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Case Report

Clinical Investigator

Xanthoma disseminatum: a rare normolipemic xanthomatosis*

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Summary. Xanthoma disseminatum (XD) is a rare benign histiocytic disorder with extensive cutaneous and mucous membrane xanthomas in normolipemic patients. We describe the 9-year course of a 25-year-old white man who presented with multiple brownish-reddish papulous skin tumors that developed over 3 years and remained relatively constant, with spontaneous regression and progression of individual lesions since. In addition, there was asymptomatic xanthomatous infiltration of the epipharnyx and symptomatic infiltration of the synovial membrane of the left knee joint leading to restriction of movement. Histologically, the corium was infiltrated by large lipid-storing macrophages, polynucleated histiocytic giant cells of the Touton and the foreign body type. Immunhistochemically, the lipid-storing cells could be classified as macrophage/monocyte derived cells distinctly different from Langerhans' cells without proliferative activity. The clinical picture and course as well as laboratory findings indicating normolipidemia made it possible to differentiate XD from other normolipemic xanthomatosis, especially juvenile xanthogranuloma, eruptive histiocytoma, and histiocytosis X. The etiology of XD is still unknown. It is possible to differentiate xanthoma disseminatum from malignant histiocytosis X by the clinical picture and immunhistochemical studies. Thus it is no longer justified to administer cytostatic treatment for this disorder.

Key words: Xanthoma disseminatum – Normolipemic xanthomatosis – Normocholesterolemic xanthomatosis – Non-X histiocytosis – Immunhistochemistry

Xanthoma disseminatum (XD) [2, 19, 29, 33, 36, 41] is a rare benign histiocytic disorder characterized by widespread cutaneous xanthomas in normolipemic patients. Xanthomatous involvement of the pituitary gland leading to diabetes insipidus [2, 28], ocular lesions [4, 17], and involvement of the upper respiratory tract [2, 4, 27, 35, 36], skeletal system and muscles [6, 15, 35], and abdominal organs [2] has been observed. Here we report the 9-year course of a patient with this disorder and the evaluation for systemic manifestation of the disease as well as histological and immunhistological studies.

Abbreviation: XD = xanthoma disseminatum

* Dedicated to Prof. Dr. N. Zöllner on the occasion of his 70th birthday

Case report

Clinical findings and course

This 25-year-old white man was first examined at the age of 16 years when he developed yellowish-red, painless, nonitching, pinhead-sized papules in both axillae. Over the next 3 years the lesions spread to the lateral portions of the trunk and neck, flexure surfaces of the elbows and knees, perioral and periorbital regions of the face, groin, perineum, anus, and scrotum. The papules were concentrated around the flexural and intertriginous areas and preferred to follow Langer's lines. The size of individual lesions varied between 1 mm and 2 cm. In the axillae and at the flexural surfaces of both elbows the lesions merged to the size of up to 3 cm and around the anus and at the perineum to 5×8 cm. The lesions formed nodules which rose as much as 1 cm above the skin level. On palpation these lesions were solid but compressable and not painful (Fig. 1). The skin lesions, particularly those in the flexural areas, showed phases of regressive changes up to complete disappearance as well as phases of extension and growth. Phases of growth were heralded by a feeling of tension and itching within the lesions. Over the past 5 years lesions had not spread to any other region of the body.

Three years after the first skin changes appeared the patient became extremely sensitive to blinding. Corneal infiltrations commencing at the upper margin and extending toward the center of the cornea were visible. Within 1 year the right cornea became nearly completely infiltrated; the left eye followed 6 months later. Vision became re-

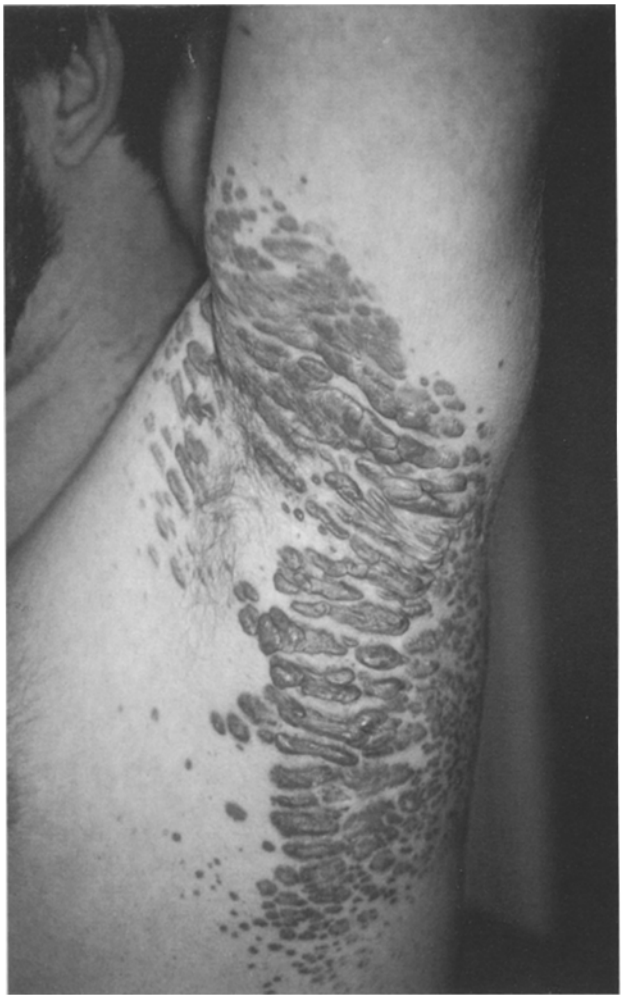

Fig. 1. The skin of the left axilla is covered with numerous, yellowish-red, painless, firm nodules measuring 1 mm–2 cm representing typical lesions of xanthoma disseminatum

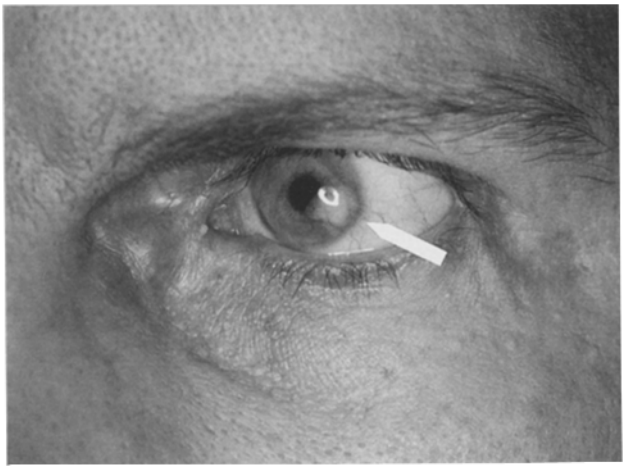

Fig. 2. The left cornea is infiltrated by a yellowish, vascularized xanthoma leading to blinding sensitiveness and reduced visus

stricted up to hand movements. Lamellar keratoplastics was performed on both eyes, which markedly improved vision but did not lead to restitution. Histologically, corneal infiltrations consisted of diffuse agglomerations of histiocytic cells, which were concentrated just below the Bowman membrane and were accompanied by a focal destruction of this membrane. Three years after the first transplantation the right cornea had to be retransplanted due to recurrent subtotal infiltrations. Currently the patient again complained of glimmer vision, double pictures, and blinding sensitiveness which had slightly progressed since the last operation. Infiltrations of both corneae were visible with the naked eye (Fig. 2). Visus was reduced to 0.25 and 0.50 in the right and left eyes, respectively.

Three years after the disease began the patient noticed a painfull swelling of his left knee, reduction of movement, and recurrent locking and giving way. Arthroscopically, the inner sides of the joint capsule at both flanks of the condyles appeared covered with atheromatous plaques. A large synovial tuft was trapped at the posterior horn of the lateral meniscus and was removed. As symptoms persisted, a synovectomy of the left knee joint was performed 1 year later. Intraoperative evaluation revealed a markedly thickened synovia which extended beyond the cartilage-bone border at some areas. Other joint structures were intact. Histologically, the synovial membrane appeared structured as villi. Within the tuft stroma lymphoid infiltrates with multinucleated giant cells and isolated foam cells were seen, consistent with a xanthomatous granulomatous reaction of the synovial membrane. Movement of the left knee is still restricted to 0-0-105° (right knee −10-0-125°).

Most recently the patient was admitted to the hospital because of increasing pain at the perineum and around the anus while sitting, due to growing xanthomas in this area. The patient reported drinking a volume of 2–3 l a day with no changes in recent years. He was not urged to drink at night and had no nycturia. On the occasion of this recent admission for surgical excision of the most painful xanthomas around the anus and the perineum, a complete evaluation for systemic manifestations of the disease was performed. In addition to the above findings, an ENT examination demonstrated submucous yellowish pads in the whole meso- and hypopharynx and in the laryngeal mucosa.

Laboratory findings

Serum cholesterol was 252 mg/dl, with a low-density lipoprotein cholesterol of 184 mg/dl and a high-density lipoprotein cholesterol of 41 mg/dl on one

occasion; otherwise the values were within normal limits, with a range from 184 to 225 mg/dl. Urine osmolarity was 1012, increasing to 1020 after a 12-h period of thirst. All routine laboratory examinations were within the normal range.

Technical examinations

Ultrasound examination of the left knee revealed a small effusion; the right knee was normal. Ultrasound examinations of the abdomen and the carotid arteries yielded normal results. A chest roentgenogram demonstrated the axillary skin changes, but was otherwise normal. Contrast computed tomography scans of the thorax were normal. Abdominal contrast computed tomography scans showed a slightly enlarged spleen, but was otherwise normal. Abdominal magnetic resonance imaging showed no evidence of focal lesions within the abdominal organs. Magnetic resonance scans of the brain and sella region were normal. A technetium bone scan showed an isotopic hot-spot activity at the left knee joint consistent with the xanthomatous involvement of this joint and slightly increased activities at both sternoclavicular joints and at the left big toe consistent with degenerative changes.

Histological examinations

Skin specimens taken at the perineum, anus, and at the elbow yielded similar histopathological findings. The epidermis appeared normal with a reactive hyperkeratosis at some areas. Below a narrow and slightly fibrosized subepidermal layer in the stratum papillare the corium was infiltrated by large pale eosinophilic cells with polymorphic hyperchromatic nuclei, representing lipid storing macrophages. Between many polynucleated histiocytic giant cells of the Touton type, single large cells of the foreign body type were seen. There were no epitheloid granulomas with Langerhans' giant cells. The accumulation of cells was interlaced with irregularly twisted bundels of fibers and new vessels.

Immunoperoxidase staining of frozen sections revealed that the large lipid storing cells reacted with Ki-M1P and PG-M1 antibodies as small mononucleated macrophage/monocyte-derived cells and showed a strong reactivity with the antibody CR3.43 against HLA-DR. There was no reactivity with antibodies against the B-cell marker L26, T-cell marker beta-F1, epithelium cell marker MNF116, lymphatic cell marker CD45/LC.DAK0, Langerhans' cell marker S-100, or the follicular dendrite cell marker CD21. The proliferation-associated antigens KI-67 and PC10 were negative.

Discussion

Hyperlipoproteinemias, especially hypercholesterolemia, often result in the deposition of cholesterol in various tissues, which among other reactions leads to xanthoma formation. This clinical sign is even used as a diagnostic tool as various types of xanthoma represent types of primary hyperlipoproteinemias [9, 18, 26, 31]. The extent of xanthomatosis in these disorders correlates with the degree of elevation of plasma lipoprotein and cholesterol levels, although a massive cutaneous xanthomatosis is a rare event in daily clinical practice.

On the other hand, normolipemic and normocholesterolemic patients have been described who presented with tuberous, papular or tendinous xanthomas. It is obvious that additional factors besides serum lipid levels are involved in xanthoma formation in normolipemic patients. Parker [30] suggested a classification of normolipemic xanthomatosis based on three supposed pathogenetic processes responsible for the accumulation of lipids in histiocytic foam cells in the dermis and tendons. The first group includes disorders with accumulation of unusual lipids other than cholesterol within lipoproteins such as cholestanol in cerebrotendinous xanthomatosis or plant sterols in phytosterolemia [5] and with altered apolipoprotein content and structure of lipoproteins such as normocholesterolemic dysbetalipoproteinemia [1] or hyperapobetalipoproteinemia [25]. In the second type of condition diffuse planar xanthomas over face and upper trunk may arise in patients with lymphoproliferative diseases such as multiple myeloma, Waldenström's macroglobulinemia, cryoglobulinemia, benign monoclonal gammopathy, and lymphomas. Xanthoma formation may be due to a hypothesized cutaneous lymphoreticular hyperplasia with secondary xanthomatization [37] or to paraproteins interacting with lipoprotein receptors or blocking enzymes [11]. The third group comprises patients with neither abnormal lipoprotein structure and compostion nor underlying systemic disease, where supposed local abnormalities in the dermal tissue may play a role. This includes xanthomas following distinct skin diseases such as erythroderma and epidermolysis bullosa dystrophica as well as hereditary and non-hereditary tendinous and tuberous xanthomas without lipoprotein abnormalities [14, 21], papulonodular diffusely distributed cutaneous xanthoma [34, 38], generalized eruptive xanthomas [3], juvenile xanthogranuloma [39], and XD [2, 19, 29, 33, 36, 41]. Due to similiar clinical course and ultrastructural findings in the latter three disorders, generalized eruptive xan-

Table 1. Clinical characteristics of xanthoma disseminatum

Demographic data		
Onset of the disease before the age of 25 years	36/63 patients	
Range of onset of the disease	1–70 years	
Sex ratio men:women	45:18	
Clinical symptoms	**Number of patients**	**References**
Mahagony-colored papules and plaques preferentially distributed on flexural surfaces and following Langer's lines	All	
Diabetes insipidus	24/26	[2, 17, 22, 23, 28, 32, 36]
Mucous membrane involvement of the upper respiratory tract	25/27	[2, 4, 7, 23, 27, 35]
Mucous membrane involvement of the lower respiratory tract	8	[2, 15, 27, 35]
Fatal complications of lower respiratory tract involvement	4	[2, 15]
Corneal and/or conjunctival lesions	13	[2, 4, 8, 17]
Involvement of intra-abdominal organs found on necropsy	5/8	[2, 24, 36]
Osteolytic bone lesions	4	[6, 27, 35]
Muscle involvement	1	[15]
Synovial membrane involvement	1	Described here

thoma, juvenile xanthogranuloma, and XD may be seen as variants of one disease and by some authors are summarized as non-X histiocytosis [8, 10, 12, 16]. Differential diagnosis of XD therefore includes the above-mentioned juvenile xanthogranuloma and eruptive histiocytoma as well as histiocytosis X, especially when associated with diabetes insipidus.

The patient presented here showed the typical clinical appearance and course of XD (Table 1). In addition to already known sites of manifestation, the patient described is the first case of xanthomatous involvement of the synovial membrane of a joint leading to a painful knee swelling, reduction in movement, and recurrent locking and giving way. Bones or muscles were spared [6, 15, 27, 35]. Blobstein et al. [6] described a patient with multiple bone lesions and recurrent swelling of joints near osteolytic spots where a synovial membrane biopsy showed a nonspecific exudative and proliferative synovitis with a synovial giant cell reaction but without foam cells or granulomas.

Light microscopy findings in XD, as in this patient, are not specific for this disorder. Similar findings can be seen in normolipemic juvenile xanthogranuloma and eruptive histiocytoma but also in hyperlipoproteinemia types IV and V with xanthomatosis and even in histiocytosis X [7, 8, 12]. Therefore it is not helpful for the differential diagnosis. However, immunhistochemistry of the lipid storing cells is diagnostic. The S-100 antigen, which is positive in Langerhans' cells of histiocytosis X [40], showed no staining in the lipid-storing polynucleated histiocytic giant cells in our patient's xanthomas. The origin of the lipid-storing polynucleated cells are blood monocytes and not dermal Langerhans' cells since they reacted as small macrophage/monocyte-derived cells. The lipid-storing cells also showed no proliferative activity as the proliferation associated antigens KI-67 and PC10 were negative. This could be due to the fact that XD is not a malignant proliferative disorder. As the patient noted phases in the growth of his xanthomas, it might be interesting to study xanthomas in this situation, as the xanthomas which were biopsied did not seem to grow. Our immunhistochemical findings were consistent with previous observations in three other patients [10, 17, 35].

Reported cases of XD usually follow a chronic course which lasts for years or decades [2, 7, 10, 22, 24]. Skin lesions usually reach a peak of severity after 1–2 years. In some cases they may be self-healing, with spontaneous resolution over a period lasting as long as 40 years; in others they remain stationary or progress only slowly. Although XD typically follows a benign course, more serious morbidity and even mortality may occur. This can be caused by airway obstruction due to glottic or bronchial involvement by xanthomas [27] or by progressive central nervous system involvement which leads to seizures, strabismus, cerebellar ataxia, and even death [13, 24]. Progressive corneal infiltrations by xanthomas may additionally lead to a progressive loss of vision [4, 17].

A promising strategy for therapy of XD has not yet been identified. There have been some anecdotal reports of trials of chemotherapeutic agents commonly used for managing Langerhans' cell histiocytosis, such as steroids, vinca alkaloids, alkylating agents, and antimetabolites, but all of these alone or in combination failed to produce objective and reproducible responses [13, 17, 22, 27, 35] as did external irradiation [27]. These results, however, are not surprising, as lipid-storing cells in XD are not identical with Langerhans' cells in histiocytosis X, which usually show a good response to chemotherapy [20]. Reports of successful therapy of XD must also be weighted against spontaneous regressions, which may also occur. Symptomatic treatment consists of surgical excision or electroco-

agulation of the most disabling xanthomas, as was performed in our patient.

In summary, this patient showed the classical clinical appearance and course of XD, with extensive skin, corneal, and pharyngeal lesions. In addition, the patient is the first with xanthomatous involvement of the synovial membrane of a joint. Immunhistochemical classification of the lipid-storing cells clearly differentiated his disorder from histiocytosis X. This is important as the prognosis of this disease is considered good in contrast to that of histiocytosis X. Therefore it is unnecessary to administer systemic antineoplastic treatment. Disabling xanthomas can be surgically excised or electrocoagulated. We conclude that it is of great importance to classify any case of normolipemic xanthomatosis by immunhistochemistry to decide about prognosis and treatment.

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