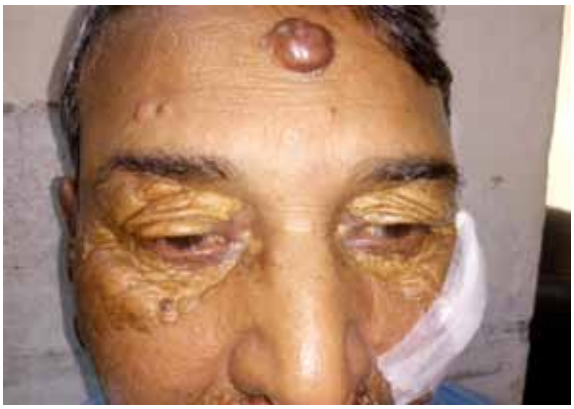

Fig. 1 Single hyperpigmented broad based nodule about 2 x 2cm with yellowish tinge over upper central part of forehead. Multiple yellowish papules over right supraorbital region

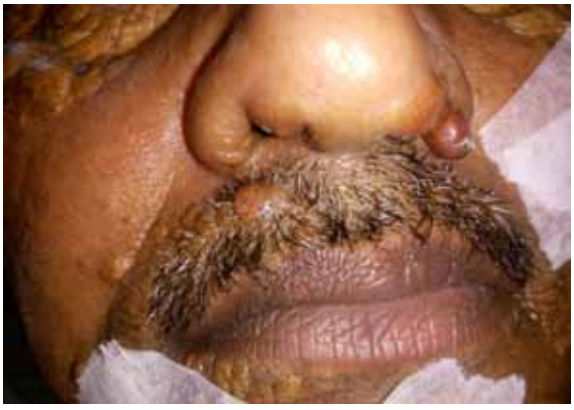

Fig. 2 Multiple yellowish grouped papules around the mouth and chin and bandages at biopsy sites. Multiple erythematous papules involving both nostrils.

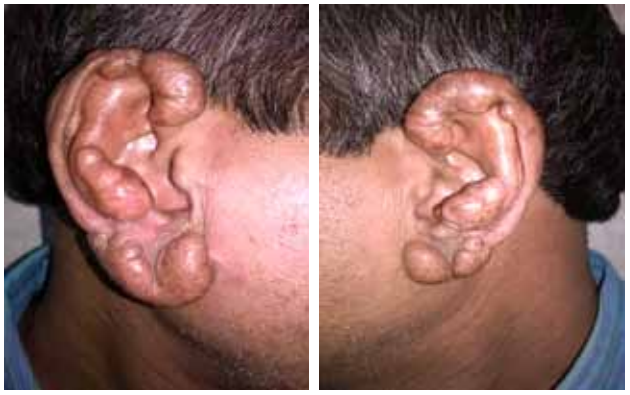

Fig. 3 Bilaterally symmetrical multiple yellowish, lobulated nodules with telangiectasia involving helices, antitraguses and lobules of both ears.

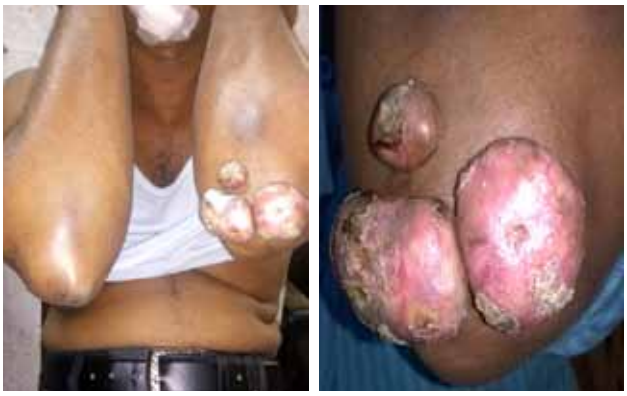

Fig. 4 Multiple yellowish tumour like masses with narrow base and violaceous hue, fine scaling and crust over the surface involving extensor aspect of left elbow. Size of the smallest one measuring about 2 x 2 cm and the largest one measuring about 5.5 x 5 cm.

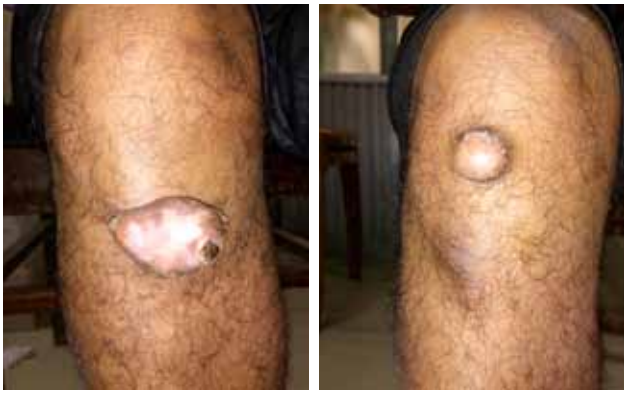

Fig. 5 Right Knee showed solitary horizontally elongated and narrow based hypopigmented tumour like mass,about 6 x 4 cm with peripheral hyperpigmentation and crusting. Left knee showed solitary skin coloured rounded tumour like mass about 3.5 x 3.5 cm with peripheral hyperpigmentation.

DISCUSSION

Zhao et al presented a 23-year-old male patient at Zhejiang Provincial People's Hospital (Hangzhou, China) in May 2008 with multiple yellowish elevated masses over the dorsum of the elbows, knees, buttocks and hands. The size of the masses varied between 1×1×1 cm (over the dorsum of the hands) and 7×5×4 cm (over the dorsum of the elbows). The lesions were originally asymptomatic; they appeared at 2 years of age and then progressively increased in size and extent. The patient had symptoms of discomfort and pain in the elbows and buttocks, which were due to the large size of the masses. The plasma TC levels of the patient were 14.95 mmol/l (reference value, 3.11-5.96 mmol/l), whereas the LDLC level was 12.69 mmol/l (reference value, 2.10-3.10 mmol/l). The apolipoprotein (Apo) A1 level was 0.74 g/l (reference value, 1.10-1.76 g/l), the Apo B level 2.84 g/l (reference value, 0.63-1.14 g/l) and the Apo A1/Apo B ratio was 3.84 (reference value, 0.40-1.96). Test results for liver enzymes, renal function, blood glucose, uric acid, free thyroxin and thyroid-stimulating hormone were normal. A Doppler ultrasound scan revealed that the two carotid arteries and the lower extremity arteries presented with progressive atherosclerosis. The carotid arteries had accumulated atheromatous plaques, and the lower extremity arteries had progressive calcific sclerosis. Magnetic resonance imaging (MRI) scans revealed decreased signal intensity on T1-weighted and T2-weighted spin-echo images of the masses in the elbows, knees and posterior malleolus. Xanthomas had infiltrated the triceps tendon and the patellar ligament. MRI scan also revealed a thickened Achilles tendon and patellar ligament. The patient was treated with a combined treatment regimen of rosuvastatin (10 mg/day) and ezetimibe (10 mg/day) for a year. Following a year of conservative treatment, no marked decrease in the plasma TC levels or substantial regression of the multiple xanthomas was observed. Due to the symptomatic nature of the lesions and for cosmetic reasons, surgical excision of the masses over the elbows and buttocks was performed. Intraoperatively, the yellowish xanthomatous masses in each elbow were found to closely adhere to the triceps tendon, which prevented the complete excision

of these lesions. Microscopic examination of the surgical specimens revealed nests composed of xanthoma tissue, which consisted of connective tissue and foam cells, containing cholesterol, cholesterol esters, triglycerides and phospholipids. Immunohistochemical staining showed that the foam cells strongly expressed cluster of differentiation 68 (CD68). Treatment with rosuvastatin and ezetimibe was continued postoperatively. One year following surgery, the serum LDLC levels of the patient were controlled at 8.50 mmol/l with no symptoms of CHD or postoperative recurrence of xanthomas.[10]

Thomas reported an 11 year old girl with multiple yellowish to skin colored raised lesions, of varying size. She was apparently asymptomatic until 5 years of age, following which she developed multiple yellowish to skin colored raised lesions, initially over her both knees which increased in number and size in the span of 4 months and later, progressed to involve the gluteal region, elbows, forearms, and feet. Those lesions were painless. She gives history of spontaneous reduction and recurrence of the lesion's size. She was incidentally diagnosed to have hypothyroidism, for which she has been on Thyroxin tablets regularly since last two years. On examination, the child was moderately nourished, alert and cooperative. Dermatological examination revealed multiple yellowish to skin colored, non tender papules over bilateral forearms, knees and gluteal region and firm, non tender nodules over bilateral elbows, gluteal region and feet, of varying size with largest nodule over the inferio-medial aspect of right gluteus measuring 3.5 x 5.0 cm in diameter, pedunculated, firm and non-tender. Nails, oral mucosa and hair were normal. Blood investigations revealed elevated levels of total cholesterol, triglycerides, LDL and VLDL with normal routine baseline investigations. Skin biopsy taken from a nodule in the right elbow revealed, atrophic epidermis with numerous foam cells (xanthoma cells) in dermis, confirming the clinical diagnosis of tuberous xanthoma associated with dyslipidemia. The patient was advised to start on oral statins and also surgical removal of the largest lesion.[11]

Jain et al reported a 60-year-old female patient presented with history of gradually enlarging nodules over both hands and elbows since one year, not associated with pain or itching. The family history was insignificant and none of the family members including parents had similar lesions. On cutaneous examination, multiple yellowish colored papules and nodules were found on the dorsum of fingers of both hands at interphalangeal joints and extensor aspect of both elbows. Examination of the eyes revealed sclerotic changes in the retinal vessels and arcus corneae. Hair, nail, mucosae as well as palms and soles were normal. She was found to have raised blood sugar and lipid levels. Her cholesterol was increased 6-folds. Electrocardiogram (ECG), treadmill test (TMT) and echocardiography were done to look for the cardiovascular effects of hypercholesterolemia and they proved to be normal. The chest X-ray was normal, while that of hands and elbows showed multiple soft tissue swellings corresponding to cutaneous lesions and normal underlying bones. Biopsy from one of the nodules showed normal epidermis and aggregates of xanthoma cells separated by fibrocollagenous bundles in the dermis.[12]

Park JR et al reported a 48-yr old female patient

of generalized weakness and right flank pain for several months. She was diagnosed with hypercholesterolemia by biochemical tests and had rouleaux formations on the peripheral blood smear analysis. According to her past medical history, she was diagnosed as autoimmune thyroiditis and primary hypothyroidism in 1992 and in 1998, she still had hypothyroidism as well as uncontrolled diabetes mellitus and dyslipidemia. On the physical examination, Diffuse goiter with firm consistency was palpated on her anterior neck and several yellowish skin nodules were observed on both her elbows and thighs. On admission, her lipid profiles were as follows; total cholesterol 18.1 mM/L, triglyceride 61.64 mM/L, HDL 3.0 mM/L, and LDL 2.54 mM/L. Amylase and lipase levels were normal. The thyroid function tests, determined by a radioimmunoassay method (Immunotech, A Beckman coulter company, France), revealed that she has chronic autoimmune thyroiditis and primary hypothyroidism; TSH 72.69 mU/L (normal range; 0.17-4.05 mU/L), free T4 0.22 ng/dL (normal range; 0.95-2.23 ng/dL), free T3 0.46 pg/mL (normal range; 1.60-3.80 pg/mL). Glycosylated hemoglobin A1c was 9.4%. The excreted protein amount in 24 hr collected urine was 413.7 mg/day. On the second day after admission, a creamy and clouded layer was found in her fasting whole blood that had been placed in the refrigerator for 30 min. The concentration of lipoprotein (a) measured by a rate rephelometry method (Beckman, CA, U.S.A.) was 9 mg/dL. Lipoprotein electrophoresis findings indicated that the patient had type V hyperlipoproteinemia. The patient was diagnosed as hypothyroidism and type 2 diabetes that presented as hyperlipidemia, and she began to take glimepiride, voglibose, levothyroxine (100 μg daily), and fenofibrate (200 mg). Currently, the level of both TSH and lipid concentration in blood have returned to the normal values. Also, the patient's yellowish skin nodules have disappeared.[13]

Yaligod et al presented a lady aged 45 years with history of swelling in the right forearm since 6 years. The swelling was not associated with pain initially, since 2 years some dull aching pain on activity. She is a known case of diabetes and hypothyroidism since three years, on regular treatment. On examination 2x2 cm bony swelling noted in the mid ulna. The radiography showed osteolytic lesion in the mid shaft of ulna - expansile in nature with sclerotic margin, suggestive of benign nature of the lesion. Excisional biopsy and curettage was planned. Peroperatively on making a cortical window, the cavity was found filled with yellowish soft material which was curetted out. On histopathological examination, sheets of lipid laden foam cells with variable background of other cells and fibrosis was noted. There were cholesterol clefts with giantcells around them in certain areas. These features were suggestive of xanthoma. Retrospectively the lipid profile of the patient which was found to be normal, however, they could find a xanthelasma lesion over left upper eyelid. Four months post operatively the bone graft incorporated well and no sign of recurrence.[14]

Hossain et al presented A 17 years boy with the history of swelling and pain around right knee, difficulty in walking and shortening of his right leg, following a slip and fall. On examination there was a diffuse swelling, tenderness and shortening of right leg. The radiography

showed fracture of the lower end of the right femur with osteolytic lesion at the fracture site. Biochemical investigation revealed that serum calcium, alkaline phosphatase and lipid profile within normal limit. He is a known case of hypothyroidism since 2 years for which he is under treatment of endocrinologist. Following this, curetting biopsy of the lesion with bone graft and nailing was done. Biopsy material was sent to private histopathological laboratory for a definitive diagnosis of the lesion. Macroscopically biopsied material was yellow in color, soft to firm in consistency. histopathological examination of the tissue showed sheets of lipid laden foam cells interspersed in to the trabeculae embedded in a variable background of other cells, including tuton giant cells and fibrosis also noted. So, histomorphologically this case was diagnosed as xanthoma of bone. Histologically benign fibrous histiocytoma and non ossifying fibroma were considered as differential diagnosis.The benign fibrous histiocytoma shows spindle cells arranged in storiform pattern which was lacking in their case, where as non ossifying-fibroma shows cellular fibrous tissue arranged in storiform patterns, scattered osteoclasts, foamy & hemosiderin laden macrophages and sometimes bizarre nuclei, and all these features were lacking in their case. And thus depending on the above findings and radiological and biochemical findings the final diagnosis was rendered as primary xanthoma of the right femoral bone. The case was treated surgically by bone graft and nailing.[15]

An 11-year old girl presented Dötsch et al to the pediatric endocrine outpatient department of the University of Erlangen with a disseminated yellow papulomatous rash on her lower limbs and yellow skin creases of the palms of her hands. The rash had been developing gradually over the past 2 years. Blood tests revealed an opaque serum with triglycerides of 820 mg/dL and a cholesterol concentration of 1050 mg/dL. Skin biopsy of one of the papules confirmed the diagnosis of xanthomas of the skin. The second most striking finding was a primary hypothyroidism with a free serum T4 concentration of 0.4 ng/L and a thyroid-stimulating hormone (TSH) concentration of 200 mU/L. Antibodies against thyroid peroxidase and thyroglobulin were massively elevated (4400 U/mL) and 2000 U/mL [normal 60 U/mL], respectively). Ultrasound examination of the thyroid gland revealed a normal-sized (7 mL) thyroid gland with reduced and inhomogenous echogeneity, confirming the diagnosis of autoimmune thyroiditis.The patient was started on 75 mcg/d of L-thyroxine and later raised to 100 mcg/d. After 3 months the patient was clinically euthyroid, had lost 2 kg of weight, but the xanthomas persisted. However, after 1 year of treatment, serum triglycerides and cholesterol were almost normal (211 mg/dL, and 149 mg/dL, respectively). Free T4 was 12.2 ng/L, and TSH was 0.4m U/L. The xanthomas had resolved completely.[16]

Ladizinski et al reported A 46-year old man with obesity, hypertension, hyperlipidemia and bipolar disorder presented with a rash accompanied by ongoing excessive urine production, excessive thirst and blurred vision. The lesions had appeared on his arms 1 month earlier and had spread to his neck, buttocks and legs. He was taking quetiapine and metoprolol. Both of the patient's parents had type 2 diabetes

mellitus. A physical examination showed crops of firm yellow-red papules (diameter 1-3 mm) distributed on the patient's neck, bilateral extremities and buttocks, suggestive of eruptive xanthomas. Laboratory investigations showed elevated levels of triglycerides (64.2 [normal 0.6-2.8] mmol/L), cholesterol (18.2 [normal 3.1-5.2] mmol/L), acetylated hemoglobin (139.3 [normal 25.6-42.0] mmol/mol) and glucose (31.2 [normal 3.3-6.1] mmol/L). Results of kidney and liver function tests were normal, as well as the results of tests for thyroid stimulating hormone, triiodothyronin, thyroxin, amylase and lipase. He was admitted to the intensive care unit, and his condition responded well to treatment with insulin, metformin and gemfibrozil. The patient's quetiapine was stopped, and he was transitioned to topiramate without complications. The patient's triglyceride levels improved to 13.8 mmol/L after 8 days of treatment, and his skin lesions improved after 8 weeks.[17]

CONCLUSION

Xanthomas are indicators of underlying lipid abnormality. Hence, it should be diagnosed and treated as early as possible to reduce the complications. All family members should be screened even in the absence of cutaneous lesions. Cutaneous lesions are often the initial finding in otherwise systemic disease processes, placing the dermatologist in a position of great importance in relation to disease prevention and management.

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