

# Eruptive Xanthoma: A Case Report

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*Eruptive xanthomatosis is a papular skin disorder resulting from hyperlipidemia, specifically hypertriglyceridemia. It is characterized by yellowish red papules concentrated on extensor surfaces of the arms and legs. The hyperlipidemia responsible for this disorder can be caused by a primary genetic defect, a secondary disorder, or both. Eruptive xanthomas often rapidly resolve after treatment of the hyperlipidemia has begun.*

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## Case Report

A 40-year-old woman was referred to our dermatology clinic for evaluation of “bumps” that had been occurring on her arms, abdomen (Figure 1), legs, and buttocks for 3 months. The patient reported the lesions being pruritic. Diphenhydramine was not helpful in resolving the pruritus. Various antibiotics were previously attempted without any improvement of symptoms. Her medical history was remarkable for hypercholesterolemia, diabetes mellitus, and hypothyroidism. Obesity also was noted. The patient’s family history was remarkable for a father and a sister with hypercholesterolemia.

On physical examination, the patient had numerous yellowish red papules concentrated on the extensor surfaces of her arms and legs. Papules also were present on her buttocks and abdomen. Some of the papules were arranged in a mulberry-type pattern. All of the papules were similar in size ranging from 3 to 5 mm. Abnormal laboratory values included the following: glucose, 247 mg/dL (reference range, 65–99 mg/dL); hemoglobin A<sub>1C</sub> (glycated hemoglobin), 8.8% (reference range, 4.5%–6.3%); total cholesterol, 821 mg/dL (reference range, 100–200 mg/dL); triglycerides, 4591 mg/dL (reference range, 0–149 mg/dL); high-density cholesterol, 26 mg/dL (reference range, 35–85 mg/dL); thyrotropin, 9.405 mIU/L (reference range, 0.350–4.940 mIU/L);

and free thyroxine, less than 0.04 ng/dL (reference range, 0.70–1.48 ng/dL). Two punch biopsies were performed. Histologic examination revealed histiocytic xanthomatous nodules and foamy histiocytes consistent with eruptive xanthoma (Figure 2).

## Comment

A xanthoma is a deposition of macrophages laden with yellowish, lipid-rich material.<sup>1</sup> They usually are found in the dermis or around tendons.<sup>2</sup> It is believed that xanthomas result from the permeation of circulating plasma lipoproteins through dermal capillary blood vessels followed by phagocytosis of the lipoproteins by macrophages forming foam cells.<sup>3</sup> Five general types of xanthomas are seen clinically: tendinous xanthoma, xanthoma planum, xanthoma tuberosum, eruptive xanthoma, and xanthoma disseminatum. To better understand the abnormality of lipid metabolism that produces eruptive xanthomas that are associated with markedly elevated triglycerides, it is helpful to review normal lipid metabolism, specifically focusing on very low-density lipoproteins (VLDLs) and chylomicron metabolism as well as their association with hypertriglyceridemia.

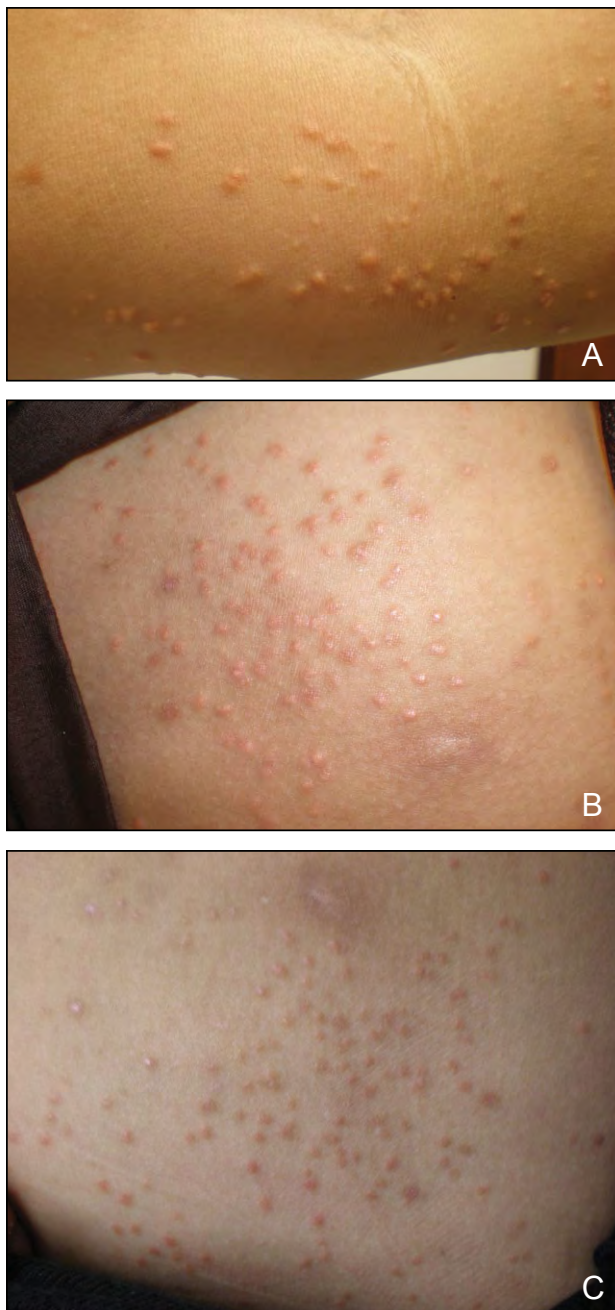
Lipids found in xanthomas are the same as those in circulation; the majority of plasma lipids are transported as lipoproteins. Plasma lipoproteins are a polydisperse collection of particles composed of lipids and specific proteins called apoproteins, the structure of which allows the delivery of triglycerides and cholesterol to peripheral cells for their metabolic needs. The plasma lipoproteins may be divided into 5 major classes: chylomicrons, VLDL (pre- $\beta$ -lipoproteins), intermediate-density lipoproteins, low-density lipoproteins ( $\beta$ <sub>1</sub>-lipoproteins), and high-density lipoproteins ( $\alpha$ <sub>1</sub>-lipoproteins). When pre- $\beta$ -lipoproteins or remnant lipoproteins accumulate in the plasma, increases in both plasma triglycerides and cholesterol occur as these aggregates transport substantial quantities of both kinds of lipids.

There are 2 lipid sources from which circulating plasma lipoproteins are formed: (1) exogenous dietary fat and (2) endogenous synthesized fats of hepatic origin. The exogenous cascade involves triglyceride-rich

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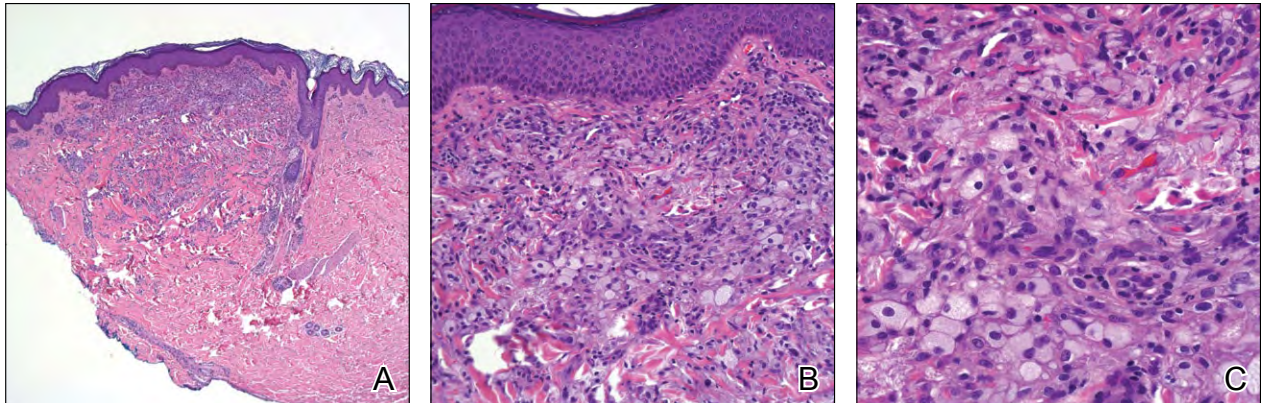
**Figure 1.** Numerous yellowish red papules on the forearm (A and B) and abdomen (C).

chylomicrons that are secreted from the intestinal mucosa following the absorption of ingested animal and vegetable fats (triglycerides) and exogenous cholesterol. Dietary triglycerides and cholesterol are packaged with apolipoprotein B-48, which forms a film surrounding the triglycerides in the core of the chylomicron. In the lymph and blood, chylomicrons acquire additional apoproteins, and these modified chylomicrons interact with lipoprotein lipase bound to the endothelial surface of blood capillaries. Lipoprotein lipase hydrolyzes the triglycerides to liberate

fatty acids, which are moved into the cells of the body where they are reesterified to form triglycerides for storage in adipose tissue. The endogenous cascade involves triglyceride-rich VLDL secreted by the liver; triglycerides are synthesized in the liver from free fatty acids derived from plasma-free fatty acids and glycerol. Ingestion of glucose, carbohydrates, and alcohol stimulates the endogenous synthesis of triglyceride-rich VLDL.

The hyperlipidemia responsible for xanthomas may be the result of a primary genetic defect that yields defective apoproteins or may be secondary to an underlying systemic disorder such as diabetes mellitus, hypothyroidism, or nephrotic syndrome.<sup>4</sup> Primary genetic defects include genetic deficiency of lipoprotein lipase, familial deficiency of apolipoprotein C-II, familial lipoprotein lipase inhibitor, and endogenous familial hypertriglyceridemia.<sup>5</sup> In 1965, Lees and Fredrickson<sup>6</sup> published a system for classifying disorders of lipid metabolism based on electrophoretic migration of the serum lipoproteins present, which is used today in a modified form (Table).<sup>3</sup> Eruptive xanthomas are associated with type I, IV, and V hyperlipoproteinemias. In its mildest form, endogenous lipemia appears in a type IV pattern (increased VLDL). However, when lipogenesis in the liver is more marked, removal mechanisms are saturated and are unable to assimilate all of the additional lipids derived from the diet; chylomicrons accumulate with VLDL giving a type V pattern. Impaired lipoprotein lipase activity leads to the defective removal of the chylomicrons, chylomicron remnants, and the endogenous VLDLs producing type I (chylomicrons) or type V (chylomicrons and VLDL) hyperlipoproteinemia.

Certain diseases or drugs raise the triglyceride level either by increased production or removal defects. Examples of pertinent diseases or drugs include obesity, pancreatitis, chronic renal failure, hypothyroidism, corticosteroids, or estrogens. Patients with a primary defect also may have 1 of these contributing secondary disorders. With this second insult, the lipoprotein lipase system can become saturated and, as a result, can no longer handle dietary lipids. Secondary disorders applicable to this case include diabetes mellitus, obesity, and hypothyroidism, which contributed to the hypertriglyceridemia. For example, whenever insulin deficiency is present, an acquired lipoprotein lipase deficiency exists, which results in impaired clearance of chylomicrons and VLDLs causing hypertriglyceridemia.<sup>7</sup> This scenario can lead to type I, IV, or V hyperlipoproteinemia. Associated conditions include pancreatitis (not noted in this patient), which can cause the hyperlipoproteinemia pattern because of a transient state of insulin deficiency resulting in a decrease in the activity of lipoprotein lipase. Another



**Figure 2.** Histology revealed collections of foamy histiocytes in the dermis abutting a thin epidermis (H&E; original magnifications  $\times 10$  [A],  $\times 40$  [B], and  $\times 100$  [C]). Photographs courtesy of Alun R. Wang, MD, PhD, New Orleans, Louisiana.

## Important Hyperlipoproteinemias

Type	Pathogenesis	Laboratory and Clinical (Systemic) Findings
Type I (familial LPL deficiency, familial hyperchylomicronemia)	Deficiency of LPL; production of abnormal LPL; apo C-II deficiency	Slow chylomicron clearance; reduced LDL and HDL levels; hypertriglyceridemia; no increased risk of coronary artery disease
Type II (familial hypercholesterolemia or familial defective apo B-100)	LDL receptor defect; reduced affinity of LDL for LDL receptor; accelerated degradation of LDL receptor due to missense <i>PCSK9</i> mutations <sup>a</sup>	Reduced LDL clearance; hypercholesterolemia; atherosclerosis of peripheral and coronary arteries
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apo E deficiency)	Hepatic remnant clearance impaired due to apo E abnormality; patients only express the apo E2 isoform that interacts poorly with the apo E receptor	Elevated levels of chylomicron remnants and IDLs; hypercholesterolemia; hypertriglyceridemia; atherosclerosis of peripheral and coronary arteries
Type IV (endogenous familial hypertriglyceridemia)	Elevated production of VLDL associated with glucose intolerance and hyperinsulinemia	Increased VLDLs; hypertriglyceridemia; frequently associated with type 2 non-insulin-dependent diabetes mellitus, obesity, alcoholism
Type V	Elevated chylomicrons and VLDLs due to unknown cause	Decreased LDLs and HDLs; hypertriglyceridemia; diabetes mellitus

Abbreviations: LPL, lipoprotein lipase; apo, apolipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; *PCSK9*, proprotein convertase subtilisin kexin 9; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

<sup>a</sup>Almost exclusively in African-Americans.

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contributing secondary disorder, obesity, can lead to overproduction of triglyceride-rich VLDL in the liver. Finally, hypothyroidism retards cholesterol conversion to bile salts and results in hyperbetalipoproteinemia, hence hypertriglyceridemia.

**Clinical Characteristics**—Eruptive xanthomas most commonly arise over the extensor surfaces of the extremities, the buttocks, and the shoulders. They appear suddenly as crops of small yellowish red papules 1 to 5 mm in diameter with waxy centers on erythematous bases. Pruritus is a common symptom, and the lesions may be slightly tender. The pruritus is believed to be associated with focal increased mass in the skin, effecting a stretching, which causes pruritus. An association between xanthomatosis and koebnerization has been described.<sup>8</sup>

**Histologic Characteristics**—Histologically, xanthomas show characteristic collections of macrophages with foamy cytoplasm, an appearance that results when lipid is extracted during routine fixation.<sup>9</sup> There are occasional Touton giant cells, small numbers of lymphocytes or neutrophils in younger lesions, and fibrosis or cholesterol clefts in older lesions.<sup>10</sup> The triglyceride-containing lipoproteins apparently pass through vessel walls and accumulate in tissue macrophages, which are seen as foam cells.<sup>11</sup>

**Treatment**—Diet and drugs have had considerable success in clearing eruptive xanthomas in endogenous lipemias. As chylomicron and VLDL concentrations are brought to normal, the eruptive xanthomas resolve completely in several weeks. Dietary manipulation alone often is effective in lowering blood lipid levels in most primary hyperlipoproteinemias. When insulin deficiency is the cause of decreased lipoprotein lipase activity, exogenous insulin administration rapidly increases the enzyme activity. Avoiding alcohol is important because it stimulates the synthesis of VLDL in the liver and subsequently increases triglycerides.

Fibric acid derivatives such as gemfibrozil, fenofibrate, and clofibrates are most useful for the treatment of hypertriglyceridemia; they activate lipoprotein lipase in peripheral tissue and decrease VLDL synthesis by suppression of the endogenous lipid pathway.

Our patient was treated with a fenofibrate, a statin, levothyroxine, ezetimibe, and insulin. Her

lesions began resolving within 1 month of beginning treatment.

### Conclusion

Our patient could be classified with type IV or type V hyperlipoproteinemia. Her family history was remarkable for hypercholesterolemia; her secondary factors of hypothyroidism, diabetes mellitus, and obesity could have easily saturated removal mechanisms resulting in an accumulation of chylomicrons and VLDL, which subsequently led to marked hypertriglyceridemia.

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