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Case Report

Eruptive xanthomas: a warning sign of future hyperlipidemia complications

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ABSTRACT

Eruptive xanthomas are localized lipid deposits in the skin or subcutaneous tissue that are associated with both primary and secondary hyperlipidemia. Typical presentation manifests as small yellow papules on the buttocks or extensor surfaces. Xanthomas can be diagnosed clinically with an extensive history and physical examination, however, can be confirmed via biopsy and histological findings. It is essential to identify the underlying cause of the skin lesions and take appropriate measures to prevent future hyperlipidemia-induced consequences. Here we report a 42-year-old female with eruptive xanthomas on her trunk and extremities. Previous visits to the primary care provider and emergency department resulted in diagnoses of viral exanthems. The consulted dermatologist ordered laboratory tests remarkable for extreme hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Lifestyle modification in conjunction with cholesterol and triglyceride lowering medications led to the resolution of abnormal laboratory findings and remission of eruptive xanthoma lesions.

Keywords: Eruptive xanthoma, Hypertriglyceridemia, Hypercholesterolemia, Hyperglycemia, Hyperlipidemia

INTRODUCTION

Xanthoma is a term that encompasses several variants of localized lipid deposition into the skin or subcutaneous tissue, presenting as nodules, plaques, or papules.[1] Xanthomas most commonly arise amongst adults and exhibit an even distribution between genders.[2,3] The mechanisms in which xanthomas arise are not well understood and vary by subcategorization. Eruptive xanthoma synthesis holds a strong association with hyperlipidemia, including both primary causes from inborn metabolic defects and secondary causes such as obesity, diabetes, and hypothyroidism.[4,5] Current models suggest that in patients with hyperlipidemia, lipoproteins carrying lipids extravasate from the blood and are phagocytosed by dermal macrophages, causing xanthoma formation.[1] As a result of their lipid composition, eruptive xanthomas' clinical appearance displays yellow coloration within papules.[6] These papules are generally small, 1.0-5.0 mm in size, and identified on the buttocks or extensor surfaces such as the elbows and knees.[7,8] Eruptive xanthomas specifically arise in the setting of excessive hypertriglyceridemia, lipid metabolism disorders, or onset of diabetes.[8] Eruptive xanthomas differentiate themselves from variants of xanthomas histopathologically by excessive extracellular lipid deposition accompanied by mixed inflammatory infiltrate.[8] The inflammatory infiltrate generally reveals several cell types and can include histiocytes, neutrophils, and lymphocytes.[8] Diagnosis is generally established

presumptively based on clinical appearance and history, but can be histopathologically confirmed with excisional, punch, or shave biopsy. Further workup to identify the underlying cause of hyperlipidemia and begin appropriate intervention to prevent recurrences is often necessary. Here we have a unique case in which a middle-aged female presented with eruptive xanthomas and concurrent extreme hypertriglyceridemia after the discontinuation of her diabetes medication regimen.

CASE REPORT

A 42-year-old Caucasian female presented to the dermatology clinic with a 4-week history of a papular eruption on her trunk and extremities which progressively worsened since its onset. In addition to the skin lesions, she also noticed nausea and fatigue. The new skin lesions exhibited neither pruritus nor pain. The patient had a past medical history of hypertension and non-insulin dependent diabetes mellitus, but recently discontinued her diabetes medications. After discontinuation, her daily medications included oral contraceptives and benazepril. Her social history was significant for a positive smoking history and abstinence from alcohol. The patient's primary care provider and local emergency department both recently managed this patient for her new skin changes, and attributed her eruption to a viral exanthem. Physical examination displayed a mildly obese female with multiple scattered, 3-4 mm, yellow papules distributed throughout all four extremities and the posterior trunk (Figure 1). Given the clinical appearance, along with her relevant past medical history, a presumptive diagnosis of eruptive xanthomas was made.

Laboratory workup included serial lipid panels and blood glucose levels (Table 1). Significant labs showed extremely elevated triglycerides, cholesterol, and glucose levels. A punch biopsy was then performed to confirm the diagnosis of eruptive xanthomas and rule out other masquerading pathologies. Aggressive lipid and triglyceride lowering therapy was initiated with gemfibrozil and atorvastatin. Given her recent discontinuation of diabetic medications, glipizide was added to manage her elevated blood glucose levels.

The patient was re-evaluated one week later. Punch biopsy exhibited tissue with foam cells, mixed inflammatory cell infiltrate, and extracellular lipid deposits, confirming the diagnosis of eruptive xanthoma. Since her initial visit, the patient had implemented significant lifestyle modifications including smoking cessation, dietary changes, and weight-loss of 11.0 pounds in conjunction to strict medication adherence. Serial laboratory testing reflected these interventions with drastic reduction of her triglycerides, cholesterol, and blood glucose levels (Table 1). The downtrend of these values exhibited the effectiveness of her treatment which correlated with the resolution of her eruptive papules (Figure 1).

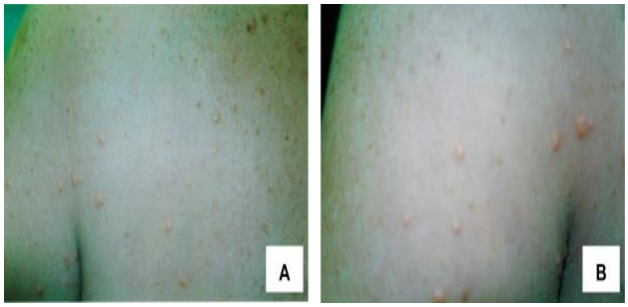

Figure 1: Eruptive xanthomas consisting of several small, yellow papules on the (A) posterior trunk and (B) extensor surface of the proximal left upper extremity.

Table 1: Significant lab values from lipid panel and blood glucose testing.

Variables	Patient value: initial visit	Patient value: 1-week post-visit	Patient value: 4 weeks post-visit	Normal range
Triglycerides (mg/dl)	14,150	1,630	356	<250
Cholesterol (mg/dl)	1,840	911	253	<200
HDL (mg/dl)	Unable to calculate	52	43	40-60
LDL (mg/dl)	Unable to calculate	Unable to calculate	139	<100
Glucose (mg/dl)	290	-	-	65-110

HDL: high-density lipoprotein, LDL: low-density lipoprotein.

DISCUSSION

When evaluating for new-onset cutaneous xanthomas, it is imperative to establish a wide differential to consider varying etiologies of its onset. Development of these lesions can manifest from a primary or secondary etiology. Delineating the source of eruptive xanthomas generally begins with the most commonly offending causes, such as medications or underlying medical disease/comorbidities.

Medicine reconciliation allows for prompt identification of possible offending medications that may have precipitated this condition. Several medications can directly or indirectly alter lipid metabolism, which influences circulating concentration of these molecules. Specifically, estrogens, androgens, glucocorticoids, cyclosporine, tacrolimus, thiazide diuretics, beta blockers, sertraline, protease inhibitors, valproic acid, isotretinoin, and olanzapine have been shown to increase triglyceride levels.[9,10] Discontinuing possible contributing

medications and evaluating for resolution of symptoms can affirm suspicion without excessive workup.

After medication-induced causes, suspicion for organic underlying disease must be considered. Evaluating for personal or familial history of lipid, glucose, or thyroid disorders can raise suspicion for these etiologic causes. Diabetes mellitus is strongly associated with hypertriglyceridemia, and eruptive xanthomas may present as the first manifestation of underlying disease.[11] In diabetic patients, lipoprotein lipase exhibits decreased ability to cleave triglycerides, as a result of insulin resistance.[12] Thus, the accumulation of triglycerides can ultimately lead to the presence of eruptive xanthomas. Laboratory testing can screen for common underlying disorders that may have contributed to the appearance of these lesions. Workup should include a fasting lipid panel, hemoglobin A1C, liver function testing, renal function testing, and thyroid testing. Patients exhibiting triglyceride levels between 150 mg/dl and 1000 mg/dl suggests moderately elevated triglycerides due to a secondary rather than primary (inherited) cause.[13] When levels exceed 1000 mg/dl, inherited disorders should be considered more readily. If no underlying secondary cause is identified, further genetic testing for inherited dyslipidemia may be indicated.

In comparison to secondary causes, inherited dyslipidemias tend to arise at earlier ages. Extreme hypertriglyceridemia can result from genetic mutations leading to inherited lipid disorders.[13]

While severe hypertriglyceridemia can carry a genetic component, these disorders are typically multifactorial with environmental influence. Generally, extensive workup for these disorders are not indicated because of their rarity. However, in cases which all secondary causes have been exhausted, this testing may prove beneficial. Patients who present with xanthomas in early childhood should also be provided testing given the increased probability of genetic abnormalities, including homozygous familial hypercholesterolemia or autosomal recessive hyper-cholesterolemia.[14] If uncontrolled, childhood dyslipi-demia correlates with a higher risk of atherosclerosis and cardiovascular problems in adulthood.[15]

Determining xanthoma etiology is imperative, as long-term sequelae can result from inadequate management of underlying disease. Appropriate diagnostic workup of eruptive xanthomas can unmask underlying hyper-triglyceridemia, which carries an attributable increase of mortality from multiple causes. This metabolic disturbance significantly increases risk of cardiovascular processes, including atherosclerosis, stroke, and myocardial infarction.[16] In addition to cardiac sequela, hypertriglyceridemia also poses a risk of acute pancreatitis which in itself demonstrates mortality risk.[17]

Many modifiable risk factors affect triglyceride and cholesterol levels. Dietary, exercise, and smoking habits all demonstrate influence of lipid concentrations in the blood. Recent studies suggest that aerobic exercise elicits a positive effect on lowering lipid profiles by increased utilization of lipids instead of glycogen.[18] Smoking negatively affects lipid profiles through nicotine-induced catecholamine secretion. This increases lipolysis and releases fatty acids into the blood. These fatty acids undergo hepatic modification to synthesize triglycerides and very low-density lipoprotein.[19] Additionally, smoking increases risk for atherosclerosis by raising atherogenic low-density lipoprotein and lowering anti-atherogenic high-density lipoprotein.[19] Carbohydrate-limited diets have demonstrated the ability to significantly reduce triglyceride levels and systemic inflammation.[20] Patients' consideration of lifestyle modifications to reduce hypertriglyceridemia may allow attainment of normal levels and reduction of cardiovascular risk.

Management of xanthomatous hypertrigylceridemia is of vital importance, as elevated triglyceride levels pose a risk of vascular events.[21] When lifestyle modification is insufficient to treat hypertriglyceridemia, the addition of pharmacologic therapy is warranted. The most appropriate medication depends on several factors such as patient age, comorbidities, medication side effects, and lipid profile. High-dose statin medications effectively lower triglyceride levels in these patients by up to 44%.[22] Fibrates and omega 3-fatty acids reduce triglycerides levels by up to 50%, but don't confer the cardiovascular mortality benefits of statins.[9,23] Additionally, case reports claim successful treatment of eruptive xanthomatosis with acipimox, a niacin derivative.[24]

While eruptive xanthoma treatment is centered around managing the underlying cause, cosmetic management may be applicable in some cases. In non-responsive cases of xanthomas, surgical excision, laser, and cryosurgery have demonstrated the ability to reduce the cosmetic burden of these lesions.[25,26] Superficial lesions can be treated with laser or cryotherapy, while deep lesions require surgical excision.[27] With all cosmetic procedures, there are risks such as scarring, recurrence of lesions, post-inflammatory hyperpigmentation and hypopig-mentation.[26] While cosmetic treatment may improve the appearance of these lesions, the underlying metabolic derangement remains unaltered by this treatment.

The significance of this particular case lies in its astoundingly elevated lipid levels and recent medication change. Literature review suggests that this case demonstrated one of the highest triglyceride values to date that did not experience acute pancreatitis. This patient's initial laboratory findings demonstrated an impressive triglyceride level, over 50 times normal value (Table 1 and Figure 1). This elevation likely reached this magnitude because of delayed diagnosis and management, as this patient had seen multiple providers

without proper diagnosis. Another possible precipitant of this patient's xanthomatous hypertriglyceridemia was the temporally related discontinuation of diabetes medication. While no previous literature suggests medication discontinuation as a cause, we postulate that acute worsening of diabetic disease could have contributed to this eruption. The delay in management and discontinuation of diabetic management could have resulted in potentially fatal secondary manifestations of disease. The increased risk of myocardial infarction, stroke, and pancreatitis stress the importance of a proper workup in presentations of xanthomatous eruptions.

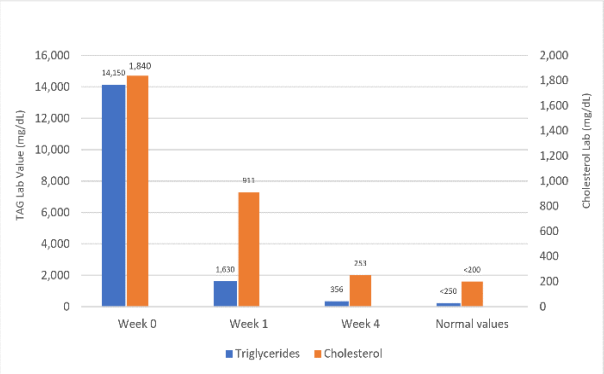

Figure 2: Downward trend of triglyceride and cholesterol levels after starting medications and making lifestyle changes.

After proper diagnosis, initiation of gemfibrozil, atorvastatin, and glipizide for management of underlying diabetes and hyperlipidemia resulted in remarkable resolution of lipid levels (Figure 2). This patient experienced a 90% and 98% reduction in triglycerides at one week and one month, respectively. This case demonstrates a drastic reduction not commonly seen in other literature. While previous cases have reported extreme hypertriglyceridemia with resolution, none, to the authors' knowledge, have accomplished it at this rate.[28-30] Exceptional reduction as seen in other literature demonstrated a triglyceride reduction of nearly 50% within days and 75% within weeks. This marked decrease suggests that the multimodal treatment with concomitant lifestyle changes can result in exceptional reduction of triglycerides, at rates not documented previously.

CONCLUSION

While eruptive xanthomas may not be extremely rare, they are often underdiagnosed. Eruptive xanthomas are strongly associated with primary and secondary causes of hyperlipidemia. The potential consequences from hypertriglyceridemia can be severe, as the risk of cardiovascular disease and pancreatitis increase exponentially. It is important for clinicians to evaluate patient lipid levels, assess modifiable risk factors, and start medications early to prevent life-threatening events from occurring.

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