

Xanthoma Disseminatum: Case Report

Dijana Celić¹, Jaka Radoš², Jasna Lipozenčić², Ivan Dobrić²

¹Medikol Outpatient Department; ²Department of Dermatology and Venerology, Zagreb University Hospital Center, Zagreb, Croatia

Corresponding author:

Dijana Celić, MD
Medikol Outpatient Department
Dobri dol 49
10000 Zagreb
Croatia
dijana_celic@yahoo.com

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SUMMARY Xanthoma disseminatum is a rare, benign, non-Langerhans' cell histiocytic disorder of unknown etiology. A case is presented of a 71-year-old man with a three-year history of disseminated symmetric yellowish papules and plaques on the skin of the face, neck, flexor regions, trunk, extremities and oral mucosa, with fatty infiltration of the liver and pancreas, and cardiac complaints. Xanthomatous rhinophyma predominated on the face. Clinical, immunohistochemistry and histology findings indicated the diagnosis of xanthoma disseminatum. Although the patient had a positive family history of cardiovascular diseases and a number of symptoms that are often associated with hyperlipidemia, repeat plasma levels were always within the normal limits. The case was interesting because of a number of etiologic factors that could be connected with the appearance of xanthomas in our patient. Therefore it was difficult to classify the disease into one of well-defined nosologic entities. The case report is supplemented with a review of relevant literature.

KEY WORDS normolipemic xanthoma, xanthoma disseminatum, non-Langerhans' cell histiocytosis

INTRODUCTION

Non-Langerhans' cell histiocytoses or type II histiocytoses are a group of rare diseases characterized by localized or generalized histiocyte proliferation (1). In contrast to Langerhans' cell histiocytoses or type I histiocytoses, the histiocytes found in type II histiocytoses contain no Birbeck granules, are S-100 and CD 1 negative, and show expression of the monocyte-macrophage antigens such as MAC 387, CD68, CD11b, CD11c and CD14 (1,2). In most cases the cells are factor XIIIa positive (1). A number of disorders from the group of non-Langerhans' cell histiocytoses have been identified and are characterized by histiocyte proliferation, increased lipid phagocytosis, and formation of foam

and giant cells (1). Some authors consider these disorders as a broad spectrum of one and the same disease (3-5). These disorders classified in the group of normolipemic xanthomatoses are called xanthohistiocytoses and include xanthoma disseminatum, papular xanthomas, juvenile xanthogranuloma, necrobiotic xanthogranuloma, and diffuse plane xanthomas (1). Some of these entities have also been found to occur in association with myeloproliferative diseases such as multiple myeloma and leukemia (1). In xanthoma disseminatum and juvenile xanthogranuloma, involvement of visceral organs is rarely described. In adults, juvenile xanthogranuloma is a rare disease and usually

manifests by solitary lesions (1). Infiltration of the mucosa (oral, nasopharyngeal, anal, conjunctival) is characteristic of xanthoma disseminatum (6,7). Diagnosis of the disorder is based on detailed history, clinical picture, extensive laboratory, radiology, histology, immunohistochemistry and electron microscopy work-up, which should rule out primary and secondary hyperlipidemias as well as malignant histiocytoses. Therapeutic attempts produce only modest results. The prognosis of the disease depends on the mucosal and systemic involvement (8).

CASE REPORT

A 71-year-old man from Osijek was initially hospitalized at our Department in April 2003 for disseminated lesions on the skin of the face, trunk and extremities. The patient showed overt adiposity (body weight 115 kg), body height 186 cm; on admission he was dyspneic; harsh systolic murmur over the precordium (III/6) was heard on auscultation, maximally audible over the aorta. The liver was palpable by 3 cm; there was mild pretibial edema and weak peripheral pulsations were recorded. The patient had been suffering from arterial hypertension for the last 20 years, thus on regular therapy with control visits to the cardiologist, with the following diagnosis: *Hypertensio arterialis, Cardiomyopathia ischaemica et hypertonica, Angina pectoris*. The patient had never been taking hypolipemics. During his hospital stay, the highest blood pressure and pulse values were 155/100 and 70/min, respectively. The patient's neurologic status was unremarkable, and he reported no bone complaints. He had been suffering from gout for five years. Several months before hospitalization, hepatomegaly, diffuse hepatic lesion, bilateral nephrolithiasis with a cyst of the left kidney, and gallbladder lithiasis were diagnosed by outpatient ultrasonography of the abdomen. The patient had been taking alcohol on a daily basis. His mother, father and uncle had suffered from arterial hypertension. His mother died from stroke, and his father from myocardial infarction. There was no family history of skin diseases. The initial skin lesions in the form of purpura and nodular enlargement of the nose had occurred three years before his presentation to the Department. Concurrently with these lesions, yellowish papules erupted on the skin of the face, trunk and

flexor regions, confluing with time to form extensive plaques. In the initial stage of the disease, therapy with tetracyclines was introduced because of the clinical impression of a rosacea, however, it failed to produce any improvement. On admission, numerous yellowish papules of 1-3 mm in diameter were seen on the skin of the face and neck, very densely clustered on the forehead, nasolabial folds and eyelids, along with diffuse erythema of both cheeks, and telangiectasias (Fig. 1). The nose was knotty, enlarged, with erythematous livid discoloration, with visible telangiectasias and occasional yellowish papules of up to 3 mm in size (Fig. 1). The entire back surface was covered by erythematous brownish infiltrated plaques of up to 7 cm in size, containing numerous yellowish papules (Fig. 2). The same but less extensive lesions were also present on the chest and abdomen (Fig. 3), in the axillae (Fig. 4), and in the inguinal region (Fig. 5). Elevated, well demarcated yellowish foci of 2-3 mm in diameter were found on the buccal mucosa, and on the hard and soft palate. The following laboratory tests were performed: erythrocyte sedimentation rate, complete blood count, hepatogram, urea, creatinine, lipido-gram and repeat lipidogram, lipoprotein and apo-protein fractions, blood glucose, oral glucose tolerance test, serum protein electrophoresis, immuno-

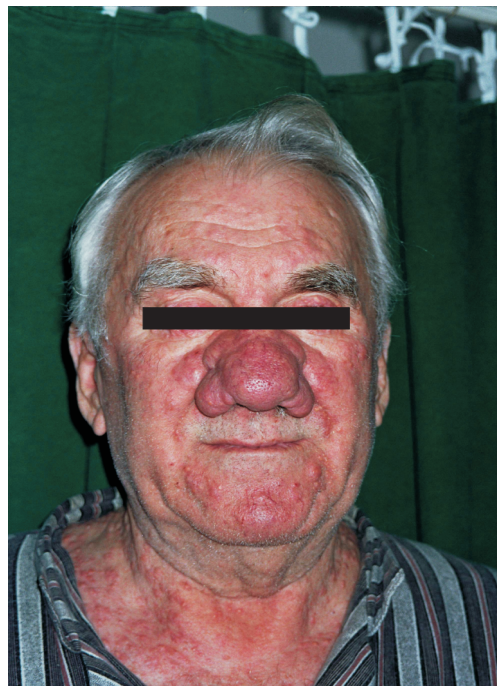


Figure 1. Xanthomatous rhinophyma and yellowish papules on the skin of the face and neck.



Figure 2. Erythematous brownish infiltrated plaques on the skin of the back.



Figure 3. Numerous yellowish papules and nodules on the skin of the chest and abdomen.

electrophoresis, tumor markers, hormones (FSH, LH, prolactin, free testosterone, dehydroepiandrosterone, androstenedione, IGF-1), coagulogram, complement and complement fractions, serum electrolytes (Na, K, Cl), calcium, phosphorus, alkaline phosphatase, and urine analysis; all values were within the normal limits. Urinary Bence-Jones protein was negative. Three skin biopsy specimens (obtained from the back, trunk and nose) showed foam cell nodules, occasional lymphocytes and numerous Touton giant cells in the upper half of the dermis, without epidermal infiltration (Figs. 6 and 7). The immunohistochemistry finding was negative for CD1 and S-100 markers. On consultation, the ophthalmologist diagnosed posttraumatic cataract on

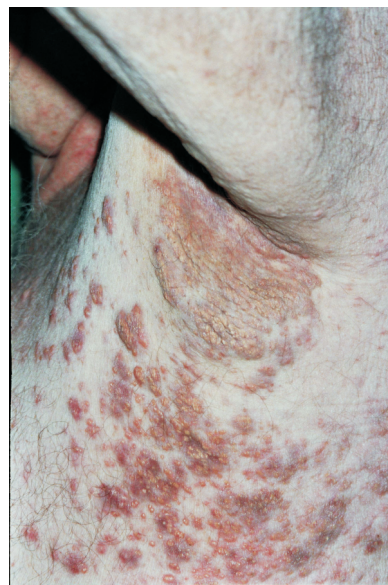


Figure 4. Erythematous brownish plaques and papules in the axillae.



Figure 5. Numerous yellowish papules in the inguinal region.

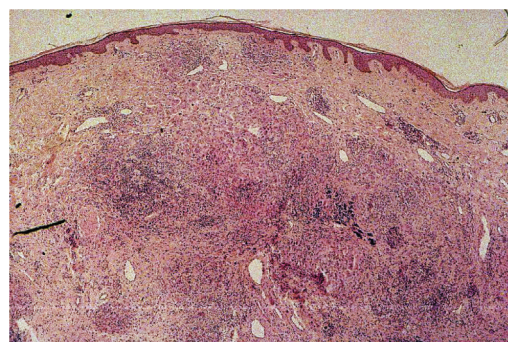


Figure 6. Hematoxylin-eosin stain. Original magnification $\times 25$. Nodular, dense infiltrate of foamy histiocytes, scattered lymphocytes and numerous Touton giant cells in the upper half of the dermis, without epidermal infiltration.

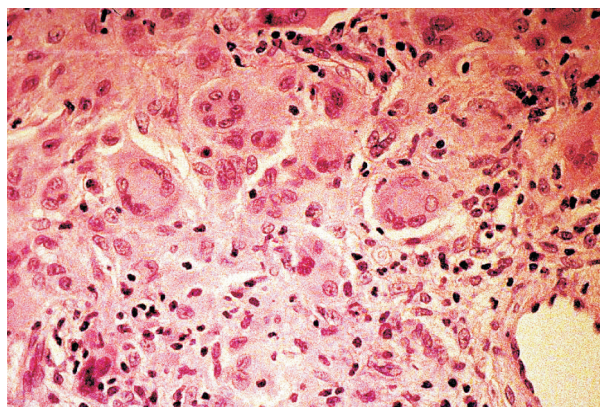


Figure 7. Detail: hematoxylin-eosin stain. Original magnification $\times 100$. Touton giant cells and foam cells.

the right eye and hypertonic fundus grade I-II, without any specific process. Ear, nose and throat (ENT) expert consultation confirmed the finding of yellowish infiltrations of the buccal mucosa and palate, without laryngeal and pharyngeal involvement, and rhinophyma. X-rays of the head, long bones and pelvis revealed no osteolytic changes. Chest x-rays showed a hypertonic heart configuration and an effusion in the projection of the left diaphragm and left phrenicocostal sinus. Ultrasonography of the abdomen showed a diffusely enlarged, fatty liver and pancreas, biliary calculus and cortical cyst of the left kidney. Ultrasonography of the heart showed a moderate aortic defect, dilated left ventricle with a hypertrophic wall and preserved contractility. Electrocardiography (ECG) showed sinus rhythm of 74/min and left ventricular hypertrophy. Exercise testing could not be performed for marked dyspnea and stenocardia on exercise. Cardiologic therapy was modified upon the cardiologist's examination, echocardiography and ECG findings. Upon examination by the endocrinologist and subspecialist for metabolic diseases, and considering normal hormone levels and repeat normal values of plasma lipids, apoprotein and lipoprotein fractions, reduction diet and absolute abstinence from alcohol were recommended. During hospital stay, the patient received regular internist therapy consisting of a salicylate, diuretic and cardiac agents.

DISCUSSION

Lipids are a heterogeneous group of compounds having in common a physicochemical property of being water insoluble (9). They are trans-

ported in the blood in complexes with proteins as lipoproteins, and accumulate in the cells if their entry or synthesis is increased, or their breakdown decreased (9). Cells of various body tissues possess protective mechanisms against excessive input of cholesterol, however, skin macrophages and smooth muscle cells lack these mechanisms, thus they easily accumulate cholesterol and turn to foam cells and Touton giant cells (9). Clinically, these skin events manifest with the occurrence of xanthomas, which are defined as yellowish papules or nodules that may appear very discretely in the form of individual, solitary foci or as grouped lesions containing triglycerides in addition to cholesterol (2,7). They are associated with hyperlipidemias, primary and secondary, which are accidentally detected on routine laboratory testing or by target screening in patients with a positive family history of lipid disorders and cardiovascular diseases (2). While the mechanism of the development of xanthomas in hyperlipidemias is well understood, their etiopathogenesis in normolipemic conditions is less known (10). The conditions associated with the reticuloendothelial system diseases such as multiple myeloma, chronic myeloid leukemia, eosinophilic granuloma, Langerhans' cell histiocytosis, mycosis fungoides, and Sezary syndrome, have been classified in the group of normolipemic xanthomas (10). In these disorders, the occurrence of xanthoma may precede the lymphoproliferative process by months or even years. Other miscellaneous coincidental diseases reported in the literature refer to the occurrence of xanthomas in association with hypogonadism, polycythemia, rheumatic diseases (rheumatoid arthritis) (10); senile dementia, acute iritis and rheumatoid arthritis (10); Ehlers-Danlos syndrome (11); inflammatory skin diseases (atopic dermatitis, erythroderma, chronic atrophic acrodermatitis, photosensitive eczema) (10,12); cicatrices after basalioma excision (13), chronic inflammatory states (relapsing polychondritis) (10), and biliary cirrhosis and atresia (14). In 1938, Montgomery and Osterberg described xanthoma disseminatum as a separate entity in the group of so-called non-Langerhans' cell histiocytoses (15). It is characterized by proliferation of histiocytes that contain no Birbeck granules, are negative for S-100 and CD-1a, and positive for the macrophage antigens MAC 387, CD68, CD11b, CD11c and CD14 (1). The etiopathogenesis of xanthoma disseminatum has

not yet been fully clarified, however, many authors agree that it is a primary disorder of histiocyte proliferation with secondary accumulation of intracellular and extracellular lipids (6,16). They develop between the age 5 and 25 years in 60% of cases, however, the occurrence of xanthoma disseminatum in a 9-month-old infant has been reported (8). Altman and Winkelmann found xanthoma disseminatum to show a 2:1 male predominance (17). The occurrence of symmetrically distributed, reddish-brownish or yellowish papules confluing to form plaques and nodules, with flexor and periorbital regions as predilection sites, is one of the characteristic clinical features of xanthoma disseminatum (7). Mucosal involvement is described in 40%-60% of patients, which is of a high diagnostic relevance (8). Mucosal lesions of the mouth, pharynx and larynx, trachea, epiglottis and tongue have been described. These lesions may cause significant functional problems (7,18). The conjunctiva and cornea may also be involved and eventually lead to blindness (7,18,19). Diabetes insipidus is reported in 40% of patients and is due to xanthomatization of sella turcica; it is mild, transient, and responds well to vasopressin (7). It may precede skin alterations, thus actually being the initial symptom of the disease. Three forms of the disease in terms of clinical course have been described (7). In patients with the progressive form of the disease, xanthomatous bone infiltrations with consequential osteolysis, infiltration of the respiratory tract (larynx, lungs), hepatobiliary system, central nervous system, heart, kidneys, muscles, lymph nodes, uterus and testes have been described (3,8,16). As distinguished from the progressive form, patients with the persistent form of the disease have permanent lesions on the facial skin and mucous membranes, along with good general condition (7,8). The self-healing form is very rare, and is characterized by spontaneous resolution in several years from the symptom onset (7,8). A normal serum lipid level is characteristic of xanthoma disseminatum, although hyperlipidemia of unknown etiology and without positive family history of lipid metabolism disorder or skin lesions may occur in 20% of patients (7).

We have presented a patient with disseminated xanthomas and probably persistent form of the disease. Diagnostic testing provided no evidence for association of the fatty liver and pancreas infiltration

with the parenchymatous focal xanthomatous cell infiltration. Etiologically, the fatty metamorphosis can be ascribed to dietary factors in obese subjects. The advanced atherosclerosis could not be related to xanthoma disseminatum. Although systemic involvement (splanchnic organs and central nervous system) is possible in xanthoma disseminatum, it is rarely reported in the literature and requires more sophisticated diagnostic tools such as computed tomography, magnetic resonance imaging, technetium body bone scan, visceral organ biopsy, etc., which were not used in our patient because of the absence of clinical symptoms and pathologic laboratory findings.

Considering the positive family history and a number of predisposing factors for secondary hyperlipidemia (body weight 115 kg, daily alcohol consumption, arterial hypertension from 1975, anti-hypertensive therapy by beta-blockers, hyperuricemia, and gout), the question arose whether the patient may have had elevated lipid levels at some period in his life, that had led to the occurrence of xanthomas. However, the diagnosis of disseminated eruptive xanthomas had to be ruled out for the absence of involvement of the extensor aspect of the extremities (knees and elbows), non-confluence of the lesions, and normal plasma lipid level. The diagnosis of xanthoma disseminatum was based on the characteristic clinical finding including symmetric xanthomatous lesions of a typical distribution and tendency to confluence, involvement of oral mucosa, and repeat normolipemic plasma values. The diagnosis was verified by histology and immunohistochemistry.

Xanthoma disseminatum may represent the xanthomatous evolutive stage of other non-Langerhans' cell histiocytoses such as generalized eruptive histiocytoma or multicentric reticulohistiocytosis, which has been confirmed in case reports by Caputo *et al.* (8), Braun Falco *et al.* (20), and Coldiron *et al.* (21). In the past, the issue of relation between Langerhans' cell and non-Langerhans' cell histiocytoses used to be posed, whereas nowadays immunohistochemistry and electron microscopy provide considerable help in differentiating these two entities. The xanthoma disseminatum cells possess no Birbeck granules in their cytoplasm, but contain lipid vacuoles, phagosomes and cholesterol crystals (8). In our patient, proliferative

histiocytoses, Langerhans' cell histiocytoses, and disorders associated with monoclonal paraproteinemia (necrotic xanthogranuloma) were ruled out by thorough diagnostic work-up. Normolipemic xanthomas that are mostly described in association with lymphoproliferative diseases, paraproteinemia and hypocomplementemia (22,23) were also excluded. Therapeutic response to oral corticosteroids and clofibrate, described in the management of xanthoma disseminatum, is rather modest and disappointing (8). Oral corticosteroids can prevent skin lesion relapses following surgical excision or electrocoagulation (8). The treatment with clofibrate can lead to partial regression of skin lesions (8). We decided not to use oral corticosteroids in our patient, taking into account the relative contraindications and extension of lesions. As it was not a case of proliferative histiocytic disease, there was no need of cytostatic therapy. Because mucosal lesions caused no functional impairment, there was no need of antimetabolic therapy (cyclophosphamide) either, otherwise reported in the literature as a good attempt to control the progression of mucosal lesions (8). Due to cosmetically unacceptable rhinophyma, disfiguring the patient's face, the patient was submitted to CO₂ laser treatment in local anesthesia at ENT Department. The patient was lost for follow up due to cardiovascular complaints and great distance between the patient's place of residence and our Department. He was referred to his local dermatologist and internist, with recommendation to continue his internist (cardiologic) therapy, reduction diet, and strict alcohol abstinence.

CONCLUSION

The disease prognosis and patient quality of life depend primarily on the progression of mucosal lesions, progressive organ dysfunction, and possible occurrence of myeloproliferative and lymphoproliferative diseases, which may be preceded by normolipemic xanthomas by months or even years (8, 19,22). Therefore, longterm clinical follow-up that occasionally requires sophisticated diagnostic methods is needed. Systemic affection may occasionally be only confirmed by post mortem studies, i.e. on autopsy (1).

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