Xanthomas

107

Dimitrios Sotiriadis and Aikaterini Patsatsi

Key Points

- In all cases of xanthomas, a thorough detection of a lipid disorder is of great significance.
- Among the different clinical types of xanthomas, eruptive xanthomas, as well as tuberous and tendinous xanthomas, are associated with an underlying hyperlipidemia, which must be detected.
- When the type of an underlying lipid disorder is identified, proper treatment serves in the clinical remission and the prevention of atherosclerosis and pancreatitis.
- Xanthelasmas are mostly found in normolipemic patients and their treatment is based on surgical procedures or destructive modalities.

D. Sotiriadis (✉)
Professor and Head, 2nd Department of Dermatology,
Aristotle University Faculty of Medicine,
Papageorgiou General Hospital,
Thessaloniki, Greece
e-mail: iros@med.auth.gr

A. Patsatsi
Assistant Professor, 2nd Department of Dermatology,
Aristotle University Faculty of Medicine,
Papageorgiou General Hospital,
Thessaloniki, Greece
e-mail: katerinapatsatsi@gmail.com

Definition

Xanthomas are lesions characterized by the accumulation of lipid-rich macrophages, the foam cells. They may develop in the setting of an altered systemic lipid metabolism.

Basic Concepts of Pathogenesis

Xanthomas have been associated with disorders of lipoprotein metabolism, despite the fact that only a minority of individuals with such disorders develop xanthomas.

A high plasma concentration of lipids leads to the permeation of lipoproteins through the walls of dermal capillaries. The lipid is then taken up by dermal macrophages, which evolve into foam cells.

More than one clinical type of xanthomas may be present in a particular lipoprotein disorder (Table 107.1).

Clinical Presentation

Xanthomas present clinically as yellow or yellow-brown papules, nodules, or plaques.

The amount of lipid present and the depth of accumulated foam cells define the color of lesions. There are distinct clinical forms of

A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_107, © Springer-Verlag Berlin Heidelberg 2015

Table 107.1 Types of xanthomas and associated type of hyperlipidemia

Eruptive xanthomas	**Planar xanthomas (palmar, intertriginous)**
Primary systemic hyperlipidemia	*Primary systemic hyperlipidemia*
Familial lipoprotein lipase deficiency (type I)	Familial hypercholesterolemia (type II)
	Familial dysbetalipoproteinemia (type III)
Apolipoprotein C-II deficiency (type I)	*Other primary dyslipidemias*
Familial hypertriglyceridemia (type IV)	Apolipoprotein A-I deficiency
Familial combined hypertriglyceridemia (type V)	Dysproteinemias
Secondary hyperlipidemia	*Special considerations*
	Biliary obstruction
Tuberous xanthomas	**Xanthelasmas**
Primary systemic hyperlipidemia	*Idiopathic – non-hyperlipidemia associated*
	Primary systemic hyperlipidemia
Familial hypercholesterolemia (type IIa, type IIb)	Familial hypercholesterolemia (type II)
Familial dysbetalipoproteinemia (type III)	Familial dysbetalipoproteinemia (type III)
Other primary dyslipidemias	*Secondary hyperlipidemia*
Sitosterolemia	*Other primary dyslipidemias*
Special considerations	Apolipoprotein A-I deficiency
Biliary obstruction	Dysproteinemias
Secondary hyperlipidemia	*Special considerations*
	Biliary obstruction
Tendinous xanthomas	
Primary systemic hyperlipidemia	
Familial hypercholesterolemia (type II)	
Familial defective apo-B100 (type II)	
Familial dysbetalipoproteinemia (type III)	
Other primary dyslipidemias	
Cerebrotendinous xanthomatosis	
Sitosterolemia	
Secondary hyperlipidemia	

xanthomas, with different clinical morphology, sites of predilection, and mode of development:

- Eruptive xanthomas
- Tuberous xanthomas
- Tendinous xanthomas
- Plane xanthomas

Eruptive Xanthomas

Eruptive xanthomas are small, yellow papules, 1–4 mm of size, with a peripheral erythematous halo. They erupt in crops over pressure points and over the extensor surfaces of the arms, legs, and buttocks (Fig. 107.1).

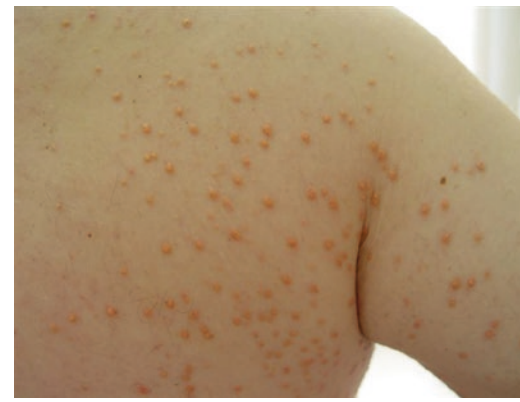

Fig. 107.1 Eruptive Xanthomas

Eruptive xanthomas are a characteristic skin manifestation in patients with familial lipoprotein lipase deficiency which leads to a massive accumulation of chylomicrons in the plasma and

a severe elevation of plasma triglyceride levels (type I pattern, according to Frederickson's classification of familial hyperlipidemia). This hyperlipidemia is extremely rare and may present in early childhood with acute pancreatitis. Apolipoprotein C-II deficiency is another form of type I hyperlipidemia, in patients with genetic defects of the apolipoprotein C-II gene, associated with the eruptive presentation of xanthomas.

This type of xanthomas rarely presents in patients with familial hypertriglyceridemia, leading to the accumulation of VLDL and to severe elevations of plasma triglyceride levels (type IV) or in patients with the combined form of hypertriglyceridemia (type V).

Tuberous and Tendinous Xanthomas

Tuberous xanthomas present as yellow or red nodules located on the extensor surfaces of the extremities, palms, and buttocks. Their initial presentation is that of soft, small, papules, resembling eruptive xanthomas. In the course of time, they enlarge and become firm but they do not attach to underlying structures like tendinous xanthomas.

Tendinous Xanthomas

Arise in tendons, ligaments, and fascia as deep, nontender, firm nodules of various sizes that move with the affected tendon. They are usually 1 cm or larger in size and are most frequently located on the Achilles tendons and the extensor tendons of the hands, elbows, and knees.

Tuberous or tendinous xanthomas may present in patients with familial LDL receptor deficiency and familial defective apoprotein B-100 defects, leading to the accumulation of LDL and elevation of plasma cholesterol levels (type II pattern of hyperlipidemia). These patients have severe atherosclerosis. They may also present in patients with familial dysbetalipoproteinemia (type III) or with sitosterolemia.

Tuberous xanthomas may develop in patients with familial combined hyperlipoproteinemia, leading to the accumulation of both LDL and VLDL, with variable elevations of both triglyceride levels and cholesterol levels in the plasma (type IIb pattern of hyperlipidemia).

Tendinous xanthomas may be found in patients with cerebrotendinous xanthomatosis.

Plane Xanthomas

Plane xanthomas present as soft yellow macules and slightly elevated papules and plaques located anywhere on the body, with a predilection for surgical or acne scars.

This clinical type may present in patients with familial hypercholesterolemia (type II), with familial dysbetalipoproteinemia, leading to the accumulation of LDL (beta-VLDL) and an increase in both triglyceride levels and cholesterol levels in the plasma (type III), with apolipoprotein A-1 deficiency, with dysproteinemias or with biliary obstruction.

Depending on their location, plane xanthomas are further subdivided into xanthelasmas, intertriginous xanthomas, palmar xanthomas, and diffuse (generalized) plane xanthomas.

The most common type, *xanthelasma palpebrarum (XP)*, occurs on the eyelids (Fig. 107.2). Patients with this type of xanthomas are mostly normolipemic. Xanthelasmas may present in patients with type II or type III pattern of hyperlipidemia, as well as in patients with apolipoprotein A-1 deficiency, with dysproteinemias, with biliary obstruction, or with secondary hyperlipidemias.

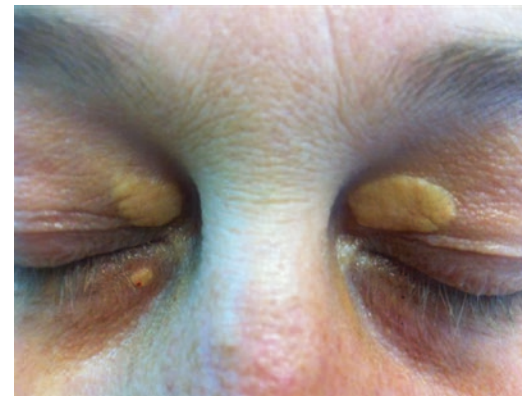

Fig. 107.2 Xanthelasma Palpebrarum

Intertriginous xanthomas present at the intertriginous areas and are pathognomonic of homozygous (type II) familial hypercholesterolemia.

Palmar xanthomas are yellow to orange, flat, linear lesions in the creases of the palms and fingers. They are sometimes subtle, requiring proper lighting in order to be recognized. They are most commonly seen with type III hyperlipidemia.

Diffuse (generalized) plane xanthomas present as macular, yellowish discoloration or plaques, involving particularly the trunk and neck. There is a significant association with lymphoreticular neoplasms and not with lipemic disorders.

Differential Diagnosis

- Lichen amyloidosis
- Disseminated granuloma annulare
- Necrobiotic xanthogranuloma
- Erythema elevatum diutinum
- Necrobiosis lipoidica
- Sarcoidosis

General Principles of Treatment

The most important principle in the treatment of xanthomas is to first detect the presence or not of an underlying hyperlipidemia. Treatment of the underlying disease aims not to improve the aesthetic outcome but to reduce the risk of atherosclerosis associated with lipoprotein disorders.

Eruptive xanthomas usually respond within weeks after initiation of systemic treatment, tuberous xanthomas resolve after months, while tendinous xanthomas take years to resolve or may persist indefinitely.

Xanthomas are very often, but not always, associated with underlying hyperlipidemia.

Treatment of hyperlipidemia consists of diet and lipid-lowering drugs, e.g., statins, bile acid-binding resins, fibrates, and nicotinic acid. Although there are only few well-documented studies to establish the therapeutic efficacy of these agents, eruptive and tuberous xanthomas usually resolve within weeks or months after treatment initiation (Table 107.2). Local surgical or destructive approaches are used mainly for xanthelasmas (Table 107.3).

Table 107.2 Treatment of xanthomas (summary)

Xanthomas (non-xanthelasmas) – treatment options
Diet
Drugs
Nicotinic acid
Bile acid-binding resins
HMG-CoA reductase inhibitors
Fibric acid derivatives
Ezetimibe
Combination of lipid-lowering agents
LDL apheresis

Table 107.3 Treatment of xanthelasmas (summary)

Xanthelasmas – treatment options
Surgical excision
Micrographic surgery
TCA
BCA
Cryosurgery
Electrodesiccation
Lasers (ablative – nonablative)
Diet (?)
Lipid-lowering agents (?)

Diet Therapy

Although diet remains the first step to reduce hyperlipidemia, several studies have reported only modest cholesterol-lowering benefits, generally in the range of a 5–10 % decrease in LDL cholesterol levels. Some patients, however, will have remarkable reduction, up to 25 %, in LDL cholesterol, on diet therapy. In any case, the results of diet should be assessed at least after 4 weeks.

Decreasing total caloric intake and body weight are very important and make a significant impact on lipid levels.

Diet should be very low in total fat or in saturated fats and high in poly- and nonsaturated fats.

There are several nutritional processes to diet therapy. "Mediterranean diet" is a very famous strategy, which maintains total fat at approximately 35–40 % of total calories but replaces saturated fat with nonsaturated ones, such as that found in olive oils. Unfortunately this diet is less likely to reduce HDL cholesterol and to lead to weight loss.

Low-fat, high-carbohydrate diet may result in reduction in HDL cholesterol and dietary changes may also decrease lipid levels in blood. Soluble fiber, garlic, vitamin C, soy protein, and plant sterols may result in reduction of LDL cholesterol. In addition, diet rich in antioxidant vitamins, such as found in fruits and vegetables may also be helpful.

Finally, diet therapy is the most effective management for all types of chylomicronemia.

Systemic Treatments

Several lipid-lowering agents have been proposed for primary hypercholesterolemia treatment, including niacin (nicotinic acid), bile acid-binding resins, HMG-CoA reductase inhibitors, and fibric acid derivatives. In general, the therapeutic goal is approached slowly, following up for side effects and being supportive to diet or other, non-drug therapies.

Nicotinic Acid (Niacin)

Nicotinic acid acts probably through decrease of the hepatic synthesis of VLDL with secondary reduction in LDL and increase in HDL cholesterol levels. This agent will also reduce triglycerides by half, will significantly lower lipoprotein-a levels, and will also increase plasma homocysteine levels. However, because of the need of high doses of nicotinic acid (~3–4.5 g/day) for its hypolipidemic effects, only 50–60 % of patients are able to take full doses due to the increased incidence of side effects.

Flushing, nausea, skin dryness, acanthosis nigricans-like eruption, urticaria, and hyperpigmentation are common side effects. Exacerbation of gout or peptic ulcers may occur. Although nicotinic acid may increase blood sugar in some patients, recent data have shown that it may be administered to diabetics.

Bile Acid: Binding Resins (Cholestyramine, Colestipol)

The resins cholestyramine and colestipol have the advantage of being not absorbed and they work by binding bile acids in the intestinal tube, causing reduction of their enterohepatic circulation. The result of this action is the increase of liver bile acids production, using hepatic cholesterol to do so. Thus, hepatic LDL receptor activity increases with decrease in plasma LDL levels. It has been observed that in some patients, treated with these agents, triglyceride level tends to increase slightly. Therefore, bile acid-binding resins should be used with caution in those with high levels of triglycerides.

Cholestyramine may be most effective in children with inherited hyperlipidemia, in young women of childbearing age, and during pregnancy – but it is contraindicated in type I hyperlipoproteinemia. However, patients – especially children – do not comply, due to the side effects of these drugs, including gastrointestinal symptoms, nausea, gas, and taste disturbance. The dose of cholestyramine is 12–36 g/day (in divided doses) and of colestipol is 20 % higher.

HMG-CoA Reductase Inhibitors (Statins)

These drugs act by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase, the enzyme that facilitates the intracellular cholesterol biosynthesis, with a consequent upregulation of hepatic LDL receptor expression and increased clearance of the LDL from the circulation. Statins are the most effective drugs that reduce cholesterol levels. They have also a moderate action to increase LDL and a slight action to decrease triglyceride levels. Statins have proven to be effective in patients with heterozygous FH and familial defective apolipoprotein B-100 and in patients with secondary dyslipidemias. Atorvastatin (10–80 mg/day), lovastatin, pravastatin (10–40 mg/day), simvastatin (5–40 mg/day), rosuvastatin, and fluvastatin, usually given once a day in the evening, may be used alone or in combination

with other agents such as cholestyramine. In severe cases the combination therapy with statins and LDL apheresis has been particularly effective.

The major side effects of statins are myopathy and hepatotoxicity but they are rare; higher doses cause more side effects. Coadministration of drugs such as fibric acids, erythromycin, or cyclosporine increases the risk of myopathy. Females of childbearing age should be informed about the teratogenicity of statins.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Clofibrate)

Fibrates' main effect is to reduce the synthesis and increase the breakdown of VLDL particles, with secondary effects on LDL (reduce about 10–15 %), triglyceride (reduce about 40 %), and HDL (raise about 15–20 %) levels. These agents are the treatment of choice of severe hypertriglyceridemia and of type III hyperlipoproteinemia. The usual doses, given in the morning, are gemfibrozil (600–1,200 mg/day), fenofibrate (150 mg/day), and bezafibrate (400 mg/day).

Side effects include hepatitis, chololithiasis, myopathy, and increase serum levels of creatinine. The incidence of hepatitis and myopathy may be higher among patients who are also taking other lipid-lowering agents (e.g., the combination of gemfibrozil and statins increases the risk of myopathy).

Ezetimibe

It is the newer lipid-lowering drug that reduces total and LDL cholesterol levels.

It works by inhibition of the intestinal lipid transporter Niemann-Pick C1-like protein. Ezetimibe reduces LDL cholesterol about 15–20 % when used as monotherapy and can further reduce LDL levels in combination with statins. It is generally well tolerated and is the drug of choice in sitosterolemia treatment.

LDL Apheresis

This treatment has been indicated for the most severe cases of hypercholesterolemia. Immunoabsorption, dextran sulfate absorption (DSAL), and heparin-induced extracorporeal LDL precipitate are the most common methods of LDL apheresis.

This therapeutic approach may be applied every 1–2 weeks and can be combined with statins or with other hypolipidemic drugs and suitable diet.

Topical Treatment Approaches

Surgical procedures or destructive modalities are mainly used for xanthelasma palpebrarum treatment. Although XPs are not strictly considered to be treated, patients very often seek removal for aesthetic reasons.

There are many methods available, e.g., microsurgical techniques, blepharoplasty, electrodesiccation, cryosurgery, chemical cauterization (TCA, BCA), and lasers, each with its advantages and disadvantages.

Electrodesiccation and cryosurgery were used mainly in the past for small, stable, and isolated XP, but the cosmetic results of those modalities are generally not acceptable enough.

Surgery is the classical method of treatment for xanthelasma removal. Microsurgical techniques provide excellent results, especially for small XPs. Unfortunately there is a high risk rate (30–40 %) of recurrences, and therefore, patients do not opt gladly this method.

Surgical excision is also indicated for a few cases of tuberous xanthomas.

Trichloroacetic acid (TCA) in different concentrations has been used as tissue cauterant since 1926.

In a recent, well-documented paper, Haque and Ramesh evaluated various strengths of TCA (50, 70, 100 %) in XP lesions. The lesions were categorized according to size and clinical form (flat, papular, or papulonodular). The authors conclude that the selected concentration of TCA for short use is proportional to the clinical severity. Each lesion should be treated for about 1–2 min until the development of frosting. TCA 100 % is recommended for papulonodular XP, TCA 70 % for flat plaques, and TCA 50 % for macular XP.

In any case, according to the current available literature, TCA 70 % seems to be a simple and effective method which achieves a higher rate of patients' satisfaction, despite the fact that TCA 95 % has an overall higher clearance rate.

Main problems of TCA application are determination of the sufficient quantity of the solution that should be applied, the potential need of reapplication and the appropriate time for this action, and, of course, the possibility of side effects.

Most common side effects associated with TCA application include hypo- and hyperpigmentation, while atrophy, scarring, and ectropion are rare and occur usually with higher concentrations (95–100 %).

Use of bichloroacetic acid (BCA) is relatively restricted and seems to be less effective, compared to TCA.

Ablative laser surgery for treating XPs was introduced more than 30 years ago.

Carbon dioxide (CO2) laser, Erbium:ND-YAG laser, Argon laser, and KTP laser are popular options and the results seem satisfactory. Main disadvantage of this option is the induction of pain, and thus, some form of anesthesia is required. Moreover, patients are unable to work for several days.

Nonablative laser (pulsed dye laser) therapy promises good clearance rates in approximately two thirds of the lesions, usually without local anesthesia or major side effects.

Hypo- and hyperpigmentation in about 5–15 % of patients are the most common complications of laser therapy, while persistent erythema, scars, or ectropion rarely occurs. Care must be taken always to protect the eyes.

Combined ablative and nonablative laser surgery may be recommended for the treatment of tuberous lesions. It is very important to emphasize that the risk of recurrence is estimated to be about 40 % and remains almost the same in comparison with the surgical removal. In addition, the wavelength, pulse duration, number of passes, and number of sessions may vary.

In conclusion, management of XPs is difficult, mainly because of the strong possibility of recurrences, regardless of the mode of selected modality.

Further Reading

Baron RB. Lipid abnormalities. In: Tierney LM, McPhee SJ, Papadakis MX, editors. Current medical diagnosis and treatment. New York: McGraw-Hill; 2005. p. 1202–13.

Brunzell JD. Clinical practice. Hypertriglyceridemia. N Engl J Med. 2007;357(10):1009–17.

Cannon PS, Ajit R, Leatherbarrow B. Efficacy of trichloroacetic acid (95%) in the management of xanthelasma palpebrarum. Clin Exp Dermatol. 2010; 35(8):845–8.

Clark LT. Treating dyslipidemia with statins: the risk-benefit profile. Am Heart J. 2003;145(3):387–96.

Digby M, Belli R, McGraw T, Lee A. Eruptive xanthomas as a cutaneous manifestation of hypertriglyceridemia: a case report. J Clin Aesthet Dermatol. 2011;4(1):44–6.

Fusade T. Treatment of xanthelasma palpebrarum by 1064-nm Q-switched Nd:YAG laser: a study of 11 cases. Br J Dermatol. 2008;158(1):84–7.

Haque MU, Ramesh V. Evaluation of three different strengths of trichloroacetic acid in xanthelasma palpebrarum. J Dermatolog Treat. 2006;17(1):48–50.

Karsai S, Schmitt L, Raulin C. Is Q-switched neodymium-doped yttrium aluminium garnet laser an effective approach to treat xanthelasma palpebrarum? Results from a clinical study of 76 cases. Dermatol Surg. 2009;35(12):1962–9.

Karsai S, Czarnecka A, Raulin C. Treatment of xanthelasma palpebrarum using a pulsed dye laser: a prospective clinical trial in 38 cases. Dermatol Surg. 2010;36(5):610–7.

Loeckermann S, Braun-Falco M. Eruptive xanthomas in association with metabolic syndrome. Clin Exp Dermatol. 2010;35(5):565–6.

Nahas TR, Marques JC, Nicoletti A, Cunha M, Nishiwaki-Dantas MC, Filho JV. Treatment of eyelid xanthelasma with 70% trichloroacetic acid. Ophthal Plast Reconstr Surg. 2009;25(4):280–3.

Spanou Z, Borradori L. Diffuse plane xanthomas, a cutaneous marker for monoclonal gammopathies and lymphoproliferative diseases. Eur J Haematol. 2011;86(1):91.

Tsouli SG, Kiortsis DN, Argyropoulou MI, Mikhailidis DP, Elisaf MS. Pathogenesis, detection and treatment of Achilles tendon xanthomas. Eur J Clin Invest. 2005;35(4):236–44.

White L, Horenstein M, Shea CR. Xanthomas. In: Lebwohl M, editor. Treatment of skin diseases: comprehensive therapeutic strategies. 3rd ed. New York: Saunders/Elsevier; 2010. p. 786–8.