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A case of eruptive xanthomas associated with pregnancy unmasking a G188E heterozygous mutation of the lipoprotein lipase gene: A case report

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Abstract

A case of eruptive xanthomas with exceptionally high levels of blood triglycerides without any complication during pregnancy is reported. Eruptive xanthomas may develop in the setting of severe hypertriglyceridemia. Clinically, patients present with small and smooth papules with a characteristic yellow hue. The condition can also be associated with morbid systemic complications. Estrogen replacement therapy is a known cause of secondary hypertriglyceridemia. Estrogen increase in pregnancy is associated with a physiologic elevation of blood triglycerides in order to provide sufficient nutrition for the fetus. However, in the setting of primary dyslipidemia, severe hypertriglyceridemia can occur. The case presented here was explained by a partial primary lipoprotein lipase deficiency with a heterozygous G188E mutation of the *LPL* gene. The delivery by induced labor and the introduction of fenofibrate led to a rapid decrease of triglycerides and a resolution of cutaneous lesions without any complication for the patient or her baby.

Keywords

Eruptive xanthomas, hypertriglyceridemia, pregnancy, lipoprotein lipase gene

Introduction

Cutaneous xanthomas result from lipids deposition in the dermis—primarily in macrophages (foam cells) but also extracellularly. They develop in the setting of primary or secondary disorders of lipid metabolism.[1] Cutaneous xanthomas are easily recognizable by the characteristic yellow to orange hue. Eruptive xanthomas are a subtype of cutaneous xanthoma associated with a severe hypertriglyceridemic state (>10 mmol/L). Clinically, patients present with multiple small, smooth, and yellow papules usually distributed on the extensor surfaces of the extremities, buttocks, and lower abdomen. Many primary disorders of triglyceride metabolism are known, including familial lipoprotein lipase (LPL) deficiency and familial dysbetalipoproteinemia. Eruptive xanthomas due to secondary hypertriglyceridemia have been associated with different conditions such as diabetes mellitus, hypothyroidism, nephrotic syndrome, systemic retinoids, obesity, high caloric intake, alcohol abuse and estrogen replacement therapy. The association between the increase of estrogen during pregnancy leading to hypertriglyceridemia in predisposed women has been demonstrated. To the best of our knowledge, only one other case of eruptive xanthomas associated with pregnancy has been described.[2] We

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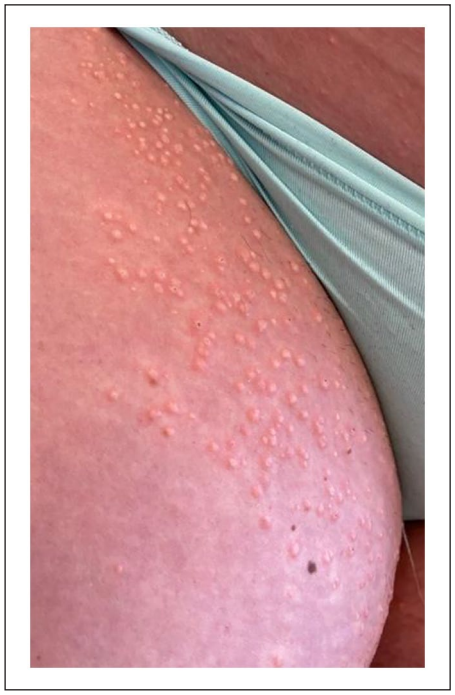

Figure 1. Multiple small, smooth, and yellow papules located in the inner tight.

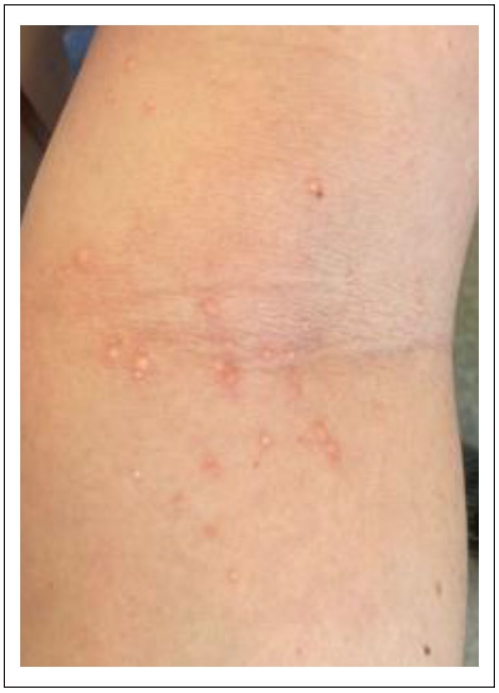

Figure 2. Eruptive xanthomas of the right antecubital pit.

are reporting a case of a healthy 32-year-old woman who presented extremely high levels of blood triglycerides and eruptive xanthomas without any systemic complications during pregnancy.

Case

A 32-year-old healthy primiparous woman presented to our clinic with more than 100 1–3 mm, smooth, round, yellow, and extremely pruriginous papules with an erythematous halo at their base. The lesions started to develop in less than 48 h during her 38th week of gestation. They were distributed in the inner thighs, inframammary fold, neck, and antecubital pits (Figures 1 and 2). The patient was not presenting any bullous or urticarial lesion or interdigital furrow. The umbilicus and stretch marks were spared. She did not have any past medical history except for a pancreatitis at 18 years old of an unknown cause. All her pregnancy follow-ups were normal, but no pre-pregnancy lipid profile was available. She did not have gestational diabetes. Her mother was known for a hypercholesterolemia.

Her blood sampling had a milky appearance and contained chylomicrons. Her triglyceride levels were at 142 mmol/L, and her cholesterol level was 10 mmol/L. Her complete blood count (CBC), random glucose test, HbA1c, lipase, hepatic, and renal function were normal. Abdominal and obstetrical ultrasounds were also normal. A skin biopsy showed a subtle dermal interstitial infiltrate composed of xanthelasmized histiocytes compatible with the diagnosis of eruptive xanthomas (Figure 3).

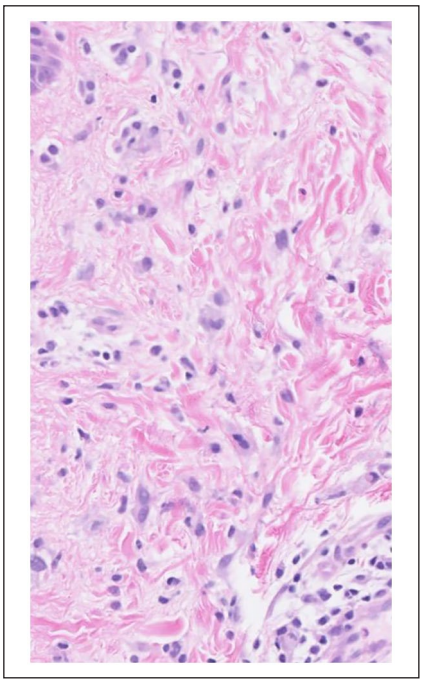

Figure 3. Subtle dermal interstitial infiltrate composed of xanthelasmized histiocytic elements compatible with the diagnosis of eruptive xanthomas.

The patient was ordered NPO, fenofibrate 200 mg PO daily was started, and her labor was induced the next day. The patient gave birth to a 3350 g healthy baby. In the 3 days postpartum, her triglyceride levels rapidly improved and the cutaneous lesions resolved. A heterozygous null mutation of

the *LPL* gene (G188E, exon 5) was identified, and the patient was diagnosed with a partial primary lipoprotein LPL deficiency. With the continued use of fenofibrate in postpartum and a healthy diet, her triglyceride level stayed controlled without recurrence of eruptive xanthomas.

Discussion

We are reporting a case of eruptive xanthomas associated with pregnancy that unmasked a heterozygous null mutation of the *LPL* gene. Familial LPL deficiency is a rare autosomal recessive genetic metabolic disorder characterized by a deficiency of the LPL enzyme.[3,4] To date, over 80 mutations in the *LPL* gene have been reported, with the G188E mutation being known for many years over the world.[5–7] Molecular genetic testing has been used to identify the G188E heterozygous mutation. To the best of our knowledge, only one other case of severe hypertriglyceridemia presenting with eruptive xanthomas during pregnancy has already been published in 1992.[2] In that case, the patient had most likely a combined familial hyperlipidemia that led to severe hypertriglyceridemia during two consecutives pregnancies with eruptive xanthomas and important systemic complications such as fulminant pancreatitis and acute respiratory distress syndrome. Surprisingly, although our patient presented almost two times the levels of triglycerides of the first patient reported (142 mmol/L vs 85 mmol/L), she did not develop any systemic complications. This is the first case reported of eruptive xanthomas associated with a heterozygous mutation G188E of the *LPL* gene unmasked by the hyperestrogenic state associated with pregnancy without any systemic complication even in the setting of extremely high levels of triglycerides.

The province of Quebec in Canada is known for his high incidence of familial LPL deficiency and has the highest frequency of mutation in G188E worldwide due to a founder effect.[4,8–11] The patient reported here was native of Quebec.

Individuals with an LPL deficiency are at risk of recurrent acute and chronic pancreatitis, hepatosplenomegaly and eruptive xanthomas without an increased risk of developing atherosclerosis. Most individuals who are carrier of a heterozygous LPL mutation without exacerbating metabolic or exogenous factors do not develop chylomicronemia syndrome.[10] However, the physiologic hyperestrogenic state associated with pregnancy leading to important elevation of triglycerides has been already demonstrated for women suffering from primary dyslipidemia.[12–14] In order to provide sufficient nutrition for the fetus during pregnancy, there is a physiological increase in total cholesterol and triglycerides plasma concentrations related to an increase in insulin resistance, estrogens, progesterone, and placental lactogen.[12,13] The triglycerides increase is more important for women with gestational diabetes mellitus.[13–15] Our patient had a hemoglobin A1c (HbA1c), random blood sugar level, and previous glucose challenge test that were all normal. Even if the genetic causes of gestational hypertriglyceridemia are less prevalent, they are associated with a higher risk of maternal–fetal complications such as acute pancreatitis, pre-eclampsia, and preterm labor.[12–14] The proportion of maternal and fetal deaths from pancreatitis during pregnancy reported in the literature is about 20%.[16] In conclusion, individuals who are only a carrier of heterozygous mutation of the *LPL* gene generally do not develop chylomicronemia syndrome in the absence of a second hit. However, in the setting of the hyperestrogenic state associated with pregnancy, severe hypertriglyceridemia may occur. Eruptive xanthomas are a rare manifestation of severe pregnancy hypertriglyceridemia, but their presence should alert the clinician of an underlying primary dyslipidemia at risk for systemic complications. Each pregnancy should be considered at high risk and aggressive management should be promptly initiated in order to prevent the potential morbid complications for the mother and her baby.[14] The resolution of the xanthomas is expected with a rapid decrease of triglyceride levels.

Declaration of conflicting interests

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Informed consent

A verbal consent of the patient was obtained for the publication of the case report and the photos.

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