The clinical significance of cutaneous xanthomas

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During the past decade there have been significant new contributions to the field of lipid diseases. The combined utilization of serum lipid profiles and plasma lipoprotein patterns added new parameters for the identification and classification of this heterogeneous group of diseases. In view of these new developments it appears timely to review the clinical significance of cutaneous xanthomas found in association with these disorders.

Cutaneous xanthomas were first introduced in the medical field by Rayer in 1835, when he published a picture of xanthelasma. In 1851, Addison & Gull described various forms of xanthomas associated with liver disease and diabetes mellitus. Since then numerous reports appeared in the European literature, although it was thought that these tumours represented benign neoplasias or chronic inflammations. In 1908, Pick & Pinkus demonstrated that xanthomas may be accompanied by an increase in serum cholesterol. In 1938, Thannhauser & Magendanz proposed the first biochemical classification of the dyslipidoses, which was based on the patterns of serum lipids. Three groups were recognized: hypercholesterolaemias, hyperlipaemias (hypertriglyceridaemias) and normolipemias. More recently, Frederickson, Lees & Levy (1967) proposed a new classification of familial hyperlipidaemias based on the electrophoretic patterns of plasma lipoproteins. We should review xanthomatoses accompanying hyperlipidaemias as well as those associated with normal plasma lipid concentrations.

Classification of xanthomas

Cutaneous and tendon xanthomas may or may not be accompanied by an increase in plasma lipids. The following clinical forms have been recognized:

(a) Xanthelasmas: Yellowish plaques, well circumscribed, localized on or near the eyelids. They usually involve the inner canthus, although sometimes may be present in the outer canthus. Diffuse xanthelasma involving the upper and lower eyelid, sometimes extending beyond the eyelids, is usually associated with liver disease. The serum may be normal, hypercholesterolaemic or hypertriglyceridaemic.

(b) Plane xanthomas: are yellowish, indurated plaques, slightly raised, well circumscribed, which usually involve the neck, chest, palms and sometimes the trunk. The serum may be normal or hyperlipidaemic. Plane xanthomas are frequently associated with liver disease and myeloma.

(c) Tubercous xanthomas: consist of nodules and tumours, yellowish and indurated, with a tendency to coalesce, which are commonly localized on the elbows and knees. They are usually associated with hypercholesterolaemias or hypertriglyceridaemias, although on rare occasions the plasma lipids may be normal.

(d) Eruptive xanthomas: appear suddenly in crops and consist of multiple yellow-orange papules, raised, solid, sometimes surrounded by an erythematous halo. They have predilection for the extensor surface of the arms, legs and buttocks, although they may also involve the trunk and oral mucosa. Eruptive xanthomas are always associated with hypertriglyceridaemias.

(e) Tubero-eruptive xanthomas: are papules and nodules, red, of inflammatory appearance, with a tendency to coalesce. According to Fredrickson et al. (1967) this clinical type could be considered an intermediary form between tuberous and eruptive xanthomas. They are associated with hypertriglyceridaemias.

(f) Striated xanthomas: appear as yellowish streaks following the distribution of the creases of the palms and fingers. They may be associated with hypercholesterolaemias or hypertriglyceridaemias.

(g) Palmar xanthomas: consist of nodules and irregular plaques, yellowish, involving the palms and flexural surfaces of the fingers. They are seen in familial hyperlipoproteinaemias (Type III) and quite frequently in biliary atresia.

(h) Tendon xanthomas: are characterized by multiple, indurated nodules and tumours, which may be skin colour or yellowish, and frequently involve the elbows, knees, Achilles tendon and dorsum
of hands and feet. They are most frequently seen with hypercholesterolaemias, although they may accompany hypertriglyceridaemias. In rare instances the serum may be normolipaemic.

**Hyperlipidaemic dyslipidosis**

Lipid metabolic disorders associated with hyperlipidaemias may be familial or acquired. Cutaneous xanthomas may or may not be present, usually depending on the severity of the lipid abnormality. The classification of these disorders was based on the clinical picture and serum lipid profile, namely, the relationship of cholesterol and triglyceride levels. At present, a more widely used classification is that suggested by Frederickson et al. (1967) which is based on the patterns of plasma lipoproteins separated by means of paper electrophoresis. In order to interpret this classification, we should review briefly the chemistry and physiology of plasma lipoproteins.

In 1929, Macheboeuf demonstrated that blood lipids do not circulate freely, but are bound to proteins in the form of large molecular complexes. Further investigations showed that these lipoproteins are composed of varying proportions of triglycerides, cholesterol and phospholipids, bound to a protein. By means of analytical ultracentrifugation, it is possible to separate different groups of lipoproteins, since these molecules have different size and density and, thus, migrate in different medium densities, at varying measurable rates under a great centrifugal force. With this technique it was possible to separate the serum lipoproteins into four major groups: (a) chylomicra, (b) very low density lipoproteins, (c) low density lipoproteins and (d) alpha lipoproteins (Lindgren, Elliot & Gofman, 1951). The unit of flotation is known as the Svedberg unit (Sf). It is also known that plasma lipoproteins differ sufficiently, not only in density, but also in electrostatic charges, to permit their separation by electrophoretic techniques. Lees & Hatch (1963), utilizing paper electrophoresis with barbital buffer, pH 8-6, containing 1% albumin were able to separate four distinct lipoprotein fractions, which were labelled as chylomicra, beta, pre-beta and alpha lipoproteins. These fractions correlate well with those separated by the ultracentrifuge. These lipoproteins have been isolated and their chemical composition determined (Bragdon, Havel & Boyle, 1956). Their composition is as follows: **chylomicra** (triglycerides 81%; cholesterol 9%, phospholipids 7% and protein 2%); **beta** (triglycerides 9%; cholesterol 47%; phospholipids 23%; protein 21%); **pre-beta** (triglycerides 52%; cholesterol 22%; phospholipids 18% proteins 7%); **alpha** (triglycerides 8%; cholesterol 19%; phospholipids 26%; proteins 46%). For the purpose of this discussion one should remember the concentration of triglycerides and cholesterol in the chylomicra, pre-beta and beta fractions. (Fig. 1.) The alpha lipoproteins have little diagnostic significance in the classification of familial lipoproteinemias. Chylomicra and pre-beta lipoproteins contain large amounts of triglycerides. An increase in chylomicra and/or pre-beta lipoproteins will produce a creamy or cloudy fasting plasma. On the other hand, beta lipoproteins are characterized by their high content of cholesterol. The determination of plasma lipoprotein patterns is not only a diagnostic tool, but it may also give significant information as to the pathophysiologic mechanism of a particular lipid metabolic derangement. The increase in chylomicra is associated with hyperlipidaemias of exogenous origin. Following the ingestion of a fatty meal, there is an increase in plasma chylomicra. In a normal individual the chylomicra will be removed from the plasma in about 8–12 hr, by the action of an enzyme, lipoprotein lipase, which splits the triglycerides of the chylomicra into free fatty acids and glycerol. This enzyme is present in the wall of the blood vessel and can be released into the circulation by the administration of heparin. (Post-heparin lipolytic activity of PHLA.)

The pre-beta lipoproteins are synthesized in the liver from free fatty acids, triglycerides and carbohydrate and are the expression of an endogenous hyperlipidaemia: beta lipoproteins are more related to cholesterol metabolism, either of endogenous or exogenous origin. Moreover, it has been shown also that reduction or absence of certain plasma lipoproteins may have serious clinical implications. Two genetically determined disorders characterized by the absence or deficiency of beta and alpha-lipoproteins have already been recognized: abeta-lipoproteinaemia (Isselbacher et al., 1964) and familial alpha-lipoprotein deficiency (Tangier disease) (Fredrickson, 1964).

We should like to summarize the implications and advantages of the determination of plasma lipoprotein patterns:

(a) It is now known that the estimation of plasma lipid levels alone may not be enough to identify accurately a specific lipid metabolic disorder, since

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*Fig. 1. Electrophoresis of plasma lipoproteins and their triglycerides and cholesterol concentration.*
patients with similar plasma lipid levels may have different lipoprotein patterns.

(b) The determination of plasma lipoprotein patterns may not only have diagnostic significance, but also may reveal important information as to the possible mechanism of a lipid metabolic derangement.

(c) One of the major difficulties in analysing plasma lipoproteins was the complexity and expense of the ultracentrifugation techniques. Today the utilization of paper electrophoresis allows all medical centres to perform such studies. The simplicity of this technique not only makes the study of patients feasible, but also allows rapid screening of their relatives, when a genetic mode of transmission is suspected.

Classification

Paper electrophoresis of normal fasting plasma reveals the following picture: chylomicra are absent; there is an intense beta band which represents approximately 85% of the total lipoproteins; a faint pre-beta and an alpha band which represents about the remaining 15%.

On the basis of the abnormal plasma lipoprotein patterns, five types of familial hyperlipoproteinemia have been identified and designated with roman numerals from I to V. (Fig. 2.)

Type I: reveals a marked chylomicra band. The fasting plasma is turbid and following an overnight standing at 4°C it will show a creamy supernate (chylomicra) and a clear infranate. There is a marked increase in triglycerides, while the cholesterol is normal or slightly increased. The increase of chylomicra is indicative of an exogenous hyperlipidaemia.

Type II: shows an increase in the beta band. The fasting and overnight plasma will be clear. There is a marked increase in cholesterol, while the triglycerides may be normal or slightly increased.

Type III: reveals a 'broad beta' band. This band contains pre-beta lipoproteins and a fraction consisting of abnormal beta lipoproteins due to their high content of triglycerides. The abnormal beta, also known as 'floating beta', behave like very low density lipoprotein (D < 1·006). Normal beta lipoproteins are low density lipoproteins (D 1·006–1·063). The plasma reveals an increase in triglycerides and cholesterol with an approximate ratio of 1 : 1. The fasting and overnight plasma is usually turbid.

Type IV: shows an increase in the pre-beta fraction. There is an increase in triglycerides, while the cholesterol may be normal or increased. The fasting and overnight plasma is turbid. The increase of pre-beta lipoproteins is indicative of an endogenous hyperlipidaemia.

Type V: is characterized by the increase of chylomicra and pre-beta lipoproteins. There is a marked increase in triglycerides, while the cholesterol is usually moderately increased. The fasting plasma is turbid. The overnight plasma reveals a creamy supernate (chylomicra) and a turbid infranate (pre-beta). This type represents a mixed hyperlipidaemia (exogenous and endogenous).

Clinical description of familial hyperlipoproteinemia

Type I. This rare disorder, also known as Bürger-Grütz disease is transmitted as an autosomal recessive. The onset takes place during childhood, and the clinical picture consists of hepatosplenomegaly, crises of acute abdominal pain, sometimes due to
panreatitis and eruptive xanthomas. Cardiovascular disease appears to be rare. Glucose tolerance is normal. The plasma reveals an increase in triglycerides due to the marked increase in chylomicra. These patients have an impairment of the clearing mechanism of chylomicra following ingestion of a fatty meal, thus, representing an exogenous hyperlipidaemia. They have a deficiency in lipoprotein lipase and PHLA is low. They respond well to a low fat diet. None of the lipid-reducing drugs available is effective in this type.

Secondary Type I has been reported in systemic lupus erythematosus and lymphomas.

**Type II.** This disease is also designated as essential familial hypercholesterolaemia. It is transmitted as a simple Mendelian dominant, with the homozygous having the severe form. The onset takes place during childhood, although the clinical manifestations may not appear until middle age. There is a high incidence of tendon xanthomas and arcus cornea. Cutaneous xanthomas appear as xanthelasma and the tuberous form. There is accelerated atherosclerosis, particularly coronary heart disease. Glucose tolerance is usually normal. The plasma reveals an increase in cholesterol due to the increase in beta lipoproteins. In some cases there is a moderate increase in triglycerides and in those instances the pre-beta band may be increased. The mechanism of Type II is not well understood, although there appears to be a derangement in cholesterol metabolism, either an increase in synthesis, or an impairment in its catabolism. The treatment consists of a low-fat, low cholesterol diet, supplemented by polyunsaturated fats. The following drugs may prove to be helpful; clofibrate, 2 g daily; d-thyroxine, 4–10 mg daily; cholestyramine 12–32 g daily; nicotinic acid 3 g daily; oestrogens in females, conjugated equine oestrogens 1.25 mg three times a day, or ethinyl-estradiol 0.1–0.2 mg daily.

A Type II pattern may be seen in association with hypothryroidism, nephrotic syndrome, myeloma, liver disease and macroglobulinaemias.

**Type III.** This disorder was previously included in the idiopathic hyperlipaemias. The mode of transmission is not well-known, but it appears to be a recessive. The patients frequently present xanthomas of the palms (plaques or striae) and xanthoma tuberosum. Tendon xanthomas may be present, but they are not as common as in Type II. There is a high incidence in cardiovascular disease. The glucose tolerance test usually reveals latent or chemical diabetes. The plasma shows about an equal increase in triglycerides and cholesterol and a 'broad beta' by electrophoresis. The hyperlipidaemia in Type III is frequently carbohydrate-dependent. The treatment consists of weight control, low carbohydrate diet and clofibrate 500 mg q.i.d. Most patients respond well to this regime, which results in the normalization of plasma lipids and frequent disappearance of cutaneous xanthomas (Fleischmajer, 1969).

**Type IV.** This disorder was previously referred to as an idiopathic hyperlipaemia. It is transmitted as a simple Mendelian dominant and is the most common familial hyperlipoproteinemia. These patients are usually obese, and may complain of acute abdominal crises, sometimes due to pancreatitis. Xanthomas are of the eruptive form, although xanthelasma and tuberous xanthomas have been noted also. They frequently show lipaemia retinalis. Cardiovascular disease is not as frequent as in Type II or III. Glucose tolerance is abnormal and the hyperlipaemia is usually carbohydrate-dependent. The plasma reveals an increase in triglycerides, while the cholesterol may be increased or normal. The electrophoretogram reveals a dense pre-beta band. This is an endogenous hyperlipidaemia, although its basic mechanism is not well understood. It was suggested that the liver releases triglycerides at a high rate, so the subcutaneous tissue is unable to remove them from the circulation. It was also suggested that there may be a deficiency in the subcutaneous fat for the removal of circulating triglycerides. The treatment consists of weight control, restriction of carbohydrates, clofibrate and nicotinic acid. Hypoglycaemic agents may be of value.

Secondary Type IV patterns may be found with diabetes mellitus, pancreatitis, glycosgen storage disease, nephrotic syndrome, pregnancy, gestational hormones, myeloma, hypothyroidism, progeria and total lipoatrophy.

**Type V.** It is not known whether this disease represents an entity or may be a variant of Type IV. The disease is probably genetically determined, and the onset takes place during early adulthood. The clinical picture consists of obesity, hepatospleno-megaly, abdominal pain and lipaemia retinalis. Xanthomas are of the eruptive type. Cardiovascular disease does not appear to be frequent among patients or relatives. The glucose tolerance test is usually abnormal. The plasma shows an increase in triglycerides with normal or elevated cholesterol. Plasma lipoprotein electrophoresis reveals an increase in both chylomicra and pre-beta fractions. This disorder represents a mixed hyperlipidaemia, which is carbohydrate and fat-sensitive. PHLA may be low or normal. The treatment consists of weight control, diet low in carbohydrates and fats, high in protein, clofibrate and nicotinic acid. Hypoglycaemic agents may be of help.

Secondary Type V was noted with insulin dependent diabetes mellitus, pancreatitis and alcoholism.
Clinical significance of cutaneous xanthomas

Normolipemic dyslipidosis

This refers to a group of disorders, where lipid storage may occur in the reticuloendothelial system (RES) or tendons without a concomitant increase in plasma lipid levels.

(a) Xanthelasma. About 65% of adult patients with xanthelasma may show normal plasma lipid levels. In these cases the presence of xanthelasma has little clinical significance, and just represents a local deposition of fats within the cells of the RES. On the other hand, the presence of xanthelasma in teenagers or young adults is frequently the expression of a systemic derangement in lipid metabolism. Xanthelasma can be removed by topical applications of trichloracetic acid, although sometimes they may recur.

(b) Normolipemic plane xanthomas. This disorder usually affects adults, although it has been noted in children (Fleischmajer, Hyman & Weidman, 1964). It manifests itself by the appearance of macules and plaques, well circumscribed, yellowish or brownish, indurated, slightly raised, which may involve the head, eyelids, neck, chest, trunk and extremities (Altman & Winkelman, 1963). Plasma lipid levels are usually normal. Recently, a high incidence of myeloma and leukemia have been noted in association with plane xanthomas (Lynch & Winkelman, 1966). However, in those patients without associated systemic disease, the course appears to be chronic and benign.

(c) Juvenile xanthogranuloma. This disease was previously referred to as nevoxanthoendothelioma. The onset usually takes place during the first 6 months of life. There may be single or multiple lesions, with predilection for the scalp, face, ears, neck and shoulders. The lesions are papules and nodules, indurated, dome-shaped, yellow-orange or brownish and may remain discrete or become confluent. Plasma lipids and lipoprotein patterns are within normal limits. Spontaneous resolution of the lesions takes place 1–4 years after the onset (Fleischmajer, 1960). There have been isolated reports of juvenile xanthogranuloma affecting other organs than the skin, namely, eyes (iris and epibulbar conjunctiva), lung, testicle, tongue, vulva, neck, tissues and pericardium (Webster, Reister & Harman, 1966). In these cases the prognosis remains good since the lesions usually disappear spontaneously.

(d) Xanthoma disseminatum. This is a rare non-hereditary disease which may affect children or adults. The skin and mucous membranes are affected by xanthomatos granulomas. The skin lesions have predilection for the flexural surfaces, namely, eyelids, side of the neck, axillae, groins, and sometimes the trunk. The lesions are sessile or pedunculated nodules, yellowish or mahogany in colour, which have a tendency to coalesce forming large plaques. Yellowish infiltration is also noted in the oral mucosa, pharynx, larynx and bronchi. Some patients have a husky voice and may complain of respiratory distress which sometimes requires an emergency tracheotomy. The initial manifestation may be diabetes insipidus, although it is usually mild and may disappear spontaneously. The histology of the skin lesions is that of a typical xanthoma. Plasma lipid levels are usually within normal limits. Xanthoma disseminatum runs a chronic but benign course, except for isolated instances where it is found in association with histiocytosis X.

(e) Hereditary tuberous and tendinous xanthomas. This is a rare, hereditary disease, probably transmitted as a recessive, characterized by the appearance of tuberous and tendinous xanthomas accompanied by normal plasma lipids. Lipoprotein patterns are normal. One case reported by Harlan & Still (1968) had nodular densities in the lung which resulted in impairment of gaseous exchange. The histology reveals the typical picture seen in xanthomas. It is believed that this disorder represents a hereditary reticuloendotheliosis.

(f) Histiocytosis X. The term histiocytosis X was introduced by Lichtenstein (1953) as a common denominator to include Letterer–Siwe disease, Hand–Schüller–Christian disease and eosinophilic granuloma. These disorders represent hyperplastic processes of the reticuloendothelial system, with secondary xanthomatization resulting in the formation of granulomas in various organs, namely, lungs, bones, lymphnodes, etc. Letterer–Siwe disease, the acute or subacute form of histiocytosis X affects children, and its clinical picture consists of hepatosplenomegaly, lymphadenopathy, respiratory distress due to granulomatous infiltration of the lungs, terminating in fibrosis, bone destructive lesions, abdominal distension and diarrhoea. A variety of skin lesions may accompany Letterer–Siwe disease and may be summarized as follows: (a) erythematous-crusted lesions simulating seborrhoeic dermatitis, (2) petechiae and ecchymoses, (3) papular xanthomas, (4) bullae and vesiculopustular dermatitis, (5) vulvar lesions, consisting of ulcerating granulomas and (6) palmar and plantar keratoderma with purpura (Fleischmajer, 1965).

Hand–Schüller–Christian disease is characterized by the classic triad of bone defects, diabetes insipidus and exophthalmos. In very rare instances, xanthelasma and xanthoma disseminatum have been observed.

Eosinophilic granuloma is considered the mono-symptomatic form of histiocytosis X and usually affects lungs or bone. Most of the reported cases of eosinophilic granuloma of the skin had diabetes insipidus or bone lesions and should be considered
as instances of Hand–Schüller–Christian disease. There were a few reports where only the skin was involved and the lesions consisted of indurated papules and ulcerated granulomas.

(g) Lipoid dermatoa rthritis: This is a rare non-familial disease which usually affects Caucasian females and is characterized by the appearance of papular-nodular lesions in the skin and subcutaneous tissue, and a destructive arthritis.

Skin manifestations are always present and consist of papules, nodules and tumours, which are firm, usually confluent, and may range in colour from red-brown to yellow, to flesh coloured. (Orkin et al., 1964.) The areas most frequently involved are the hands, forearms, elbows, scalp, forehead, nose, ears, neck and upper trunk. About 40% of the patients have xanthelasma. (Barrow et al., 1967.)

The mucosae are frequently involved and papules and nodules have been noted on the lips, tongue, sclera, mouth, gums, pharynx and larynx.

The arthritis is usually symmetric, affects several joints and simulates rheumatoid arthritis. The joints more frequently involved are the knees, fingers, hands, shoulders, wrists, elbows, ankles, hips, vertebral, feet and temporomandibular. (Orkin et al., 1967.) Symptoms consist of pain, stiffness, swelling and decreased range of motion. This process is progressive and eventually results in incapacitating deformities. Shortening of the fingers due to the destruction of the interphalangeal joints and sub-articular bone results in ‘opera glass’ deformities. Other symptoms described refer to loss of weight, pruritus, weakness, fever, tendon sheath swelling and paresthesiae. The most important laboratory findings are elevated erythrocyte sedimentation rate and anaemia. Hypercholesterolaemia was present in 39% of the cases reported. (Barrow et al., 1967.)

The histology reveals lipid-laden histiocytes and multinucleated giant cells ranging in size from 25 to 100 μ in diameter. The cytoplasm is granular or vacuolated and stains positively with oil red O and Sudan black B. The periodic-acid-Schiff reaction is usually positive, suggesting the presence of mucin. Recently, Barrow et al. (1967) performed biochemical analyses and found that the involved tissues contained 16% lipid, wet weight, consisting of tri-glycerides (51%), cholesterol esters (25%), free cholesterol (2%) and phospholipids (22%). These authors believe that lipid dermatoa rthritis is properly classified as a granulomatous lipid-storage disease.

(h) Inflammatory xanthoma. Secondary xanthomatization has been reported in scars from herpes zoster, gummas, laparatomies and following curettage and desiccation of basal cell epitheliomas (Fleischmajer et al., 1964). It has also been noted in discoid lupus erythematosus (Netherton, 1945). A similar process has been described in chronic osteomyelitis, chronically inflamed gall bladder, chronic salpingitis, and walls of old abscesses (Thannhauser, 1950). Since many of these cases had normal plasma lipids, it is likely that the xanthomatization was a local process resulting from intracellular synthesis or phagocytosis of lipids by cells of the reticuloendothelial system.

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