A case of xanthoma disseminatum: A rare type of non–Langerhans cell histiocytosis

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Abstract
Xanthoma disseminatum (XD) is a rare non-Langerhans cell histiocytosis that may involve skin, mucous membrane and internal organs. It manifests as symmetrically distributed, yellow-brown papules and nodules, involving face and flexures of body. We describe a case of XD in a 22-year-old female. She presented with multiple yellow-brown papules and plaques over face and body folds. Skin lesions were accompanied by visual disturbances. Examination revealed xanthomatous infiltration of cornea and oral mucosa. The case was confirmed with histopathological assessment.

Key words
Non–Langerhans cell histiocytosis, xanthoma disseminatum.

Introduction
Xanthoma disseminatum is a subset of non-Langerhans cell histiocytosis (NLCH). It is characterized by normolipemic disseminated xanthomatosis that tends to localize on the face, trunk, flexural and intertriginous surfaces, is often associated with diabetes insipidus, and appears to run a chronic benign course. The disease predominantly affects male children and young adults. It may also manifest in the central nervous system, ocular structures, respiratory and gastrointestinal tracts.

Due to the asymptomatic and self-healing characteristics of NLCH, most forms do not require early and intensive treatments. Although many conservative treatments are unsatisfying, active intervention may still be warranted for the noninvoluting or disfiguring type for cosmetic reasons or to prevent permanent functional impairments.

Case Report
A 22-year-old female patient attended at Bangabandhu Sheikh Mujib Medical University, Dhaka with multiple yellow-brown, smooth papules and plaques over both axillae, both antecubital fossae, periocular and perioral areas, tongue, neck, submammary folds, truncal folds, groins, buttocks and natal cleft for 4½ years. She also had visual disturbance for 2½ years. She was the first sibling of nonconsanguineous parents. She had no history of bone pain, dysphagia, respiratory distress, polyuria or epilepsy. Clinical examination revealed multiple, bilaterally symmetrical, yellow-brown, smooth, firm papules and plaques over both periocular areas and perioral area. Yellowish, smooth, discrete, firm, round to oval papules and keloid-like plaques were present over both axillae, both antecubital fossae (Figure 1), neck, groins, buttocks and natal cleft. Multiple
Brownish, smooth papules were present over submammary and truncal folds. Koebnerization was present. Multiple erythematous papules and plaques were present over oral mucosa and tongue (Figure 2). Lower lip was hyperpigmented. Multiple erythematous nodules were seen over sclerocorneal junction of both eyes (Figure 3). There was total opacity of right cornea and partial opacity over left one. Slit-lamp examination showed vascularized corneal opacity with early band keratopathy with 360 degree limbal stem cell deficiency (LSCD) with cholesterol deposition over right cornea and vascularized corneal opacity from 7 to 4 o’clock position with cholesterol deposition and LSCD over left one. Visual acuity of right eye was H/M and no improvement by pinhole and that of left eye was 6/18 (unaided), 6/9 p (with -2.50 Dcl X 180). Intraocular pressure of both eyes was digitally normal. Histopathology of lesional skin showed collections of foamy histiocytes and occasional multinucleated giant cell in dermis (Figure 4). The epidermis was unremarkable. The features were consistent with xanthoma. Azathioprine (100mg/day), fenofibrate (435mg/day) and atorvastatin (20 mg/day) were prescribed for three months. Skin lesions did not involute but no new lesions appeared. Patient is under regular follow-up.

Discussion

Xanthoma disseminatum (XD) is a rare non-familial disease, characterized by proliferation
of histiocytic cells in which lipid deposition is a secondary event. It was first described by Montgomery and Osterberg in 1938. Since then, fewer than 100 cases have been reported. XD usually starts before the age of 25 years in about 60% of patients. It is more common in males and male-to-female ratio is 2:1.

It manifests as asymptomatic, symmetrical, yellow-brown or red-brown papules and nodules over face, trunk, proximal extremities, flexures of the body like axillae and groins, buttocks etc. Flexural lesions may coalesce to form plaques and may become verrucous. In 40-60% patients, mucous membranes are involved especially conjunctivae, cornea, oropharynx, larynx and bronchus. Meninges, liver, spleen and bone marrow may also be affected. Xanthomatous lesions in critical anatomical locations may result in morbidity and mortality. Corneal and oropharyngeal involvement may result in blindness and dysphagia, respectively. Respiratory tract involvement may lead to stridor, respiratory distress requiring tracheostomy and bronchiectasis. Meningeal involvement with xanthomatoid cell infiltration of hypothalamic-posterior pituitary axis lead to diabetes insipidus in up to 40% of cases. Other manifestations of meningeal involvement are seizures and growth retardation. Progressive bone disease with lytic lesions have been reported but is very rare presentation. Hepatic infiltration by xanthoma may lead to liver dysfunction presenting as sclerosing cholangitis has been reported.

Our patient had skin lesions with visual disturbance due to corneal involvement. She had no other systemic complaint. The prognosis is highly unpredictable for individual patients. Three clinical patterns have been suggested based on case reviews: i) a rare, self-healing form with spontaneous resolution leaving areas of atrophy or anetoderma; ii) a common persistent form in which lesions may never resolve; and iii) a very rare, progressive form with organ dysfunction and central nervous system involvement. We considered our patient to be affected with the persistent form as there was no symptoms and signs of systemic involvement. Disseminated xanthosiderohistiocytosis was described as a clinical variant of this disease by Halprin and Lorincz. In this variant, there is diffuse infiltration of the skin, subcutaneous tissue and muscle, giving rise to sclerodermatous changes in the skin and muscle wasting.

The pathogenesis is not clear, but it is thought to originate from the macrophage/monocyte series. XD is considered a reactive disease rather than a neoplastic disease. It is characterized by foamy-appearing macrophages postulated to be caused by increased uptake, synthesis, or decreased efflux of lipids. The development of these foamy macrophages is thought to be triggered by cytokines from the inflamed intima or by a superantigen. Therefore, inflammatory reactions are thought to be important in the pathogenesis of this disease.

Unlike other types of xanthomatous disorders, patients with XD usually show normal lipid profiles. The serum lipids are abnormal in 20% of XD cases with elevated levels of serum cholesterol or triglyceride which may lead to confusion with hyperlipidemic xanthomatosis. Our reported case was normolipemic.

Histopathological findings of XD can be explained by diffuse dermal infiltration of Touton giant cells, foreign body giant cells, and histiocytes, associated with scattered lymphocytes, neutrophils, and plasma cells. In early lesions, scalloped macrophages dominate the histology, but most well-developed lesions have a mixture of the above. Immunohistochemical studies show negative
staining for S-100, CD1a, and Birbeck granules, and positive staining for the surface markers CD68 and factor XIIIa. Our patient had typical lesion involving typical sites and histopathology of skin lesions showed foamy histiocytes and occasional multinucleated giant cell in dermis.

Local management of XD includes cryotherapy, CO2 laser, dermabrasion, electrocoagulation, and intralesional steroid injection with variable responses. Surgery appears to give the best results for readily accessible lesions. The prognosis of XD is usually good in most cases. However, it can be worse if vital organs are involved. We considered our case as a persistent form, due to no central nervous system or other vital organ dysfunctions except visual compromise. Though there was no improvement of existing lesions, there was no new lesion formation after beginning of treatment.

Our patient was treated with azathioprine (100 mg/day), fenofibrate (435mg/day) and atorvastatin (20 mg/day) for three months. There was no flattening or complete resolution of any of the existing lesions. Cryotherapy was tried with a little response. We plan to continue this regimen. Corneal lesions might be improved by keratoplasty but as there was LSCD, chances of graft failure were very high. So, LSCD had to be managed first.

References