Xanthomas and Abnormalities of Lipid Metabolism and Storage

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Efthymia Soura

Introduction

The spectrum of lipid metabolism abnormalities is wide and encompasses a variety of conditions. These include disorders that can be very common, such as xanthelasmas, disorders that are hereditary, such as primary hypercholesterolemia and disorders that can be secondary to systemic disease, such as diabetes or hypothyroidism. These conditions possess the potential to be associated with increased cardiovascular risk. Therefore, they may require systemic therapeutic interventions aimed to treat high lipid levels in addition to treatments for their cutaneous manifestations [1]. The following chapter focuses on an overview of the classification of xanthomas, dyslipidemias and their cardiovascular risk.

Overview of Lipid Metabolism

There are two main pathways of lipoprotein synthesis: the exogenous and the endogenous pathway. The initiation of the exogenous pathway requires dietary fat intake. More specifically, dietary triglycerides are catabolized in the gut to fatty acids and monoglycerides by pancreatic lipase and bile acids. These products are absorbed by intestinal epithelium, re-esterified into cholesteryl ester and triglycerides and packaged with various cholesterol esters onto apolipoprotein B-48, forming chylomicrons. Apolipoproteins can be considered as "passports" that allow access of lipoprotein particles to specific sites for delivery, storage or modification of lipids [2]. Chylomicrons gain access to systemic circulation through the thoracic duct where the core triglycerides are gradually hydrolyzed resulting to the release of free fatty acids to peripheral tissues [1]. This process is complex and requires the

E. Soura (✉)
1st University Department of Dermatology – Venereology, Andreas Syggros Hospital, National and Kapodistrian Medical School of Athens, Athens, Greece

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interaction of lipoprotein lipase (LPL), which is bound to the capillary endothelium, in tissues such as adipose tissue and muscle, apolipoprotein CII (also a chylomicron component) and other lipoproteins and proteins (e.g. GPIHBP1, apo V) [2]. Chylomicrons are, therefore, progressively degraded to chylomicron remnants that contain, mainly, cholesteryl esters. These are taken up by the liver via binding to apo B-100/E receptors, re-esterified as cholesteryl esters and triglycerides and stored, while apolipoproteins such as B-48 are degraded, or exported as lipoproteins [1, 2].

The endogenous pathway follows the metabolism of fats after they are exported from the liver. More specifically, the liver produces VLDL (very low density lipoprotein) which is a very rich in triglycerides lipoprotein. Apo B100 is the major apolipoprotein of VLDL, however, the rate of transfer of triglycerides to the apo-B peptide is mediated by microsomal transfer protein (MTP) and is directly dependent to the presence of adequate amount of triglycerides [2]. After VLDL is secreted to the plasma it acquires apo E, apo CII, and apo CIII. These apoliproteins are key in the interaction of VLDL with LPL which will gradually hydrolyze the triglycerides in VLDL to fatty acids. This process, in turn, will convert VLDL to IDL, a cholesteryl ester–rich particle containing apo B and apo E. IDL can either be taken up by the liver and degraded or interact with extracellular hepatic lipases and re-enter the circulation as LDL, which consists of one molecule of apo B100 per particle and cholesteryl esters [1, 2].

HDL (high density lipoprotein) is a major component of the dynamic process of lipid metabolism. It is produced in the liver and secreted in the peripheral circulation, containing only a phospholipid disc, Apo AI and Apo AII. HDL absorbs free cholesterol and phospholipids shed from cells, surface lipids, Apo CII, Apo CIII, and Apo E (VLDL remnants), it stores cholesterol in its core after it esterifies it with the assistance of LCAT (Lecithin–Cholesterol Acyltransferase), and transports it back to the liver for excretion directly or indirectly (by interacting with VLDL) [2].

The most concise method of classifying dyslipidemias is the one proposed by Fredrickson which has been adopted by WHO [3]. A summary of the types of dyslipidemias and their cutaneous manifestations can be found in Table 17.1.

Xanthomas

Xanthomas are subcutaneous lipid deposits that, with the sole exception of familial hypercholesterolemia type II, appear during adulthood. As the term “xanthoma” (Greek: xanthos = yellow/blonde) implies, these deposits have a yellowish to orange color [4]. Although the pathogenesis of xanthomas is not well understood, it is believed that these lipid deposits originate from lipids found in the circulation. The histological picture is similar in all types of xanthomas. More specifically, all types of xanthomas contain foam cells (macrophages filled with cholesterol and cholesterol esters) and, rarely, giant touton cells. Foam cells stain positive for CD68 and adipophilin immunoperoxidase [5]. As xanthomas are slowly being degraded the appearance of clefts or connective tissue reaction around the nests of foam cells can be observed. Fibrosis can be present in older lesions [4, 6]. It must be mentioned

Table17.1 Summary of dyslipidemias and their cutaneous and systemic manifestations

WHO classification	Serum levels	Overall symptom	Primary dyslipidaimia	Secondary causes	Cutaneous manifestations	Systemic manifestations
I (↑ CM)	↑↑ TGS ↓ HDL ↓ LDL	Hypertriglyceridaemia	• Lipoprotein lipase deficiency • ApoCII deficiency	• Alcoholism • Diabetes • Chronic renal failure	Eruptive xanthomas	• No increased risk of CV disease • Recurrent pancreatitis
IIa (↑LDL)	↑ Chol ↑ LDL	Hypercholesterolaemia	• Familial hypercholesterolaemia • Familial defective ApoB100 • Polygenic hypercholesterolaemia	• Hypothyroidism • Anorexia • Cholestatic liver disease • Nephrotic syndrome • Thiazide diuretics, corticosteroids	• Tendon xanthomas • Xanthelasmas • Interdigital planar xanthomas (homozygous FH)	Increased risk of atherosclerosis in peripheral and coronary arteries
IIb (↑LDL, ↑VLDL)	↑ Chol ↑ LDL ↑ TGS +/– ↓ HDL	Combined dyslipidaemia	Familial combined hyperlipidaemia	• Lipodystrophies • Hypothyroidism • Liver disease • Nephrotic syndrome • Chronic renal failure • Paraproteinaemias • Pregnancy • Various drugs	• Tendinous xanthomas • Tuberoeruptive xanthomas • Xanthelasmas • Interdigital planar xanthomas • Xanthomas in intertriginous areas	Increased risk of atherosclerosis in peripheral and coronary arteries
III (Broad β-VLDL)	↑ Chol ↑ LDL ↑ TGS +/– ↓ HDL	Combined dyslipidaemia	Familial dysbetalipoproteinaemia	• Diabetes • Metabolic syndrome	• Tuberous xanthomas • Palmar xanthomas	Increased risk of atherosclerosis in peripheral and coronary arteries

(continued)

Table17.1 (continued)

WHO classification	Serum levels	Overall symptom	Primary dyslipidaimia	Secondary causes	Cutaneous manifestations	Systemic manifestations
IV (↑VLDL)	↑ Chol ↑ LDL ↑ TGS +/– ↓ HDL	Hypertriglyceridaemia and Combined dyslipidaemia	Endogenous familial hypertriglyceridemia	• Hypothyroidism • Liver disease • Nephrotic syndrome • Chronic renal failure • Paraproteinaemias • Pregnancy • Various drugs	Eruptive xanthomas	Associated with type II diabetes mellitus, obesity and alcoholism
V (↑CM,↑VLDL)	↑↑ TGS ↓ HDL ↓ LDL	Hypertriglyceridaemia	N/A	• Paraproteinaemias • Pregnancy • Various drugs (oral contraceptives, β-blockers, thiazide diuretics)	Eruptive xanthomas	type II diabetes mellitus

CM chylomicrons, *Chol* Total Cholesterol, *TGS* triglycerides, *HDL* high density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol

that although xanthomas are closely associated with increased serum lipid levels, not all patients with hyperlipidemia develop them [4]. Xanthomas are categorized as tuberous xanthomas, tendon xanthomas, eruptive xanthomas and plane xanthomas. These entities will be discussed in the sections below [6].

Tuberous Xanthomas

Tuberous xanthomas appear as pink/red-yellow nodules mainly on sites of pressure such as the elbows or knees. They usually present as small lesions that are yellowish and erythematous, and gradually increase in size ultimately attaining very large sizes that can be several centimeters in both height and diameter (can exceed 3 cm in diameter). Older lesions tend to lose their yellowish tint and become brownish and fibrotic. In some instances, tuberous xanthomas may be surrounded by smaller lesions. In this case they are called "tubero-eruptive" xanthomas. In general, tuberous and tubero-eruptive xanthomas are considered part of the same continuum [1, 4–6].

Tuberous and tubero-eruptive xanthomas have been closely associated with Type II and Type III hyperlipidemias (Table 17.1) and are considered to be linked with a high risk for cardiovascular disorders and especially coronary artery disease [6–8]. In addition, tuberous xanthomas have rarely been reported in cases of secondary dyslipoproteinemias such as nephrotic syndrome or hypothyroidism [6]. Laboratory investigations should include a complete lipid profile and, in high suspicion for primary dyslipidemias, apolipoprotein E (ApoE) genotyping and lipid electrophoresis or ultracentrifugation examinations [1]. (Tables 17.2 and 17.3).

Table17.2 Main points in the diagnosis of xanthomas [1, 6]

- The diagnosis of xanthomas is usually made clinically. If doubts exist:
  - Biopsy for histopathological assessment
- If diagnosis of xanthoma is made:
  - Personal and family history may reveal possible metabolic disorder
  - Lipid levels assessment (LDL, HDL, total cholesterol, Triglycerides, VLDL etc.)
  - Liver enzyme level assessment (AST, ALT, γ-GT, ALP, bilirubin etc.)
  - In case where abnormalities in lipid/ liver enzyme levels are observed (ultrasonography of arteries of the head and neck, intima-media thickness in the carotid arteries, ankle-brachial index) and sonography of the liver (to confirm or reject the presence of non-alcoholic fatty liver disease) should be considered especially if xanthelasmas are present
- If family hyperlipidemia is suspected:
  - Examinations specific to each type of hyperlipidemia should be performed[a]
  - Achilles tendon ultrasound could reveal thickening
- Causes of secondary hyperlipidemia should be excluded:
  - *Predominantly hypertriglyceridemia:* Obesity, Pregnancy, Diabetes mellitus, Alcoholism, Renal failure, Estrogen therapy, Steroid therapy, β-blocker therapy, Lipodystrophy, Dysglobulinemias
  - *Predominantly hypercholesterolemia*: Hypothyroidism, Nephrotic syndrome, Cholestasis, Diuretics, Cyclosporine, Hepatoma

[a]Laboratory tests are summarized in Table 17.3

Table17.3 Specific tests used for the diagnosis of dyslipidemias [9]

- *Routine testing:*
  - Serum cholesterol
  - Serum triglycerides
  - Serum HDL cholesterol
  - Serum LDL cholesterol
  - Refrigerator test Profile to rule out secondary causes
- *Additional testing:*
  - Lipoprotein electrophoresis
  - Beta-quantification Lipoprotein lipase assay
  - Apo-E genotyping
  - Apo-C-II assay
  - Familial defective apolipoprotein B-100 screening
  - Apolipoprotein B-100 and A-1 Lp(a)
- *Special tests:*
  - Fibrinogen
  - Micronutrient antioxidants
  - LDL oxidizability
  - Homocysteine
  - Anti-phospholipid antibodies
  - LDL subclasses
  - HDL subclasses

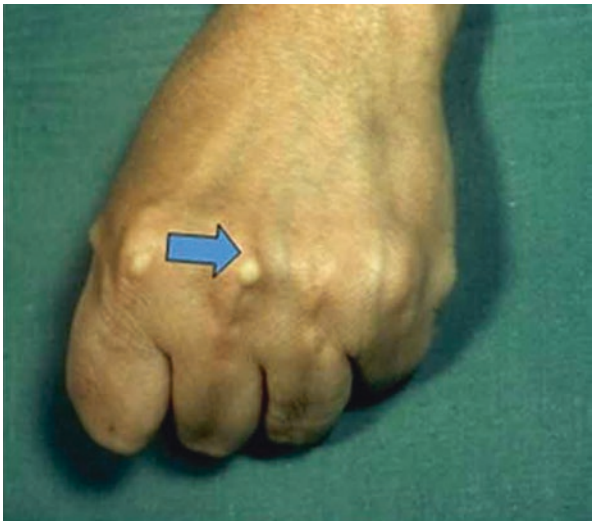

Fig.17.1 Tendon xanthomas located on the knuckles of a patient (Courtesy of Iyengar S S, et al. Journal of Clinical lipidology, Vol. 12, no. 1, 56–109)

Tendon Xanthomas

Tendon xanthomas appear as firm, smooth papules or nodules that represent deep subcutaneous lipid deposits that affect tendons. Unlike other types of xanthomas their color is more skin colored or erythematous than yellow, since the lipid deposits are located deep within the tendons and are usually not visible. Their size ranges from 5 mm to 25 mm in diameter. Lesions are commonly located on extensor tendons of hands (knuckles), (Fig. 17.1) feet and on the Achilles tendons, (Fig. 17.2) but

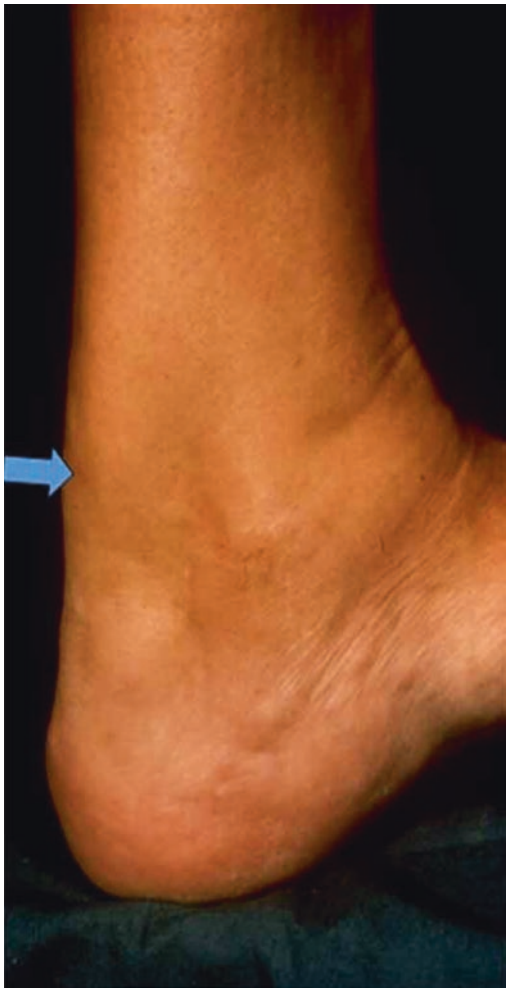

Fig.17.2 Tendon xanthoma located on the Achilles tendon of a patient. There are very subtle changes in skin color, while the lesion is only barely visible. (Courtesy of Iyengar S. S., et al. Journal of Clinical lipidology, Vol. 12, no. 1, 56–109)

other tendons may also be affected. Tendinous xanthomas can be freely moved from side to side upon clinical examination unless they involve the periosteum, which can be the case if the patellar tendon is affected [1, 2, 4]. The lesions can be occasionally painful, especially in cases where the Achilles tendon is affected (achillodynia), and may even (rarely) be associated with spontaneous tendon rupture [10].

Tendinous xanthomas are encountered in disorders with elevated LDL cholesterol levels such as type II familial hypercholesterolemia. More specifically, 20%-50% of patients with clinically diagnosed familial hypercholesterolemia have been reported to present with tendinous xanthomas [6]. The lesions can also occur in the context of secondary hyperlipidemia associated with obstructive liver disease (cholestasis), diabetes and myxedema. In addition, special care should be taken to exclude possible diagnoses of cerebrotendinous xanthomatosis, and β-phytosterolemia [1]. Investigations assisting in the diagnosis of these lesions include imaging (e.g. Ultrasound, CT, MRI to diagnose tendon thickening), lipid

assessment examinations (LDL ≥4.9 mmol/l) and liver enzyme assays [1, 9, 10]. (Table 17.2).

Tendinous xanthomas have been strongly associated with a high risk for cardiovascular disease. In a meta-analysis by Oosterveer et al. that included 22 relevant studies, it was shown that the presence of tendon xanthomas in patients with familial hypercholesterolaemia was associated with a 3.2 times higher risk of cardiovascular disease [11].

Eruptive Xanthomas

Eruptive xanthomas present as small (1 mm–5 mm) erythematous to yellow papules that arise on an erythematous base. The erythematous base is considered to be an inflammatory halo probably caused by the high triglyceride component of these lesions. They are usually located on the extensor areas of the arms and thighs, the buttocks, the inguinal and axillary folds, knees, hands and oral mucosa and their appearance is marked by a sudden eruption. (Fig. 17.3) Eruptive xanthomas can be pruritic and koebner phenomenon may be observed [1, 2, 5, 6].

The presence of eruptive xanthomas is strongly associated with severe hypertriglyceridemia (primary or secondary) and type I, IV and V hyperlipidemias. These patients may exhibit a lipaemic appearance on blood or serum levels and can present with triglyceride levels that exceed 3000 to 4000 mg/dl. Cardiovascular risk is moderately increased in these patients, mainly due to the association of eruptive xanthomas with diabetes. In addition, lipaemia retinalis is almost universaly present and is the result of the marked hypertriglyceridemia. (Fig. 17.4).

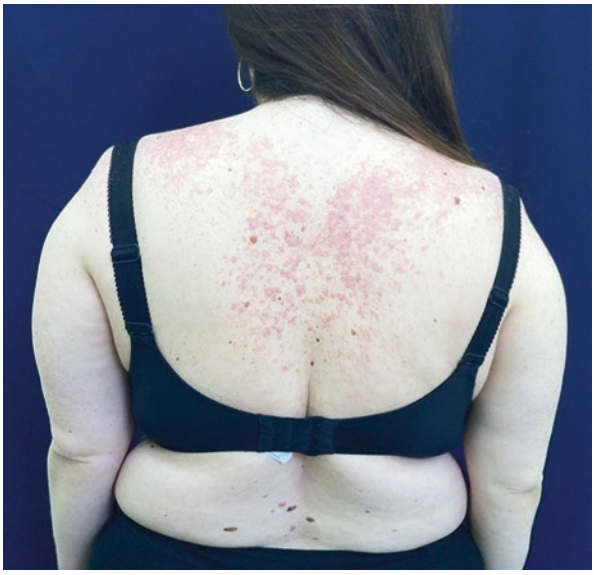

Fig.17.3 Eruptive xanthomas located on the back of a patient with type IV hyperlipidemia (Courtesy of Prof. Christina Antoniou, "Andreas Sygros Hospital of Dermatological and Venereal Diseases)

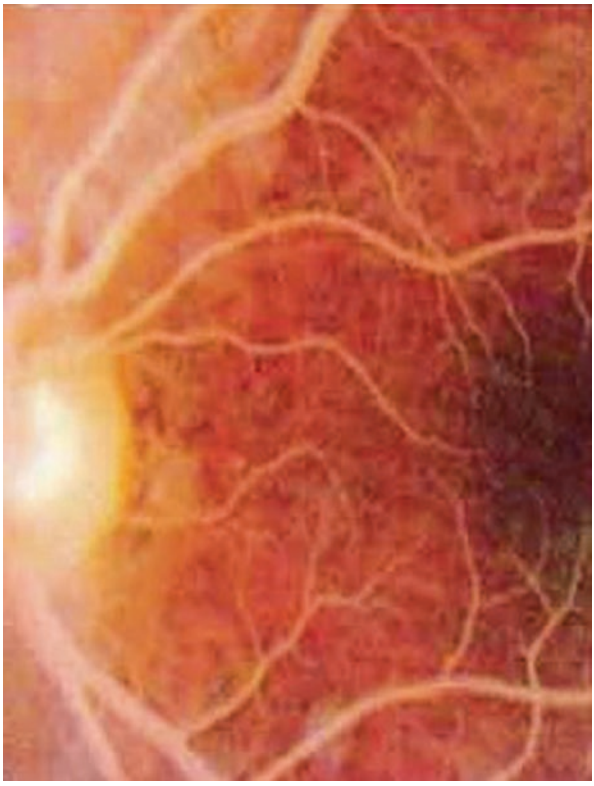

Fig.17.4 Image of a patient with lipaemia retinalis. (Courtesy of Iyengar S. S., et al. Journal of Clinical Lipidology, Vol. 12, no. 1, 56–109)

Dyslipidemic Plane (Planar) Xanthomas

Dyslipidemic plane xanthomas are divided into three categories: xanthelasmas, plane xanthomas and palmar xanthomas.

Xanthelasmas

Xanthelasmas are the most common type of xanthomas with a prevalence that has been reported to vary from 0.3% to 4.4% [6]. Females are more commonly affected than males [6]. Xanthelasmas appear as yellowish/orange plaques and affect mainly the periocular areas (upper eyelids and canthus). The lesions are usually symmetric and can be flat or nodular. In most cases they are soft when palpated but can also be solid and calcaneous [1, 12]. (Fig. 17.5) They usually appear between the fourth and sixth decades of life, however they can be observed in younger patients in the context of primary hyperlipidemias.

Although the presence of xanthelasma is indicative of hyperlipidemia, it has been reported that only half of the patients with xanthelasma actually have hyperlipidemia [5]. The clinical severity of the disorder falls under four categories: patients

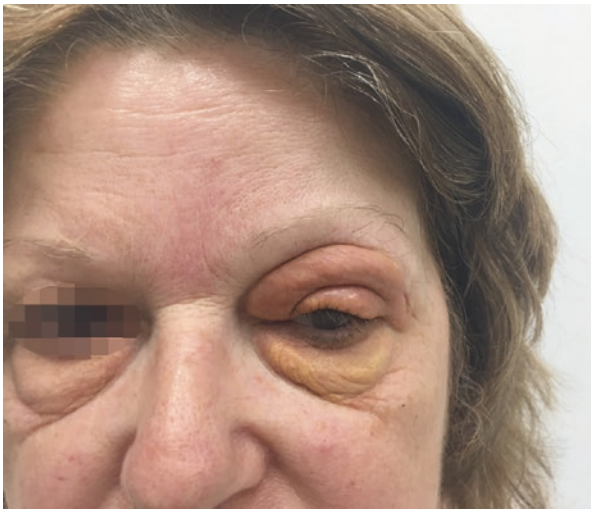

Fig.17.5 Patient with grade IV xanthomas on the right eye. The lesion is firm upon palpation. In patients with similar lesions normal lipid lowering therapy is usually not effective in the treatment of xanthelasmas and a surgical approach may be considered. (Courtesy of Dr. Dorothea Polydorou, "Andreas Sygros Hospital of Dermatological and Venereal Diseases)

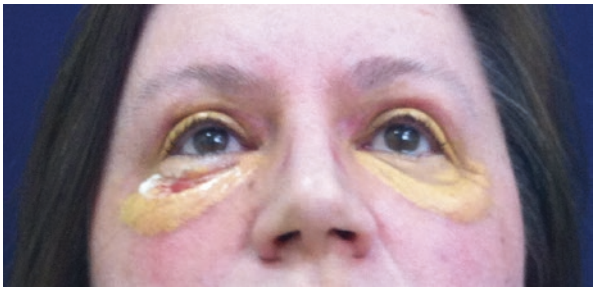

Fig.17.6 Patient with unilateral grade IV xanthomas. The lesions possess a characteristic yellowish colour, while ulceration is present in the area under the right eye. (Courtesy of Prof. Christina Antoniou, "Andreas Sygros Hospital of Dermatological and Venereal Diseases)

with lesions on the upper eyelids are Grade I, patients with lesions extending to the medial canthal area are Grade II, patients with lesions on the medial side of both upper and lower eyelids are Grade III and patients with diffuse involvement on medial and lateral sides of the upper and lower eyelids are Grade IV. (Fig. 17.6) The height and consistency of the lesions is also noted [13].

Although the data regarding cardiovascular risk in patients with xanthelasma are inconclusive, more recent studies report a possible correlation of the disorder with coronary artery disease [14]. More specifically, in a study that included 12.745 patients, it was reported that the hazard/odds ratios for myocardial infarction, for ischaemic cerebrovascular disease and for severe atherosclerosis was 1.47, 1.56 and 2.75 respectively, for patients with xanthelasma compared to the general population [14]. It is recommended that patients with xanthelasma be evaluated with a full lipoprotein profile and a liver enzyme assay in combination to a careful history and physical examination [1, 2, 9].

Plane Xanthomas

Plane xanthomas present as yellow to orange macules, patches or plaques and can be well circumscribed or diffuse. They usually appear on the axillae, neck, shoulders or buttocks. (Fig. 17.7) Interestingly, their distribution can be unique depending on the underlying disorder [1, 2]. For instance, xanthomas located on the interdigital or intertriginous spaces may be representative for homozygous familial hypercholesterolemia [15]. Plane xanthomas can also be associated with cholestasis and may occur as a complication of diseases such as biliary atresia or primary biliary cirrhosis. It must be mentioned that plane xanthomas may also present in normolipemic patients and can be associated with paraproteinemias (multiple myeloma, monoclonal gammopathy of undetermined significance) or lymphoproliferative diseases such as cutaneous lymphomas, B cell lymphomas, chronic lymphatic leukaemia and chronic myeloid leukaemia [6, 16].

Familial hypercholesterolaemia and type III hyperlipoproteinaemia should be excluded in patients with plane xanthomas. Recommended investigations include a full lipid profile, serum electrophoresis, and autoimmune screen. In normolipemic patients examinations to exclude various blood dyscrasias should also be performed (e.g. PET/CT, flow cytometry and histological examination of lymphatic nodes) [1, 6, 9].

Palmar Xanthomas

Palmar xanthomas can affect the palms, the flexural surfaces of fingers and the creases of the palms and soles *("Xanthomata striata palmaris")*. They usually appear as yellowish nodules or plaques. In the cases that the palmar creases are affected, they can present as orange/yellow lines that follow the palmar creases and may occasionally involve the flexor creases of the wrists as well [1, 2, 5, 6].

These lesions are commonly associated with familial dysbetalipoproteinemia (Type III dyslipidemia) and are considered by some authors as pathognomonic for the condition (homozygous) [2]. Other associations include secondary dyslipidemia

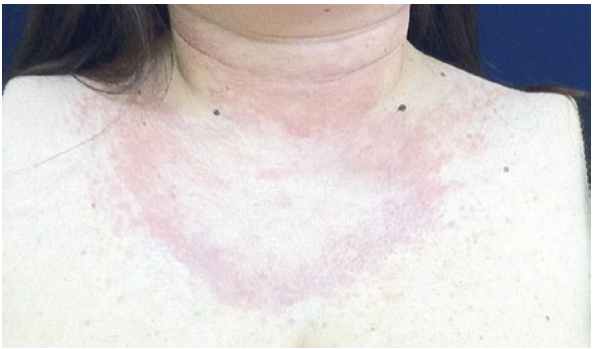

Fig.17.7 Plane xanthomas located on the neck of a female patient. (Courtesy of Prof. Christina Antoniou, "Andreas Sygros Hospital of Dermatological and Venereal Diseases)

as a result of multiple myeloma or primary biliary cirrhosis, diabetes mellitus and hypothyreosis [17]. It has been suggested that the presence of palmar xanthomas (in the context of type III dyslipidemia) may be associated with an increased risk for coronary artery atherosclerosis [1, 6].

Investigations for patients that present with palmar xanthomas should include a complete lipid profile, fasting glucose level, liver function tests and urine and electrolytes assays. In addition, thyroid hormone levels may be useful in uncovering a possible hypothyroidism. Specific testing for primary dyslipidemia such as ApoE genotyping, lipid electrophoresis or ultracentrifugation may be suggested in specific subsets of patients [1].

Overview of Primary Dyslipidemias

Hypelipoproteinemia Type I

Type I hyperlipoproteinemia is an extremely rare condition that is caused by a deficiency of lipoprotein lipase. Several mutations affecting the function of LPL have been associated with the condition. In general, individuals that exhibit homozygous defects in the LPL gene present with lipid serum alterations during infancy. However, gene penetrance may vary. Some authors suggest that there are monogenic and polygenic forms of the disorder, with the monogenic familial forms presenting during childhood and the polygenic forms typically requiring a "trigger", such as the presence of a secondary illness, for the expression of the disease [1–3, 5].

Typical cutaneous manifestations of Type I hyperlipoproteinemia include the appearance of eruptive xanthomas. Lipemia retinalis may also be present as a result of the extremely high levels of circulating triglycerides. Blood, serum and plasma from these patients can appear milky and if the samples are centrifuged a creamy top layer may be observed. Similarly to lipemia retinalis, this observation comes as a result of the extremely prominent chylomicronemia (hypertriglyceridemia) with triglyceride levels that usually exceed >1000 mg/dL. In some patients hypercholesterolemia may also be observed. The extremely high levels of triglycerides may be associated with an increased risk of pancreatitis (which can be life-threatening). Patients may also present with hepatosplenomegaly, dyspnea, lymphadenopathy and neurologic dysfunction [1, 2, 5].

Hyperlipoproteinemia Type II

Familial hypercholesterolemia (FH, hyperlipoproteinemia type IIa) is an autosomal dominant form of hypercholesterolemia caused by defects in the LDL receptor. Various mutations have been associated with the disorder; with the majority of patients exhibiting mutations on the LDL receptor gene (receptor synthesis, receptor transport, receptor clustering and internalization, receptor recycling etc. can be affected). Other mutations include familial defective apo B (mutations that affect

the ability of LDL to bind the LDL receptor) and mutations of *PCSK9* [1, 2, 5, 18, 19].

Typical cutaneous manifestations of FH include the appearance of tendon xanthomas, xanthelasmas (very rarely) and interdigital planar xanthomas (only in homozygous FH). Tendon xanthomas may first appear during childhood in patients with the homozygous type of the disease, while in patients with the heterozygous type of the disease their prevalence increases with age (e.g. 90% at age ≥ 40 years). Thickening of the Achilles tendon as well as xanthomas at the extensor tendons of the knees and hands are usually present, although it must be mentioned that clinically apparent (visible) tendon xanthomas tend to be rare and the diagnosis can be set with the use of an ultrasound examination. Other manifestations include the presence of corneal arcus (although not pathognomonic) and arthralgias. Patients usually present with high total cholesterol levels (> 300 mg/dL) and LDL cholesterol levels (> 200 mg/dL) while triglyceride levels may be normal [1, 2, 5, 20].

The condition has been closely associated with a high cardiovascular risk. Interestingly, although LDL receptor mutations are rare (1:500) it has been reported that they may be responsible for up to 5% of myocardial infarctions occurring in men younger than 55 years and women younger than 65 years. Patients that are homozygotes for the condition (1:1,000,000) present with total cholesterol levels ≥800 mg/dL and require liver transplantation to survive beyond childhood. Children and adolescents with this disease may develop aortic valve disease, although the cardiovascular risk of homozygotes may vary widely [1, 2, 7, 11].

Familial Combined Hyperlipidemia (FCH, hyperlipoproteinemia type IIb) is an autosomal dominant form of hyperlipidemia that has been reported to be present in up to 2% of the general population. Although the exact genetic defect is not yet known, it has been suggested that a secondary condition (Table 17.1) is required as a trigger for the expression of this disorder. Although the appearance of xanthomas is rare in patients with FCH, several types of xanthomas have been associated with it, including tendinous xanthomas, tuberoeruptive xanthomas, xanthelasmas, interdigital planar xanthomas and xanthomas located in intertriginous areas. Serum lipid profile includes elevated levels of triglycerides, elevated levels of LDL cholesterol or hypertriglyceridemia with low levels of HDL cholesterol [2, 5].

FCH has been associated with a high risk for cardiovascular disease and it has been suggested that it may account for up to 20% of cases of premature coronary artery disease [2].

Hyperlipoproteinemia Type III

Hyperlipoproteinemia type III is a rare condition that is associated with mutations in *ApoE*. ApoE is an apolipoprotein that mediates the binding of remnant apolipoproteins to the LDL receptor and the LDL receptor-related protein. Overall, there are three common variants of the apo E protein: E2, E3 and E4. Patients with two E2 alleles are considered to be at risk for dysbetalipoproteinemia. It must be mentioned that less than 10% of ApoE2 homozygous patients develop the condition,

indicating that another key factor (environmental or genetic) may be necessary for the expression of the disease. For instance, hypothyroidism has been associated with the condition. Interestingly, patients with one or more E4 alleles have been reported to be at risk for Alzheimer's disease [1, 2, 21].

Cutaneous manifestations of hyperlipoproteinemia type III include the appearance of palmar and tuberous xanthomas. In cases where marked hypertriglyceridemia is present, lipemia retinalis and eruptive xanthomas may also be observed. Patients with dysbetalipoproteinemia present with a very characteristic serum lipid profile. More specifically, increases in the levels of VLDL and IDL are observed, while the levels of LDL may be decreased. However, since the levels of VLDL and IDL are not routinely checked, it must be mentioned that the accumulation of VLDL and chylomicron remnants is usually expressed as a marked increase in both total cholesterol (300–600 mg/dL) and triglyceride levels (300–600 mg/dL) [2, 21].

Hyperlipoproteinemia type III is considered to be highly atherogenic, and is associated with an increased risk for coronary and peripheral artery disease. More specifically, up to 50% of patients with clinical and biochemical symptoms of the disease have been reported to present with premature cardiovascular disease. Other conditions associated with hyperlipoproteinemia type III include proteinuria or nephrotic syndrome (lipoprotein glomerulopathy) [1, 2].

Hyperlipoproteinemia Type IV

Hyperlipoproteinemia type IV is a rare autosomal dominant hypertriglyceridemia disorder with heterogeneous gene penetration. It is believed that the disorder is caused by abnormalities in the metabolism of VLDL such as overproduction of VLDL in the liver or decreased VLDL catabolism (or both). The appearance of eruptive xanthomas could be a cutaneous manifestation of hyperlipoproteinemia type IV. Patients and all affected family members present with isolated elevated triglycerides that are consistently elevated on repeat analyses. In general, patients with this disorder can also present with increased plasma VLDL, while plasma cholesterol may be normal. Glucose intolerance may also be observed in these patients [1, 2, 22].

Although the association of hyperlipoproteinemia type IV and the risk for cardiovascular disease is uncertain, special care should be taken for patients that present with comorbidities (e.g. diabetes mellitus type II) that could potentially aggravate the already present hypertriglyceridemia [2].

Hyperlipoproteinemia Type V

Hyperlipoproteinemia type V is a condition that has been attributed to both genetic and environmental causes, including LPL deficiency, disorders of triglyceride production (increased) or catabolism (decreased), obesity, diabetes, alcoholism, hypothyroidism and renal failure, among others. (Table 17.1) Overall, the interplay

between genetic and environmental factors has not yet been elucidated in the pathogenesis of this disorder. Patients with hyperlipoproteinemia type V may present with eruptive xanthomas. Similarly to type 1 hyperlipoproteinemia, blood serum may have a milky consistency. VLDL and chylomicron levels are elevated, while glucose intolerance and hyperuricemia may also be present. Patients with this type of hyperlipoproteinemia may present with increased cardiovascular risk, if chylomicron levels are very high. In addition, the condition may present with similar features to those of type I hyperlipoproteinemia, including high risk for pancreatitis and lipaemia retinalis [1, 23].

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