Eruptive xanthomas as a marker for metabolic disorders: A specific form of xanthoma that reflects hypertriglyceridemia

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Abstract

Eruptive xanthomas are skin manifestations associated with hypertriglyceridemia. Accordingly, improvement of hypertriglyceridemia can ameliorate this condition. We report a case of a patient with type 2 diabetes mellitus who was diagnosed with this skin lesion. Clinicians should be aware that eruptive xanthomas could indicate metabolic disorders associated with atheroscle-rosis.

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Key Clinical Message:

Eruptive xanthomas are associated with hypertriglyceridemia due to dysregulated lipid and glucose metabolism. Clinicians should not overlook eruptive xanthomas as possible indicators of metabolic disorders associated with cardiovascular disease.

Abstract

Eruptive xanthomas are skin manifestations associated with hypertriglyceridemia. Accordingly, improvement of hypertriglyceridemia can ameliorate this condition. We report a case of a patient with type 2 diabetes mellitus who was diagnosed with this skin lesion. Clinicians should be aware that eruptive xanthomas could indicate metabolic disorders associated with atherosclerosis.

Key words:

Eruptive xanthomas; Hypertriglyceridemia; Diabetes mellitus; Insulin action failure; Atherosclerosis.

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1 | INTRODUCTION

Early diagnosis and treatment of dyslipidemia are required to prevent the progression of atherosclerosis. Hypertriglyceridemia has been shown to increase the risk of atherosclerosis, which can lead to the development of cardiovascular disease.¹ Diabetes mellitus is frequently associated with dyslipidemia, particularly type IIb, III, or IV hyperlipidemias, which can promote hypertriglyceridemia.^{2, 3}

Xanthomas are typical skin lesions associated with dyslipidemia that occur as accumulations especially in the Achilles and patellar tendons, extensor tendons of the hands and elbows, eyelids, trunk, and buttocks.⁴ These skin lesions have been associated with marked hypercholesterolemia, which is typically observed in patients with familial hyperlipidemia type IIa.⁵

With regard to hypertriglyceridemia, evidence suggests that eruptive xanthomas were associated with serum triglyceride levels.⁶ Considering the availability of studies on the clinical courses of eruptive xanthoma,^{7–9} clinicians should familiarize themselves with the details of this condition for correct diagnosis in the early stage.

We herein report on a patient with dyslipidemia complicated with type 2 diabetes mellitus, in whom eruptive xanthoma served as an indicator for hypertriglyceridemia. After improvement of hypertriglyceridemia through diet and medical treatment, the color tones of the skin lesions had changed from red to white, ultimately disappearing after several months.

2 | CASE HISTORY/EXAMINATION

A 35-year-old Chinese man was admitted to Kurume University Hospital on May, 2020 owing to fatigue and hyperglycemia. He stated that hyperlipidemia and hyperglycemia started 2 years prior but that he discontinued any treatment. He had neither any familial history of dyslipidemia and diabetes mellitus nor a life history of drug, alcohol, or smoking abuse. On examination, his body mass index and abdominal circumference were 32 kg/m^2 and 106.1 cm, respectively. Multiple clustered papules were observed on the bilateral extremities (Figure 1). Histopathological examinations of skin biopsy specimens led to the diagnosis of eruptive xanthomas (Figure 2). Laboratory examinations demonstrated high levels of fasting serum triglyceride (1871 mg/dL) and total cholesterol (371 mg/dL) and low levels of high-density lipoprotein cholesterol (22 mg/dL). However, low-density lipoprotein (LDL) cholesterol levels were within the normal range. Examination of lipoprotein fraction showed that the mid-band and small-dense LDL was contained (Figure 3). Chronic hyperglycemia was also denoted, with a fasting plasma glucose level of 203 mg/dL and HbA1c value (NGSP) of 9.9% (Table 1). Other examinations, including electrocardiogram and chest radiograph, were unremarkable. Ultrasonography revealed moderate to severe fatty liver (Figure 4). Diet therapy with 1600 kcal/day calorie restriction and 0.2 mg/day of pemafibrate, which was ultimately increased to 0.4 mg/day orally, were initiated to reduce serum lipids. Additionally, 500 mg/day of metformin and 10 mg/day of empagliflozin were administrated to improve insulin sensitivity and hyperglycemia. Finally, both serum triglyceride and plasma glucose levels improved to 425 and 101 mg/dL, respectively, with a concomitant change in color of the skin lesions from red to white and a decrease in the number of eruptions until total eradication.

3 | DISCUSSION

Eruptive xanthomas develop along with marked hypertriglyceridemia and are an important indicator of metabolic disorders, including dyslipidemia and diabetes mellitus. Grouped papular eruptions 1–4 mm in diameter are specifically observed in the skin over the buttocks, posterior portion of the thigh, elbows, and lumbar region.^{10, 11} Accumulation of foaming cells derived from macrophage phagocytosis of remnant lipoprotein is observed on histopathological examination.^{11, 12}Hypertriglyceridemia is the highest risk factor for the development of eruptive xanthomas, with 8.5% of the patients with hypertriglyceridemia above 20 mmol/L (1772 mg/dL) developing this condition and subsequently improving after a reduction in serum triglyceride level.^{8, 13} In this context, hypertriglyceridemia and diabetes mellitus have been considered major causative factors for eruptive xanthoma and need to be treated to prevent the progressions of systemic atherosclerosis.¹⁴ Clinicians should be aware that this type of skin lesions can indicate the presence of metabolic disorders, which need to be addressed in order to improve the eruptions¹¹ and prevent cardiovascular events.¹⁴

Insulin insufficiency is a major factor for increased remnant lipoprotein, including chylomicron or very lowdensity lipoprotein (VLDL), and the manifestation of xanthoma and systemic atherosclerosis. A putative relationship between eruptive xanthoma and atherosclerosis is summarized in Figure 5. Obesity and diabetes mellitus can promote insulin insufficiency in extra adipose tissues due to insulin insensitivity caused by the following factors: (1) lipotoxicity, increased skeletal muscle triglyceride content followed by elevation of free fatty acids¹⁵; (2) changes in adipokines, including low adiponectin¹⁶ and high leptin¹⁷ levels; (3) elevations in proinflammatory cytokines, including tumor necrosis factor- α , IL-1 β , and IL-6 levels, in the adipose tissues¹⁸; (4) activation of the endoplasmic reticulum and related signaling networks¹⁹; and (5) elevated hexosamine flux in adipose tissues.²⁰ Insulin insufficiency decreases lipoprotein lipase activity by activating angiopoietinlike protein 3 (ANGPTL3)^{21–23} expressed in the liver, which increases the levels of VLDL and triglyceride via suppression of lipoprotein lipase activity²⁴ and overproduction through lipolysis-derived free fatty acids and glycerol.²³. Thus, high ANGPLT3 activity in patients with hyperglycemia or obesity can induce elevations of serum remnant lipoproteins, chylomicron, or LDL, and VLDL levels.²⁴Remnants infiltrating into the vessel walls or skin²⁵ are recognized and engulfed by macrophages. After phagocytosis, macrophages change to foam cells and are deposited into the vessel walls and skin,¹¹ which lead to arthrosclerosis²⁶ and eruptive xanthoma,¹² respectively.

Hypertriglyceridemia should be treated early to prevent progression to acute pancreatitis and cardiovascular events. Severe hypertriglyceridemia over 1000 mg/dL has been found to markedly increase the risk of developing acute pancreatitis.²⁷Postprandial hypertriglyceridemia is positively associated with the development of ischemic heart disease, myocardial infarction, and cardiovascular events independent of serum cholesterol levels.²⁸ In this context, casual hypertriglyceridemia, including postprandial levels as high as fasting levels, have also been indicated to significantly increase the risks of developing cardiovascular events.²⁹ Additionally, triglyceride-rich lipoprotein and remnant apo-B48-positive chylomicron derived from short intestine are increased during hypertriglyceridemia.³⁰ Patients with high fasting levels of apo-lipoprotein B48 have been found to be at significant risk for developing coronary artery stenosis.^{31, 32} Thus, hypertriglyceridemia requires interventions to prevent the progression of cardiovascular diseases and improve prognosis.

In conclusion, this report details our experience with a patient who presented with hypertriglyceridemia and type 2 diabetes mellitus concurrent with eruptive xanthoma, which was ameliorated by the treatment of dyslipidemia and hyperglycemia. Eruptive xanthoma can help clinicians determine the presence of hypertriglyceridemia and insulin insensitivity induced by obesity and diabetes mellitus, as well as genetic disorders related with lipoprotein metabolism. Clinicians should therefore be aware of skin manifestations of metabolic disorders, which can lead to atherosclerosis.

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CONSENT

All procedures complied with the ethical standards of the Institutional Review Board of the Kurume University School of Medicine and the 2013 Declaration of Helsinki. This report was approved by the Ethics Committee of Kurume University Hospital (2021-067). The patient provided written informed consent for publication of this study.

AUTHOR CONTRIBUTIONS

SO: study design, data collection, drafting, interpretation of data, and revision.

KA: study design, data collection, drafting, interpretation of the data, review, and revision.

YM: data collection, interpretation of the data, and review.

KM: data collection, interpretation of the data, and review.

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TN: data collection, interpretation of the data, and review.

MN: study design, drafting, interpretation of the data, review, and revision.

All authors provided inputs for preparation of the manuscript and have read and approved the final version for submission.

CONFLICT OF INTEREST

The authors have no competing interests.

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 Table 1. Laboratory data at admission

Parameters

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Complete blood cell count Red blood cell count, $\times 10^4 / \mu L$

White blood cell count, $/\mu L$

Platelet, $\times 10^4 / \mu L$ **Endocrinology** Adrenocorticotropic hormone, pg/mL Cortisol, $\mu g/dL$ Dehydroepiandrosterone-sulfate, $\mu g/dL$ Growth hormone, ng/mL Insulin-like growth factor-1, ng/mL Prolactin, ng/mL Thyroid stimulating hormone, $\mu IU/mL$ Free thyroxine, ng/dL Luteinizing hormone, mIU/mL Follicular stimulating hormone, mIU/mL Abbreviations: HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Star

Figure legends:

Figure 1. Clinical images of eruptive xanthomas

Multiple red to salmon pink papule clusters. (a) Bilateral thigh, front. (b) Bilateral thigh, back. (c) Left forearm.

Figure 2. Histological findings of a skin biopsy specimen from the left forearm

Pathophysiological examination with hematoxylin eosin staining. (a) Appearance of eruptions. An eruption surrounded by four dotted markings was investigated using microscopy. (b) Low magnitude (\times 40). Massive foam cells (indicated by arrows) infiltrating into the superficial layer of dermis. (c) High magnitude (\times 400). Eosinophilic substrate (asterisks), probably indicating extracellular lipids, were observed between collagen fibers. Additionally, foam cells are indicated by arrows.

Figure 3. Lipoprotein profiles

Lipoprotein fractions are demonstrated using polyacrylamide gel electrophoresis. (a) Results of lipoprotein fraction in wave expression method. (b) Results of polyacrylamide gel staining. Compared to control subjects.

Figure 4. Ultrasonography

Abdominal ultrasonography revealing a bright liver.

Figure 5. Summary of the pathological relationships between eruptive xanthoma, hypertriglyceridemia, and atherosclerosis

Obesity and diabetes mellitus have potentials to increase serum remnant lipoproteins, namely TG-rich lipoproteins, and lead to the hypertriglyceridemia. Marked increase in the levels of serum TG-rich remnant lipoproteins infiltrate into the subcutaneous tissue and would be taken up by migrated macrophages, which turn into lipid-filled foam cells. The accumulation of these foam cells increases the risks of developing eruptive xanthomas in the subcutaneous tissue or atherosclerosis in the vessels.

Abbreviations: ANGPLT3: angiopoietin-like protein 3, FFA: free fatty acid, IL-1 β : interleukin-1 β , IL-6: interleukin-6, LPL: lipoprotein lipase, TG: triglyceride, TNF- α : tumor necrosing factor- α , VLDL: very low-density lipoprotein.







Figure 7



Figure 3



Figure 4

