Eruptive xanthoma = اﻠاﻨدﻔاﻌﻴﺔ اﻠﺼﻔﺮ اﻠاوراﻢ
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Lipids are insoluble in water; therefore, they are transported as complexes of lipoproteins and specific apoproteins. These proteins also serve as ligands to specific receptors, they facilitate transmembrane transport, and they regulate enzymatic activity. Lipoproteins may be classified according to their density, as follows: chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Lipoproteins may also be separated by electrophoresis into beta (LDL), prebeta (VLDL), and alpha (HDL) lipoproteins. Beta-VLDL (IDL) can be determined by ultracentrifugation and electrophoresis.

The metabolic pathways of lipoproteins can be divided into exogenous and endogenous pathways. The exogenous lipoprotein pathway refers to the metabolism of intestinal lipoproteins, the triglyceride-rich chylomicrons, primarily formed in response to dietary fat. The endogenous lipoprotein pathway refers to lipoproteins and apoproteins that are synthesized in tissues other than the intestines, predominantly in the liver. The liver secretes the
triglyceride-rich VLDL that contains apoproteins B-100, C-II, and E into the circulation.

In the peripheral tissues, particularly adipose and muscle tissue, VLDL is cleaved by lipoprotein lipase (LPL), extracting most of the triglycerides and forming an IDL that contains apoproteins B-100 and E. IDL can be taken up by the liver through the LDL receptor, or it can be converted to the cholesterol-rich LDL that contains apoprotein B-100. LDL is removed from the circulation primarily by the liver through the LDL receptor. HDL particles that contain apoproteins A-I and A-II interact with other lipoproteins, particularly VLDL and LDL, through lipolysis and the action of lecithin cholesterol acyltransferase (LCAT) enzyme. The main role of HDL is to accept cholesterol and to transport it back to the liver (reverse cholesterol transport).

Lipoprotein (a) (Lp[a]) consists of an LDL-like particle with apoprotein B and a side chain of a highly glycosylated protein. Lp(a) has a role not only in atherogenesis but also in thrombogenesis because of its homology with plasminogen.

Alterations in lipoproteins result either from genetic mutations that yield defective apolipoproteins (primary hyperlipoproteinemia) or from some other underlying systemic disorder, such as diabetes mellitus, hypothyroidism, or nephrotic syndrome (secondary hyperlipoproteinemia). The biochemical and genetic basis for the inherited disorders of lipid and lipoprotein metabolism differ considerably.

Traditionally, hyperlipidemias have been classified according to 6 phenotypes described by Fredrickson. These phenotypes are based on the electrophoretic patterns of lipoprotein level elevations that occur in patients with hyperlipoproteinemia. In recent years, the understanding of the genetic and biochemical basis of these disorders has revealed a large and diverse group of diseases, many of which have similar clinical expressions, exposing the limitations of the Fredrickson classification system. Despite the system's shortcomings, Fredrickson phenotypes are a useful tool for the discussion of these disorders. The understanding of the pathophysiology of these defects provides a basis for diagnosis and treatment.

Familial lipoprotein lipase deficiency is an example of a primary disorder in which a deficiency of lipoprotein lipase in tissue leads to a type I pattern of hyperlipidemia, with a massive accumulation of chylomicrons in the plasma. This effect results in a severe elevation of plasma triglyceride levels. Plasma cholesterol levels are not usually elevated. Patients with type I may present in early childhood, often with acute pancreatitis. Eruptive xanthomas are the most characteristic skin manifestation of this disorder.
Cholesterol is bound to apolipoprotein B-100 as LDL in interstitial fluid. Cells may acquire cholesterol via an LDL receptor on the cell membrane. Familial LDL receptor deficiency and familial defective apoprotein B-100 are examples of primary defects that can lead to the accumulation of LDL, which corresponds to a type IIa pattern of hyperlipidemia. Plasma cholesterol levels are severely elevated, but plasma triglyceride levels are typically normal. Patients with type IIa have severe atherosclerosis and may present with tendinous or tuberous xanthomas as well as xanthelasmas.

The type IIb pattern is characterized by the accumulation of both LDL and VLDL, with variable elevations of both triglyceride levels and cholesterol levels in the plasma. Patients with familial combined hyperlipoproteinemia have such a pattern of hyperlipidemia, but a specific genetic defect has not been established. Patients with type IIb may present as adults with tendinous or tuberous xanthomas as well as xanthelasmas.

Type III hyperlipidemia is characterized by the accumulation of IDL (beta-VLDL), which is manifested by increases in both triglyceride levels and cholesterol levels in the plasma. A genetic basis for the primary disorder, familial dysbetalipoproteinemia, has been well established. Various mutations of apoprotein E impair its ability to bind to the IDL receptor. Patients with type III present as adults with premature atherosclerosis and xanthomas, particularly plane (palmar) xanthomas.¹

Familial hypertriglyceridermia is an example of a primary defect resulting in type IV hyperlipidemia. Accumulation of VLDL causes severe elevations of plasma triglyceride levels. Plasma cholesterol levels are typically normal. A definitive molecular defect has not been established. Patients with type IV may present with eruptive xanthomas.

Genetic defects of the apolipoprotein C-II gene result in the accumulation of chylomicrons and VLDL, which is the type V pattern of hyperlipidemia. Patients with this type have severe elevations of triglyceride levels in the plasma. These patients, like those with lipoprotein lipase deficiency, may present in early childhood with acute pancreatitis and eruptive xanthomas.

Decreased synthesis of HDL due to decreased formation of apoprotein A-I and apoprotein C-III leads to decreased reversed cholesterol transport, resulting in increased LDL levels, premature coronary artery disease, and plane xanthomas.
Hyperlipidemia is also related to a variety of secondary causes. Secondary hypercholesterolemia can be found in pregnancy, hypothyroidism, cholestasis, and acute intermittent porphyria. Secondary hypertriglyceridemia can be associated with oral contraceptive use, diabetes mellitus, alcoholism, pancreatitis, gout, sepsis due to gram-negative bacterial organisms, and type I glycogen storage disease. Combined hypercholesterolemia and hypertriglyceridemia can be found in nephrotic syndrome, chronic renal failure, and steroid immunosuppressive therapy.

History

- A family history of xanthomas may be encountered in hereditary hyperlipoproteinemias.
- Prior history of myocardial infarction and other forms of atherosclerosis as well as pancreatitis may be encountered in some of the syndromes.
- Cutaneous manifestations may precede a diagnosis of hyperlipidemia.

Physical

Cutaneous xanthomas associated with hyperlipidemia can be clinically subdivided into xanthelasma palpebrarum, tuberous xanthoma, tendinous xanthoma, eruptive xanthoma, plane xanthoma, and generalized plane xanthoma. Xanthoma disseminatum and verruciform xanthoma are usually not associated with hyperlipidemia.

- Xanthelasma palpebrarum is the most common of the xanthomas. The lesions are asymptomatic and usually bilateral and symmetric. The lesions are soft, velvety, yellow, flat, polygonal papules around the eyelids. Xanthelasmases are most common in the upper eyelid near the inner canthus. Usually, the lesions have evolved for several months and enlarged slowly from a small papule. Xanthelasma may be associated with hyperlipidemia. When associated with hyperlipidemia, any type of primary hyperlipoproteinemia can be present. Some secondary hyperlipoproteinemias, such as cholestasis, may also be associated with xanthelasmas.

- Tuberous xanthomas are firm, painless, red-yellow nodules. The lesions can coalesce to form multilobated tumors. Tuberous xanthomas usually develop in pressure areas, such as the
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extensor surfaces of the knees, the elbows, and the buttocks. Tuberous xanthomas are particularly associated with hypercholesterolemia and increased levels of LDL. They can be associated with familial dysbetalipoproteinemia and familial hypercholesterolemia, and they may be present in some of the secondary hyperlipidemias (eg, nephrotic syndrome, hypothyroidism).

- Tendinous xanthomas appear as slowly enlarging subcutaneous nodules related to the tendons or the ligaments. The most common locations are the extensor tendons of the hands, the feet, and the Achilles tendons. The lesions are often related to trauma. Tendinous xanthomas are associated with severe hypercholesterolemia and elevated LDL levels, particularly in the type IIa form. They can also be associated with some of the secondary hyperlipidemias, such as cholestasis.

- Eruptive xanthomas most commonly arise over the buttocks, the shoulders, and the extensor surfaces of the extremities. Rarely, the oral mucosa or the face may be affected. The lesions typically erupt as crops of small, red-yellow papules on an erythematous base, and they may spontaneously resolve over weeks. Pruritus is common, and the lesions may be tender. Eruptive xanthomas are associated with hypertriglyceridemia, particularly that associated with types I, IV, and V (high concentrations of VLDL and chylomicrons). They may also appear in secondary hyperlipidemias, particularly in diabetes.

- Plane xanthomas are mostly macular and rarely form elevated lesions. They can occur in any site. Involvement of the palmar creases is characteristic of type III dysbetalipoproteinemia. They can also be associated with secondary hyperlipidemias, especially in cholestasis. Generalized plane xanthomas can cover large areas of the face, the neck, and the thorax, and the flexures can also be involved. They may be associated with monoclonal gammopathy and hyperlipidemia, particularly hypertriglyceridemia.

- Xanthoma disseminatum and verruciform xanthoma are particular forms of xanthomas that occur in normolipemic patients. Xanthoma disseminatum develops in adults as red-yellow papules and nodules with a predilection for the flexures. Characteristically, the mucosa of the upper part of the aerodigestive tract is involved. It has a benign clinical course and usually resolves spontaneously. Verruciform xanthoma predominantly occurs in the oral cavity of adults as a single papillomatous yellow lesion. Verruciform xanthoma is considered to be a reactive condition with benign behavior, and it is treated with local excision.

Laboratory Studies

- Primary hyperlipidemia is primarily a diagnosis of exclusion. Appropriate blood, urine, and radiographic workups are required to rule out a secondary cause of hyperlipidemia. Lipoprotein profiles are primarily used to assess cardiac risk and to aid in the diagnosis of lipid metabolism disorders.

- Plasma levels of triglyceride, cholesterol, and HDL-cholesterol are measured following a
12-hour fast before venipuncture. Cholesterol and triglyceride levels are usually measured by enzymatic methods. HDL-cholesterol levels can be measured after the apoprotein B-containing lipoproteins (chylomicrons, VLDL, IDL, LDL, Lp[a]) are removed by polyanion-divalent cation precipitation. LDL and VLDL can then be calculated as follows:
- LDL = Total Cholesterol Level – (Triglyceride Levels/5 + HDL Level)
- VLDL = Triglyceride Levels/5* *If triglycerides are greater than 700, the denominator is 10.

- Chylomicrons, because of their high lipid-protein ratio, are less dense and form a creamy layer when plasma is left standing for several hours. Ultracentrifugation fractions can be electrophoretically examined for the presence of beta-VLDL and Lp(a). Quantification of apolipoproteins, particularly B and A-I, can be achieved by immunologic methods.
  - Lipoprotein patterns can be determined as follows:
    - I - Elevated triglyceride levels with increased chylomicron levels
    - IIa - Elevated cholesterol level because of increased LDL level
    - IIb - Elevated cholesterol and triglyceride levels because of increased LDL and VLDL levels
    - III - Elevated cholesterol and triglyceride levels, with the presence of beta-VLDL
    - IV - Elevated triglyceride levels because of increased VLDL level
    - V - Elevated triglyceride levels because of increased VLDL level and the presence of chylomicrons

- The risk for cardiovascular disease can be determined on the basis of the total cholesterol, LDL-cholesterol, and HDL-cholesterol values in adults and children.

**Histologic Findings**

Changes in the skin and the tendons are characterized by the presence of vacuolated macrophages (foamy macrophages). These macrophages are filled with lipid droplets, which are dissolved and removed from the tissue during histologic processing. Lipid stains are of no use in routinely processed tissue. In contrast, frozen sections can be stained with lipid stains. Foamy histiocytes usually have 1 nucleus, but multinucleated histiocytes (Touton giant cells) are often identified.

Eruptive xanthomas may contain infiltrates of lymphocytes and typically contain extracellular lipid. Xanthelasma differs from other xanthomas because of the superficial location of the foamy cells and the characteristic appearance of eyelid skin. Tendinous and tuberous xanthomas can contain prominent fibrosis and occasional cholesterol clefts. Verruciform xanthoma demonstrates prominent hyperplasia of the squamous epithelium and foamy macrophages
within dermal papillae.

Medical Care

Xanthomas not always associated with underlying hyperlipidemia, but when they are, diagnosing and treating underlying lipid disorders is necessary to decrease the size of the xanthomas and to prevent the risks of atherosclerosis. Treatment of the hyperlipidemia initially consists of diet and lipid-lowering agents such as statins, fibrates, bile acid–binding resins, probucol, or nicotinic acid. The lipid-lowering effects of these agents have been well documented, but few studies mention the efficacy of these drugs for resolving xanthomas. Eruptive xanthomas usually resolve within weeks of initiating systemic treatment and tuberous xanthomas usually resolve after months, but tendinous xanthomas take years to resolve or may persist indefinitely.

The main goal of therapy for hyperlipidemia is to reduce the risks of atherosclerotic cardiovascular disease. In patients with severe hypertriglyceridemia, the goal is to prevent pancreatitis. The detailed therapy of hyperlipidemia is beyond the scope of this article.

- Inazu et al\textsuperscript{4} investigated whether pravastatin or probucol was better at regressing tendon xanthomas and xanthelasma in patients with primary hypercholesteremia. In both the pravastatin and probucol groups, xanthelasma regressed in 2 of 4 patients. Achilles tendon xanthoma regressed in 4 of 5 patients treated with pravastatin and 2 of 5 patients treated with probucol.

- Fujita and Shirai\textsuperscript{5} studied 54 patients treated with probucol or pravastatin. Xanthelasma regressed in 13 of 36 patients treated with probucol and in 1 of 18 patients treated with pravastatin. Total cholesterol levels decreased in both treatment groups, while HDL cholesterol levels decreased only in those treated with probucol.

- Yamamoto et al\textsuperscript{6} examined 51 patients with familial hypercholesterolemia. Patients were treated with combinations of probucol, cholestyramine, clofibrate, and compactin. The size of Achilles tendon xanthomas was decreased in all patients who received probucol.

- Kuo et al\textsuperscript{7} investigated 21 patients with atherosclerosis and cutaneous, tendinous, or corneal xanthomas who were followed for up to 7.5 years. Patients were placed on a low-fat, low-cholesterol diet and colestipol, a bile acid–binding resin. This regimen caused tendinous xanthomas to disappear in 2 of 11 patients and improve in 9 of 11 patients. Xanthelasma disappeared in 2 of 4 patients and improved in 2 of 4 patients.

Surgical Care

Surgery or locally destructive modalities can be used for idiopathic or unresponsive xanthomas.
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Xanthelasmas are often treated with topical trichloroacetic acid, electrodesiccation, laser therapy, and excision; however, recurrences can occur. Care must be taken to protect the eyes during any procedure used to treat xanthelasma. Such procedures should be performed only by individuals who are thoroughly familiar with and skilled in the procedure.

- Mendelson and Masson\(^8\) studied surgical excision of xanthelasma performed in 100 patients. Of patients who were having their lesions treated for the first time, 26 (40\%) of 68 recurred. Factors that predicted recurrence were systemic hyperlipidemia, involvement of all 4 eyelids, and a previous history of recurrent xanthelasma.

- Raulin et al\(^9\) studied 23 patients with 52 xanthelasmata treated with an ultrapulsed carbon dioxide laser, which delivers high energy in short pulses and reduces the risk of scarring and hyperpigmentation seen with continuous-mode carbon dioxide lasers. All xanthelasmata were completely removed. One patient experienced mild erythema for 4 months, but no permanent hyperpigmentation or ectropion developed. Three patients had recurrent lesions at an average follow-up time of 10 months.

- Borelli and Kaudewitz\(^10\) studied 15 patients with 33 xanthelasmas treated with an Er:YAG laser. All xanthelasmas were completely removed. Postoperative erythema resolved within 2 weeks. No scarring or ectropion developed. No lesions recurred over a 7- to 12-month follow-up period.

- Basar et al\(^11\) studied 24 patients with 40 xanthelasmas treated with an argon laser. Complete removal of all lesions occurred with 1-4 sessions at intervals of 2-3 weeks. Six lesions recurred over 8-12 months and required re-treatment. Erythema persisted for 1 month in 8 lesions. Hyperpigmentation occurred in 1 patient and persisted for 3 months, while hypopigmentation occurred in 2 lesions. No bleeding, infections, or ectropion occurred.

- Haygood et al\(^12\) studied 13 patients with 25 lesions. Ten patients had complete clearing with bichloracetic acid application. Five lesions recurred and required a second treatment to achieve complete resolution. No infections, scars, or complications were reported.