Xanthomas: clinical and pathophysiological relations

Ales Zak*, Miroslav Zeman, Adolf Slaby, Marek Vecka

Background. Xanthomas are well circumscribed lesions in the connective tissue of the skin, tendons or fasciae that predominantly consist of foam cells; these specific cells are formed from macrophages as a result of an excessive uptake of low density lipoprotein (LDL) particles and their oxidative modification.

Results. Until recently, xanthelasma was considered to be only a cosmetic lesion; however, according to the results of recent prospective studies it is connected with an increased cardiovascular risk and reduced average lifespan. Pathogenetic mechanisms involved in the development of xanthomas resemble early stages of atherogenesis. In clinical practice, xanthomas can signal various congenital or acquired dyslipidemias. The most prevalent form of xanthomas is xanthelasma palpebrarum. Tendinous and tuberous xanthomas are typical for autosomal dominant hypercholesterolemia, as well as for some rare conditions, such as cerebrotendinous xanthomatosis and familial β-sitosterolemia. In patients with familial hypercholesterolemia, the presence of tendinous xanthomas has been shown to be associated with a two to four times higher risk for cardiovascular disease. Eruptive xanthomas are skin manifestations of a severe hypertriglyceridemia and implicate an elevated risk for acute pancreatitis or type 2 diabetes mellitus. Xanthoma striatum palmare is pathognomonic for primary dysbetalipoproteinemia, whereas diffuse plane xanthomas are frequently associated with paraproteinemia and lymphoproliferative disorders.

Conclusion. Thorough familiarity with the clinical presentation of xanthomas helps in the diagnosis and follow-up of different forms of dyslipidemia. Moreover, xanthelasma palpebrarum, the most prevalent form of xanthomas, is connected with increased risk of atherothrombotic disease independently of conventional cardiovascular risk factors. To fully understand the pathogenesis, further experimental and clinical research is required.

Key words: xanthoma, dyslipidemia, oxidatively modified low density lipoproteins, foam cells, inflammation, cardiovascular risk

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INTRODUCTION

Xanthomas evolve as clusters of foam cells in the connective tissue of the skin, tendons and fasciae and occasionally in the peristome. Foam cells are formed from macrophages as a consequence of gradual intracellular accumulation of lipids taken up by specific receptors or by the mechanism of phagocytosis1. The clinical picture of xanthomas is variable, from soft to semisolid skin macules or papules to large nodules, usually of a yellow colour (Greek xanthos = yellow), due to the presence of carotene contained in lipids2.

In recent years, interest in xanthomas has been stimulated for several reasons. The mechanisms involved in the development of these pathological lesions appear to be analogous to those participating in early stages of atherosclerotic plaques. From the clinical point of view, xanthomas are often associated with inborn or acquired dyslipidemias and can be pathognomonic for some of them. Of inborn errors of lipid metabolism, autosomal dominant hypercholesterolemia caused by mutations in the genes encoding the LDL-receptor (LDLR), familial defective apolipoprotein B-100 with mutations in the gene APOB, and non-FH/non-FDB hypercholesterolemia with mutations in the gene PCSK9. Other types of xanthomas are helpful diagnostic markers of severe hypertriglyceridemia3 and primary dysbetalipoproteinemia4. Xanthomas can also call attention to the presence of some uncommon conditions, such as cerebrotendinous xanthomatosis caused by mutations in the sterol 27-hydroxylase gene (CYP27A) which induce a 27-hydroxylase deficiency, and familial β-sitosterolemia (phytosterolemia) with mutations in the genes encoding the specific sterol transporters ABCG5 and ABCG8 (ref.13). The development of xanthomas can signalise an elevated risk for serious metabolic and cardiovascular diseases, as well as for lymphoproliferative malignancies. The aim of this article is to give an overview of some recent research studies concerning xanthomas, mainly from the clinical point of view.

PATHOGENETIC MECHANISMS

The development of xanthomas starts by an increased local extravasation of lipids through the vascular wall to the interstitial space of connective tissues. Monocytes

1
and macrophages that have accumulated there take up lipid particles by specific receptors or by means of phagocytosis of LDL aggregates and lipid complexes with antibodies: In this way, foam cells can be formed. From the formal pathological viewpoint, the following factors take part: 1) high local concentrations of lipids in the connective tissue, 2) the presence of qualitatively different lipoproteins at normal plasma lipid concentrations, 3) increased extravasation of lipids (increased vascular permeability, increased local circulation, chronic inflammation), 4) lipid synthesis \textit{in situ} and their deposition in histiocytes, 5) dysfunction of the reverse cholesterol transport\textsuperscript{4,7}.

Native lipids (lipoproteins) do not induce foam cell formation. Intracellular LDL catabolism by LDL-receptors (apoB/E receptors) goes on slowly and cholesterol homeostasis is effectively regulated. Free cholesterol, released from LDL after its internalisation, inhibits its \textit{de novo} synthesis. Moreover, free cholesterol inhibits synthesis of LDL-receptors and thus suppresses LDL endocytosis by cells. On the other hand, chemically, mainly oxidatively modified LDL particles are taken up by macrophages much more rapidly. Macrophages express scavenger receptors that mediate binding and uptake of ox-LDL. As a result of the modified structure, their affinity to LDL-receptors is low and they mostly bind to scavenger receptors [SR-A, SR-B1, CD36, lectin-like oxidized LDL (ox-LDL) receptor-1 (LOX-1)]. Cholesterol caught by scavenger receptors does not activate the feed-back regulation of \textit{de novo} synthesis. When cholesterol uptake exceeds the capacity of cholesterol efflux, cholesterol accumulation results in droplet formation. The cholesterol efflux is mediated by the reverse cholesterol transport\textsuperscript{8,9}.

In the course of gradual lipid oxidation, minimally modified LDL (mm-LDL) is formed with chemical changes limited to the lipid component (conjugated di-

![Fig. 1. The reverse cholesterol transport.](image)

High concentration of cholesterol (CH) in macrophage (Ma) leads to its transformation into a foam cell. Homeostasis and equilibration of CH in Ma is ensured by several mechanisms facilitating externalisation (efflux) of CH from the cell through specific translocators or simple diffusion: (i) CH can be externalised by passive diffusion (governed by concentration gradient) to spherical HDL\textsubscript{3} particles; (ii) using ABCA1, CH is actively transported with phospholipids (PL) onto the complexes of PL and apoA1, giving rise to discoidal HDL (dHDL) particles; (iii) CH is actively transported through transporters ABCG1 and ABCG4 which bind to HDL\textsubscript{3} particles thus forming HDL\textsubscript{2}; SR-B1 receptors enable the transfer of cholesterol (with the help of concentration gradient) to the surface of spherical particles HDL\textsubscript{2} and HDL\textsubscript{3}. Free (nonesterified) cholesterol is esterified with LCAT. The HDL\textsubscript{2} particles are selectively depleted of cholesteryl esters after binding to liver SR B1 receptors. Expression of ABCA1, ABCG1, ABCG4 transporters is regulated by cellular concentration of oxysterols. These molecules are ligands for the liver X receptors (LXR) and after the heterodimerization with retinoic acid receptors (RXR), the oxysterol-LXR-RXR complex collocalizes with specific binding sites within the sequences of promoters of genes responsible for the expression of respective transporters.
Table 1. Xanthomas in various types of dyslipidemias.

<table>
<thead>
<tr>
<th>Gnosological unit</th>
<th>Molecular defect</th>
<th>Heritability</th>
<th>Prevalence</th>
<th>Type of xanthoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>LDLR</td>
<td>AD</td>
<td>1.500 (ht); 1.10³ (hm)</td>
<td>xanthoma tendineum,</td>
</tr>
<tr>
<td>FDB</td>
<td>APOB</td>
<td></td>
<td>1.800 (ht); 1.4 × 10⁴ (hm)</td>
<td>xanthoma tuberosum</td>
</tr>
<tr>
<td>FH3</td>
<td>PCSK9</td>
<td>AD</td>
<td>2.5 × 10⁶ (ht)</td>
<td>xanthelasma arcus lipoides corneae¹</td>
</tr>
<tr>
<td>β-sitosterolemia</td>
<td>ABCG5/ABCG8</td>
<td>AR</td>
<td>1.5 × 10⁴</td>
<td>xanthoma tendineum</td>
</tr>
<tr>
<td>CTX</td>
<td>CYP27A</td>
<td>AR</td>
<td>1.5 × 10⁴</td>
<td>xanthoma tuberosum</td>
</tr>
<tr>
<td>Type III HLP³</td>
<td>E2/E2</td>
<td>AR</td>
<td>1.5 × 10⁴</td>
<td>xanthoma striatum palmar eruptive (tuberoeruptive) xanthomas²</td>
</tr>
<tr>
<td>Familiar</td>
<td>LPL</td>
<td>AR</td>
<td>1.10⁴</td>
<td>xanthoma eruptivum</td>
</tr>
<tr>
<td>hyperchylomicronemia</td>
<td>APOC-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familiar HTG</td>
<td>?</td>
<td>AD</td>
<td>rare</td>
<td>xanthelasma palpebrarum</td>
</tr>
<tr>
<td>Severe HTG⁴</td>
<td>?</td>
<td>AD</td>
<td>1.10⁷</td>
<td>xanthoma eruptivum</td>
</tr>
<tr>
<td>PHC5</td>
<td>?</td>
<td>Polygenic</td>
<td>1.100–150</td>
<td>xanthelasma palpebrarum</td>
</tr>
<tr>
<td>FCH⁶</td>
<td>?</td>
<td>AD, polygenic</td>
<td>1.100</td>
<td>arcus lipoides corneae</td>
</tr>
</tbody>
</table>

FH - familial hypercholesterolemia; FDB - familial defect of apolipoprotein B-100; FH3 - non-FH/non-FDB hypercholesterolemia;
Type III HLP - hyperlipoproteinemia type III (primary/familial dys-β-lipoproteinemia); CTX - cerebrotendinous xanthomatosis; severe HTG - severe hypertriglyceridemia; PHC - polygenic hypercholesterolemia; LDLR - gene for LDL-receptor; APOB - gene for apolipoprotein B-100; PCSK9 - gene for proprotein convertase subtilisin/kexin 9; LPL - gene for lipoprotein lipase; APOC-II - gene for apolipoprotein C-II; AD - autosomal dominant; AR - autosomal recessive; hm - homozygous; ht - heterozygous; DLP - dyslipoproteinemia; FCH - familiar combined hyperlipidemia.

Explanations and remarks:
1) the presence of xanthelasma palpebrarum and arcus lipoides corneae is important for diagnosis of familial autosomal dominant hypercholesterolemias (FH, FDP, FH3) only in individuals under 20 years;
2) when relapse of the disease and worsening of dyslipidemia;
3) type III HLP - needs combination of homozygocity for apoE2/E2 (with autosomal recessive heritability) and other hyperlipidemia-forming factor (familiar DLP) or the presence of secondary DLP (decompensated DM, hypothyreosis, obesity, alcohol intake, pharmacologic dosage of estrogens);
4) onset of severe HTG (type V HLP with high VLDL and presence of chylomicrons)
5) PHC is caused by combination of exogenous and genetic factors (mutations/polymorphisms in apoE4, CETP, hepatic lipase, LPL, PCSK9, ABCG5/8, LCAT, CYP7A1);
6) FCH - it is supposed that the polymorphisms of apoB-100, LPL, apoE, cluster of apoCII/apoA-I/apoAIV take part in the pathophysiology of the disease; the defects/polymorphisms of apoCII and receptor for acylation stimulating protein (ASP) are also possible.
7) FH3 - some patients have mutations in the PCSK9 gene encoding neutral apoptosis regulated convertase 2 (NARC-1) which enhances the degradation of LDL-receptors. The mutations connected with upregulation of PCSK9 (gain of function) are linked to hypercholesterolemia.

These particles induce synthesis of the monocyte colony-stimulating factor (M-CSF) and promote differentiation of macrophages. After binding to glycosaminoglycans, oxidation of LDL particles continues, affecting both lipid and apolipoprotein components and giving rise to oxidised LDL (ox-LDL) characterised by a high demand for cholesterol. The defects/polymorphisms of PCSK9 and receptor for acylation stimulating protein (ASP) are also possible.

Moreover, the transport of lipid particles from the intracellular space to the blood stream depends on the functional integrity of the lymphatic circulation. Recent studies challenge the older view that macromolecules can passively enter the blind ends of lymphatic capillaries. A specially regulated uptake mechanism for transcytosis of HDL was demonstrated in lymphatic endothelial cells expressing scavenger receptors SR-B1 (ref.12).
phatic drainage and increased lipid accumulation in peripheral tissues13.

The relationship between oxidatively modified lipoproteins, reverse cholesterol transport and the development of xanthomas is supported by the results of clinical studies. In patients with familial hypercholesterolemia, the size of Achilles tendon xanthomas correlated positively with the titre of antibodies against oxidised LDL, negatively with the plasma concentration of HDL}(ref.19). The incidence of tendon xanthomas in patients with familial hypercholesterolemia was significantly associated with age, sex, plasma concentration of LDL cholesterol and arterial hypertension20. Disorders of reverse cholesterol transport and low plasma concentrations of HDL have been described even in normolipidemic subjects with Achilles tendon xanthomas21. In LDL particles incubated with xanthoma tissues, a considerable increase in malondialdehyde was proven (up to 15 times) simultaneously with a significant increase in the electrophoretic mobility of LDL (ref.17). Oxidative modification of native LDL that takes place in the lysosomes of macrophages is accelerated by ferritin, slowed down by high values of pH and some fat-soluble antioxidants18. In this context, it can be hypothesised that proton pump inhibitors may decrease the formation of xanthomas and the possibility of atherosclerotic lesions by increasing lysosomal pH and consequently by inhibiting lysosomal H+/K+-ATPase19.

In a group of patients with genetically diagnosed familial hypercholesterolemia, carriers of tendon xanthomas had significantly higher plasma concentrations of TNF, IL-6, IL-8 and higher activities of tryptase than those without xanthomas. Incubation of macrophages with oxidatively modified LDL particles induced higher inflammatory responses in the carriers of xanthomas. Genetic predisposition of macrophages to high inflammatory responses consequently takes part in the pathogenesis of xanthomas. Free tryptase (released from mast cells, possessing 44% homology with the serine protease) can degrade HDL, particles and decrease the efficiency of reverse cholesterol transport20.

CLASSIFICATION AND CLINICAL PICTURE OF XANTHOMAS

Xanthomas can be classified from several points of view. Detailed pathological as well as clinical schemes have been expounded with special attention to the requirements of dermatology and/or internal medicine (lipidology, haematology). For the purpose of a general review, the following groups seem useful: normolipidemic xanthomas (NX), hyperlipidaemic xanthomas (HX), and necrobiotic xanthogranuloma (NXG) (ref.22,23). Normolipidemic xanthomas mostly appear as diffuse flat skin lesions, while hyperlipidaemic types are polymorphous, often tuberous, and can affect either skin or tendons and joints. Xanthomas of both groups contain lipids (unesterified cholesterol, cholesteryl esters, and phospholipids) and collagen; histological examination reveals numerous foam cells.

Necrobiotic xanthogranuloma manifests itself as multiple skin deposits with tendency to ulcerations; histology shows Touton giant cells and necrotic foci17. Normolipidemic xanthomas and necrobiotic xanthogranuloma can be associated with monoclonal gammapathies and lymphoproliferative disorders22.

For clinical purposes, two groups have been proposed: I. papulonodular xanthomas: xanthoma eruptivum, tuberosum, tendineum and articulare. II. plane xanthomas: xanthoma diffusum planum, intertriginosum, striatum palmare, disseminatum and xanthelasma palpebrarum23. Common metabolic diseases associated with xanthomas are listed in Table 1.

Xanthoma eruptivum

Eruptive xanthoma is marked by a sudden eruption of yellowish skin papules 1-4 mm in diameter, encircled by an erythematous halo. Sites of predilection are buttocks, posterior thighs and elbows, as well as lumbar region. Eruptive xanthomas are causally associated with severe hypertriglyceridemia (TG >11.2 mmol/L) and can signalise the chylomicronic syndrome. The eruption usually appears within three weeks after the increase in plasma triglycerides.

Xanthoma tuberosum

Tuberosous xanthomas are flat or elevated yellowish nodules located in the dermis and subcutaneous tissue, from 3 millimetres to several centimetres in size. They mostly manifest themselves in the skin over joints (elbows, knees, joints of hands and feet), or on the buttocks. Tuberosous xanthomas can occur in patients with autosomal dominant hypercholesterolemia, familial dysbeta-lipoproteinemia, β-sitosterolemia, or cerebrotendinous xanthomatosis, rarely in cases of secondary dyslipoproteinemias, e.g. nephrotic syndrome or hypothyreosis6,24,25.

Xanthoma tendineum

Tendinous xanthomas can diffusely infiltrate tendons, tendon attachments, ligaments, fascia and peristeme. They form free movable hard nodules or spindles covered by normal skin. Predilection sites are Achilles tendons, tendons on the backs of the hands and fingers, as well as elbows, knees and heels. Frequently, they evolve subperiosteally in the tuberositas tibiae (patellar tendon attachment). Thickening of the Achilles tendon can be recognised and quantified by imaging techniques even before the growth of a tubercle. Tendinous xanthomas evolve in connection with the same types of dyslipidemia as tuberosous xanthomas appear, except for familial dysbeta-lipoproteinemia.

Xanthoma diffusum planum

Diffuse plane xanthomas form yellow to orange bands or plates in the dermis, usually affecting the skin of axillae, neck, shoulders or buttocks. This is a rare type of xanthoma, usually not connected with dyslipidemia. Its finding can warn of the presence of monoclonal gammapathy or lymphoproliferative disorders26.
Xanthoma striatum palmarum

Plane yellow to orange oblong structures in palmar flection lines (xanthoma striatum palmarum) or yellowish colouring (hue) of the flection lines (xanthochromia striata palmaries). This type of xanthoma is almost pathognomonic for primary dysbetalipoproteinemia. Sometimes it can be found in patients with newly diagnosed diabetes mellitus, hypothyroidism, or primary biliary cirrhosis. Patients with chronic cholestasis can also have various xanthomas on the neck and multiple xanthelasmas of the eyelids. All these efflorescences can disappear after restoration of patency of the biliary duct or after the development of hepatic failure.

Xanthoma disseminatum

A benign chronic cutaneous condition, that ranks among rare histiocytosis syndromes, preferentially affects males in childhood and adolescence. It is characterised by small orange-yellow, brown-red or blue-violet papules and nodules in the face (periorbitally, periorally) and intertriginous areas. Xanthoma disseminatum can also have extra-cutaneous manifestations, especially in the central nervous system, hypoxophis or the respiratory airways.

Xanthelasma palpebrarum

The most common type of cutaneous xanthoma presents itself as small yellowish, flat or minimally elevated plaques (Greek elasma = plate), soft or semisolid, located in the upper (in 70%) or lower eyelids. Infrequently it can spread in both lids and form circular skin lesions. In children and young adolescents, xanthelasma may signalise the presence of autosomal dominant hypercholesterolemia, together with arcus lipoides corneae, tuberous and tendinous xanthomas. Xanthelasma most commonly occurs in subjects over fifty years of age. About half of them have dyslipidemia (high LDL-C and TG, low HDL-C and apo A-1). The presence of xanthelasma palpebrarum should never be underestimated in clinical practice.

Xanthogranuloma necrobioticum

Necrobiotic xanthogranuloma is a rare progressive granulomatous disorder which manifests as multiple orange-yellow, brownish-red or blue-violet plaques and nodules. Predilection sites are periorbital regions but the condition can manifest anywhere on the head, neck and trunk; extra-cutaneous involvement is also known. Necrobiotic xanthogranuloma is usually associated with normolipidemia and can signalise monoclonal gammopathy or lymphoproliferative malignancies.

PREVALENCE OF XANTHOMAS

Exact epidemiological data on the prevalence of various types of xanthoma are lacking and textbooks in clinical lipidology give differing data. However the vast majority of cases (>95%) are xanthelasma palpebrarum, according to earlier studies, the prevalence was 0.3-1.1%, in women twice as high as in men and subjects older than 50 years prevailed. A recent prospective study found a 4.4% prevalence of xanthelasma in the population with an even distribution between men and women. Similar data were obtained from our out-patient lipid clinic. Xanthelasma palpebrarum was found in 10% of patients with isolated hypertriglyceridemia. In some pregnant women, xanthelasma evolves during the first trimester of pregnancy and after delivery mostly disappears.

Tendon xanthomas can be found in about 30% familial hypercholesterolemic patients with proven mutations in the LDLR gene. The prevalence increases from 7% in the third decennium to 40% in the sixth decennium. Similar prevalence data (20-50%) are given by other authors for clinically diagnosed patients with familial hypercholesterolemia. Abnormal texture and thickening of Achilles tendons were demonstrated in 68% of subjects with familial hypercholesterolemia.

Eruptive xanthomas are pathognomonic skin manifestations of severe hypertriglyceridemia (TG >11.2 mmol/L), a serious metabolic disorder with an estimated prevalence of 18 cases in 100 000 inhabitants. Eruptive xanthoma was retrospectively documented in 10% of patients with severe hypertriglyceridemia. According to older monographs, eruptive xanthomas can be found in up to 60% of patients with familial chylomicronemia; this disorder is very rare (1 : 1 million live births). In a group of patients with severe hypertriglyceridemia (characterized by TG >20 mmol/L), 8.5% exhibited eruptive xanthomas and 3% typical forms of xanthoma striatum palmarum.

PROGNOSTIC SIGNIFICANCE OF XANTHOMAS

Xanthelasma of the eyelids (xanthelasma palpebrarum), the most common type of xanthomas, has been until recently considered a benign cosmetic lesion. Prospective studies have however shown that its presence (unlike that of arcus senilis corneae alone) was significantly associated with a shorter life span, on average by 15 years. Individuals with xanthelasma have dyslipidemia age-dependently in 20-70% (ref.69). In a Danish prospective study (The Copenhagen City Heart Study) comprising almost 13 000 subjects followed up for more than 20 years, the presence of xanthelasma was associated with a significantly increased risk of myocardial infarction (by 48%), ischemic heart disease (by 38%), and ischemic disease of the lower extremities (by 70%), even after adjustment for some covariates, such as age, sex, diabetes mellitus, smoking, hypolipidemic treatment, and postmenopausal status. Another study confirmed a significant association of xanthelasma with the prevalence of non-alcoholic fatty liver disease, recently assumed to be independent risk factor for ischemic heart disease and with increased intima-media thickness.

Tendinous and tuberous xanthomas can signalise familial hypercholesterolemia and consequently the cardiovascular risk associated with elevated plasma concentrations of LDL cholesterol. According to a meta-analysis of 22 studies on patients with genetic diagnosis of familial hypercholesterolemia, the presence of tendon xanthomas was associated with a 3.2 times higher risk of cardiovascu-
lar disease\textsuperscript{46}. Similarly, the risk for premature cardiovascular disease was higher in genetically diagnosed patients with familial hypercholesterolemia and tendinous xanthomas, 2.3 times in men and 4.5 times in women, independently of the type of mutations in the \textit{LDLR} gene\textsuperscript{15}.

Tendinous and tuberous xanthomas can also be found in some rare metabolic disorders; elevated plasma concentrations of cholestanol (in cerebrotendinous xanthomatosis) or phytosterols (in familial β-sitosterolemia) bring about the deposition of these substances in connective tissues. Tendinous xanthomas can cause pain, especially if localised in the Achilles tendon (achillodynia). Occasionally, they can elicit a spontaneous rupture of the tendon\textsuperscript{14}.

Eruptive xanthomas call attention to severe hypertriglyceridaemia, especially in patients with newly diagnosed or decompensated diabetes mellitus; an elevated risk of acute pancreatitis occurs within the framework of the chylomicronemic syndrome\textsuperscript{35,36,41}.

Diffuse plane xanthomas can be associated with paraepinephrinemia (multiple myeloma, monoclonal gammopathy of undetermined significance) and with lymphoproliferative diseases (skin lymphomas, chronic lymphatic leukaemia, chronic myeloid leukaemia\textsuperscript{22,28}.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis of xanthomas is usually quite easy and based on the clinical picture. In unclear cases, skin biopsy for histopathological examination is indicated. Xanthomas associated with dyslipidemia and early atherosclerosis (xanthelasma, tendinous and tuberous xanthomas) require additional investigation. Personal and family histories can discover metabolic disorders and/or cardiovascular diseases, as well as the time of manifestation in the patient and his/her first degree relatives. The finding of xanthelasma should prompt a careful non-invasive examination of blood vessels (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).

If familial hypercholesterolemia is suspected, the examination should be completed by imaging of the Achilles tendon (ultrasonography, computed tomography, magnetic resonance imaging). The method of first choice is ultrasonography (US) performed 2 cms above the insertion into the calcaneum. US imaging is the less expensive noninvasive cross-sectional imaging method and depicts focal lesions that others fail to detect\textsuperscript{42}. For familial hypercholesterolemia, increased thickness of the tendon (threshold values for age and sex are tabulated) is typical as well as loss of regular fibrous texture and the presence of echolucent areas. Moreover, these findings can differentiate between familial hypercholesterolemia and other types of primary dyslipidemias, e.g. polygenic hypercholesterolemia, familial combined dyslipidemia\textsuperscript{34,42}.

For diagnosis of familial hypercholesterolemia, the following issues are to be considered: family history, clinical history of premature CHD, \textit{arcus senilis} corneae, very high LDL cholesterol (typically above the 75\textsuperscript{th} percentile of the healthy population) on repeated measurements, and/or a causative mutation detected by molecular genetics, e.g. \textit{LDLR}, \textit{APOB}, \textit{PCSK9} (proprotein convertase subtilisin-kexin subtype 9) mutations\textsuperscript{31}. Secondary causes of hyperlipidaemia must be excluded by determining that liver enzymes, renal function, and thyroid hormones are normal and that there is no hyperglycaemia or albuminuria.

To identify asymptomatic coronary atherosclerosis, exercise electrocardiography, echocardiography, coronary artery calcification scanning with the Electron Beam CT (EBCT) and CT angiography are recommended. Some guidelines underscore the value of noninvasive imaging of atherosclerosis in assessing and managing asymptomatic FH subjects\textsuperscript{44}.

The rare familial β-sitosterolemia manifests in childhood. Its clinical picture includes tendinous or tuberous xanthomas, premature atherosclerosis, and attacks of haemolysis, arthralgia or arthritis\textsuperscript{45}. Cerebrotendinous xanthogranulomatisosis is also rare (frequency 1: 50 000 live births); the signs and symptoms in infancy and early childhood are cholestasis, cataract and diarrhoea; in adults, paraparesis, ataxia, dysarthria, decreased cognitive functions and dementia can complete the clinical picture. The examination should be completed with genetic tests\textsuperscript{6,23}.

Plane diffuse xanthoma and necrobiosis xanthogranuloma require laboratory tests aimed at the presence of monoclonal gammopathy and lymphoproliferative disorders, including PET/CT, flow cytometry and histological examination of lymphatic nodes.

Dermatological and internal (incl. lipidologic) examination has to be performed in all patients with xanthomas. If indicated, specialists in other branches of medicine are consulted (cardiology, angiology, ophthalmology, immunology, rheumatology).

If possible, genetic testing should be done (mutations in \textit{LDLR} and \textit{APOB} genes, \textit{apoE} isoforms, \textit{CYP27}). In the case of suspected β-sitosterolemia, phytosterols are determined quantitatively by gas chromatography, possibly together with mass spectroscopy; plasma concentrations of β-sitosterol can be ten to sixty times higher and those of campesterol and stigmasterol three to six times higher than in normal subjects. The diagnosis can be confirmed by molecular genetic examination of \textit{ABCG5}/\textit{ABCG8} transporters (ref.\textsuperscript{35}). Laboratory examination in patients with cerebrotendinous xanthogranulomatisosis shows increased plasma concentrations of cholestanol (about six times) and high urinary excretion of bile alcohols.

**PREVENTION AND TREATMENT**

Prevention of xanthomas goes hand in hand with the management of the underlying disorders of lipid metabolism. Individuals with serious lipid disorders are indicated (according to the EBM principles) for statins as the first-choice therapy. Combined drug therapy, i.e. statin plus ezetimibe and/or bile acid resin is recommended in patients with severe hypercholesterolemia. In patients with
severe hypertriglyceridemia use of fibrates or niacin will reduce risk for acute pancreatitis. High intakes of omega-3 fatty acids are an alternative for treatment of severe hypertriglyceridemia.46

Hypolipidemic treatment can induce substantial regression of eruptive, palmar and tibial xanthomas, while decreasing plasma levels of atherogenic lipoproteins toward normal. In the early phase of tendinous xanthomas, regression can be expected after twelve months of the treatment.3,4,47. Massive xanthomas of the Achilles tendon can require surgical reconstruction48. Treatment of cerebrotendinous xanthomatosis consists in administration of chenodeoxycholic acid and statins5. Patients with β-sitosterolemia require dietary measures (restriction of phytosterols in food) and treatment with bile acid sequestrants (colestipol, cholestyramine) or cholesterol absorption inhibitors (ezetimibe). In the local treatment of disturbing forms of xanthelasma palpebrarum, laser ablation proved successful, as well as chemical ablation with trichloracetic acid49; surgical therapy is rarely indicated50.

CONCLUSION

Xanthomas are cutaneous conditions often associated with disorders of the lipid metabolism. Their evolution resembles early atherogenesis and consequently has been the object of intense biomedical research. From the clinical point of view, xanthomas cannot be considered as mere cosmetic lesions; they can signalise serious dyslipidemias, both common and rare, as well as an increased risk of metabolic, cardiovascular, and tumorous diseases. The present experience with the prevention and treatment of xanthomas has to be expanded and shared internationally.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES


