

Eruptive Xanthoma

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CASE SUMMARY

History

A two-month-old girl with unremarkable birth history presented with sudden onset of erythematous papules on the limbs and face for one week. There was no systemic upset, and she remained asymptomatic. Her sister had a history of hypertriglyceridaemia under treatment. The patient's other family members enjoyed good physical health and there was no family history of premature coronary heart disease.

Physical examination

There were multiple discrete erythematous, yellowish papules over the limbs, anterior trunk and face, more on the extensor surface, and some lesions coalesced together to form small plaques (Figure 1). The liver and spleen were slightly enlarged at two centimetres below the costal margin. No mucosal involvement or lipaemia retinalis was found. There was no dysmorphism nor other congenital abnormality detected. Darier's sign was negative.

Differential diagnosis

In view of the morphology and distribution of the cutaneous lesions, eruptive xanthoma was strongly suspected. However, papular xanthoma and xanthoma disseminatum might at some stage of the disease share comparable clinical features. Non-Langerhans' cell histiocytosis especially juvenile xanthogranuloma and generalized eruptive histiocytosis should also be considered in the differential diagnosis. Although Darier's sign was negative, mastocytosis could not be excluded clinically.

Investigations

The patient was found to have raised fasting blood sugar and lipid levels. The whole blood was milky on standing, which signified markedly elevated chylomicrons in the blood. Urine protein, sugar and ketones were negative and the amylase level was not raised. Complete blood picture with differential count was normal. The renal and liver functions were also unremarkable.

The patient's parents and elder sister were asked for blood screening and the results were stated in Table 1.

Skin biopsy showed scattered foci of a few foam cells in the superficial dermis, admixed with lymphocytes, histiocytes and eosinophils. The overlying epidermis was unremarkable. The features were suggestive of eruptive xanthoma. Since the patient's plasma lipoprotein lipase level was normal, abnormal or deficient apoprotein C-II cofactor was suspected. It was later confirmed by dramatic lowering of plasma triglycerides after infusion of plasma from a normal control.

Diagnosis

Based on the "sky-high" hypertriglyceridaemia and histological findings, the diagnosis of eruptive xanthoma



Figure 1: Multiple yellowish papules over the right thigh extensor surface

Table 1. The fasting lipids and blood sugars of the index patient and her family members. The high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels in the patient and her sister could not be performed because of very high triglycerides

	Cholesterol mmol/l	HDL mmol/l	LDL mmol/l	Triglycerides mmol/l	Glucose mmol/l
Normal Range	3.5-6.5 (ideal <5.2)	0.70-2.1 (male) 0.50-1.70 (female)	1.55-4.4	0.70-2.1 (male) 0.50-1.70 (female)	4.5-5.6
Index Patient	13.0			83.2	20.7
Mother	6.7	1.17	4.84	1.51	5.0
Father	4.5			2.76	4.2
Sister	6.0			28.48	5.4

was made. The early presentation, positive family history of hypertriglyceridaemia and apoprotein C-II deficiency point towards an underlying Type-I familial hyperlipidaemia (Fredrickson classification).

Management

The patient was put on a low fat formula with a fat content of 93% medium chain fatty acid and 7% long chain fatty acid. Her fasting lipid and sugar improved dramatically and returned towards normal (cholesterol 5.4 mmol/l, triglycerides 3.57 mmol/l and sugar 5.0 mmol/l). All skin eruption subsided about a month after the dietary control.

REVIEW ON ERUPTIVE XANTHOMA

Eruptive xanthoma is characterized by small, yellowish, cutaneous papules measuring 1-4 mm with an erythematous halo. The lesions tend to arise abruptly in crops and merge into patches on the extensor surface of arms, legs, and buttocks, but may be more generalized. This skin lesion can be found in patients with a completely normal lipid level or those with an underlying hypertriglyceridaemia, which is further subdivided into familial and acquired forms.¹ These two big categories will be discussed briefly below.

Hypertriglyceridaemia xanthomatosis

Familial

Fredrickson type I, IV and V familial hyperlipidaemia account for most of the familial hypertriglyceridaemia.² Type I and V are autosomal recessive with absent lipoprotein lipase or its activator, apoprotein

C-II. Whereas type IV is autosomal dominant and the catabolism of triglycerides rich lipoprotein is reduced with overproduction of very low-density lipoproteins (VLDL).

Other inherited metabolic diseases such as lysosomal storage diseases and type I glycogen storage disease (Von Gierke's) may also give rise to elevated triglycerides and results in eruptive xanthoma.

Acquired

Causes commonly lead to eruptive xanthoma include diabetes mellitus, alcohol ingestion, obesity, chronic renal failure, nephrotic syndrome, pancreatitis, hypothyroidism and biliary cirrhosis.³ Medications including estrogens, corticosteroids, miconazole, isotretinoin, and etretinate⁴ can lead to elevated lipid level and cutaneous xanthoma.

Normolipaemic xanthomatosis

Development of xanthomas in the absence of hyperlipoproteinaemia is not uncommon and was described in detail by Parker.⁵ Altered lipoprotein content or structure, the presence of paraproteinaemia, haematopoietic diseases such as histiocytosis, myelomas and local trauma can cause eruptive xanthoma despite the normal plasma lipid level. Other causes may include trauma or oedema.^{6,7} Normolipaemic eruptive xanthomas have also been reported during pregnancy and in acquired total lipodystrophy.⁸

Pathogenesis

The high plasma concentration of lipoproteins facilitates its permeation through dermal capillaries. However, any conditions that increase the relative vascular permeability to lipoproteins such as local

injury, oedema, altered lipoprotein structure or paraproteins in the plasma, can also lead to lipoprotein leakage into the dermis. Direct phagocytosis of lipoproteins by dermal histiocytes or a reactive process involving in-situ lipid synthesis in the histiocytes will then evolve into foam cells.⁹

Differential diagnosis

Clinically eruptive xanthoma may sometimes be confused with other xanthomatosis or non-Langerhans' cell histiocytosis (Table 2).^{10,11} Rarely the cutaneous lesions may mimic Sweet's syndrome.¹² Most of the time a skin biopsy can reliably differentiate eruptive xanthoma from other xanthomatoses and non-Langerhans' cell histiocytosis (Table 3).

Treatment

Treatment of eruptive xanthoma is directed to the underlying causes. Since eruptive xanthoma secondary to hypertriglyceridaemia typically responds well to dietary control, a dietician's advice should be sought first. In general, a low carbohydrates and saturated fat diet is the first treatment of choice. Anti-hyperlipidaemic agents should be considered when dietary control fails.¹³

Prognosis

Unless the underlying causes can be corrected, the patient should be put on life-long dietary control and regular follow-up is needed. However patients can be reassured that the cutaneous lesions and lipoprotein abnormalities can revert to normal, in terms of weeks, with appropriate treatment.¹³

Table 2. Clinical features of the common differential diagnosis of eruptive xanthoma

	Eruptive xanthoma	Papular xanthoma	Juvenile xanthogranuloma	Xanthoma disseminatum	Generalized eruptive histiocytosis
Age	Children, adult	Mainly adult	80% <2year	60% <25year	Mainly adult
Skin lesions	Red-yellow papules in crops	Discrete yellowish papules	Discrete orange-yellow nodule	Red-brown	Red-brown papules
Number of lesions	Multiple	Multiple	Solitary or numerous	Numerous	Numerous
Location	Buttocks & thighs & extensors, tends to merge	Face and trunk larger, do not tend to merge	Head & upper trunk	Face, trunk, folds, proximal extremities	Trunk and limbs
Mucous membrane	Rare	Uncommon	Uncommon	Characteristic	Uncommon
Visceral involvement	Nil	Nil	Sometimes	Characteristic	Nil
Course	Resolve over several weeks	Self-limiting, come & go	Resolve in months/years	Resolve after several years	Resolve during childhood
Hyperlipidaemia	+	-	-	-	-

Table 3. Brief summary of histological differences between eruptive xanthoma and its common differential diagnosis

Eruptive xanthoma	Papular xanthoma/ Other xanthoma	Juvenile xanthogranuloma/ Xanthoma disseminatum/ Generalised eruptive histiocytosis
<ul style="list-style-type: none"> • Monotonous infiltrate of foamy histiocytes • Few foamy histiocytes in the early lesions, pattern is similar to interstitial granuloma annulare • Perivascular infiltration of inflammatory cells, neutrophil prominent 	<ul style="list-style-type: none"> • Diffuse or nodular foamy histiocytes with scanty inflammatory cells 	<ul style="list-style-type: none"> • Heterogeneous infiltrate of histiocytes with variable composition of inflammatory cells

Learning points:

Development of eruptive xanthoma is indicative of an underlying hyper-triglyceridaemia. Appropriate dietary changes, correction of secondary factors along with antihyperlipidaemic agents, if needed, will lower plasma triglycerides and allow the xanthomatous lesions to resolve.

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