

A case of generalized xanthogranuloma with systemic involvement



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Key words: adult xanthogranuloma; Erdheim-Chester disease; histiocytosis; non-Langerhans cell; xanthoma; xanthoma disseminatum.

INTRODUCTION

Non-Langerhans cell histiocytosis (NLCH) is a group of disorders defined by the proliferation of histiocytes other than the Langerhans cell. Because of a close relationship within this group of disorders, categorizing a patient under a single disease entity is difficult.¹ Likewise, substantial clinicopathologic similarities exist among adult xanthogranuloma (AXG), xanthoma disseminatum (XD), and Erdheim-Chester disease (ECD). We report a case of generalized xanthogranuloma with systemic involvement showing overlapping features of adult-onset AXG, XD and ECD.

CASE REPORT

A 31-year-old man presented with a 2-month history of asymptomatic, progressive, multiple erythematous papules and nodules on his entire body (Fig 1, A and B). He was otherwise healthy, and none of his family members had similar skin lesions. Histopathologic examination of a punch biopsy specimen obtained from a nodule on the forehead was consistent with xanthoma showing foamy histiocytes and Touton giant cells (Fig 1, C).

Laboratory investigations showed a normal lipid profile, with a cholesterol level of 159 mg/dL, a triglyceride level of 74 mg/dL, a high-density lipoprotein cholesterol value of 50 mg/dL, and a low-density lipoprotein cholesterol value of 106 mg/dL. However, the liver enzymes were elevated: aspartate aminotransferase, 60 U/L; alanine aminotransferase, 114 U/L, and alkaline phosphatase, 399 U/L.

Abbreviations used:

AXG:	adult xanthogranuloma
BRAF:	B-Raf proto-oncogene, serine/threonine kinase
ECD:	Erdheim-Chester disease
NLCH:	Non-Langerhans cell histiocytosis
XD:	xanthoma disseminatum

Skin lesions increased in size and number after his first visit, and gingival and laryngeal lesions were observed 2 months later. Follow-up laboratory results showed sustained elevation in liver enzymes: aspartate aminotransferase, 85 U/L; alanine aminotransferase, 119 U/L; and alkaline phosphatase, 443 U/L. Serum protein electrophoresis revealed no abnormal peaks.

A skin biopsy specimen of the abdominal lesion showed a tumor consisting of foamy histiocytes and fibrosis without Touton giant cells. The tumor cells were weakly positive for S-100 and positive for CD163 and factor XIIIa; however, they were negative for CD1a.

The patient was referred 1 month later to the internal medicine department for further evaluation of the elevated levels of liver enzymes. Computed tomography of the liver revealed heterogeneous enhancements involving the left hepatic lobe, numerous low-attenuation lesions in both kidneys, and 2 pulmonary nodules in the left lung. Magnetic resonance imaging of the liver showed numerous infiltrative or nodular lesions involving the abdominal wall and musculoskeletal system. A liver biopsy

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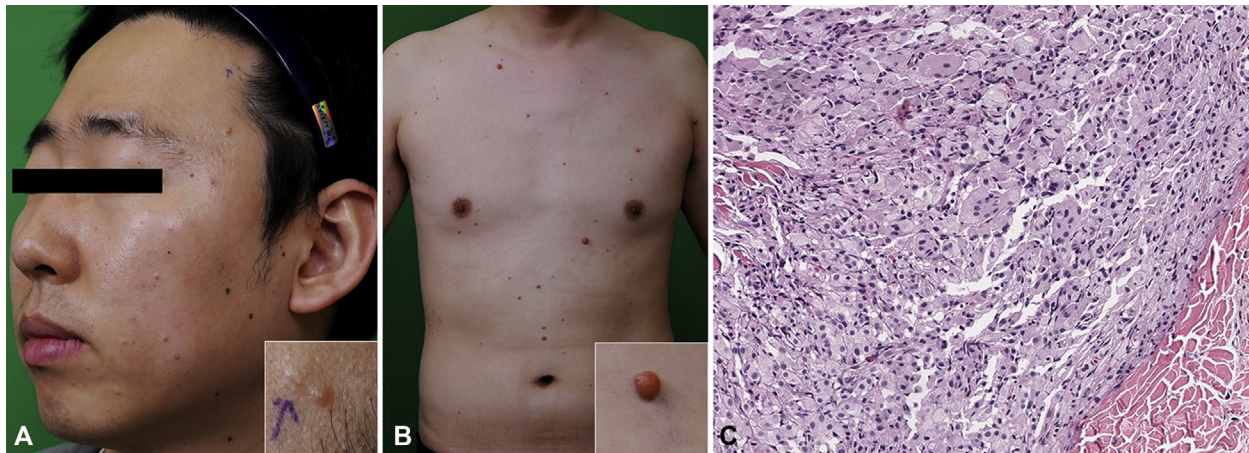


Fig 1. Multiple erythematous papules and nodules on (A) the face and (B) trunk. C, Histopathologic findings of nodular dermal infiltrates composed of foamy histiocytes along with occasional scalloped histiocytes, lymphocytes, and Touton giant cells (hematoxylin and eosin stain; original magnification: $\times 200$).



Fig 2. Positron emission tomography-computed tomography shows increased fludeoxyglucose F 18 uptake by whole-body skin and subcutaneous lesions with infiltrative nodular lesions inside liver, pancreas, intra-abdomen, bones, mediastinum, muscles, and lungs.

specimen showed histiocytic proliferation with focal S-100 expression. Computed tomography of the neck revealed multiple skin nodules, osteolytic bone lesions, and intraglandular nodules inside both submandibular glands. Positron emission tomography-computed tomography confirmed multiorgan involvement, including liver, pancreas, intra-abdomen, bones, mediastinum, muscles, and lungs, with whole-body skin and subcutaneous lesions (Fig 2).

On the basis of the clinical, histologic, and immunohistochemical features, a final diagnosis of generalized xanthogranuloma showing features of AXG, XD, and ECD was made. In the absence of any signs of malignancy or functional organ damage, we decided to monitor the patient routinely with laboratory tests. The patient's follow-up examination revealed waxing and waning skin lesions. Although all of the skin lesions were asymptomatic, the patient complained of occasional bleeding from large protruding lesions when they were traumatized during daily activities. We performed CO₂ laser therapy for the management of symptomatic lesions, and close follow-up examination is still ongoing without significant changes.

DISCUSSION

AXG manifests as solitary and oligolesional yellow-to-orange papules on the face, neck, and lower arms. Unlike juvenile xanthogranuloma, the lesions tend to persist and do not regress spontaneously. There is no association with systemic diseases such as neurofibromatosis or leukemia.²

XD is a rare, benign, normolipidemic form of NLCH, affecting the skin and mucous membranes. It

Table I. Clinical characteristics of adult xanthogranuloma, xanthoma disseminatum, and Erdheim-Chester disease, and the present patient

Variable	Adult xanthogranuloma ²	Xanthoma disseminatum ^{5,6}	Erdheim-Chester disease ^{7,9}	Case patient
Age/sex	...	Male/female ratio = 2-4:1	Middle-aged and older adults	31 y, male
Type of lesion	Yellow-orange papules	Red-colored nodules and plaques	Red-brown papules merging into plaques	Reddish-brown nodules
Pattern	Solitary and multiple (oligolesional) Persists as isolated lesions	Multiple lesions; symmetric distribution Tend to form groups or merge into plaques	Multiple lesions; diffuse distribution Tend to form groups or merge into plaques	Multiple lesions; diffuse distribution
Localization	Face, neck, and lower arms	Eyelids and flexures such as axillae, inguinal folds, and antecubital and popliteal fossae	Eyelids, axillae, groin, neck, trunk, face	Whole body
Mucous membrane involvement	GI tract involvement	40%-60% (upper digestive and respiratory tracts)	Laryngeal, oral, conjunctival involvement	Gingival and laryngeal involvement
Systemic involvement	Lungs, bone, heart, and GI tract	Bone (multiple osteolytic lesions), CNS infiltration (diabetes insipidus), and lung involvement	Bone (patchy osteosclerosis), neurologic, pulmonary, pericardium, hypothalamus, orbit, and retroperitoneum	Bone (multiple osteolytic lesions), liver, pancreas, intra-abdomen, submandibular gland, mediastinum, muscles and lung
Clinical course	Persistent	Persistent > self-healing > progressive	Usually progressive, with a high mortality	Increase in lesion size and number along with elevated liver enzymes
Management	Excisions of lesions CO ₂ laser therapies	Local treatment; cryotherapy, radiotherapy, surgery, and CO ₂ laser Systemic treatment; peroxisome proliferator-activated- γ receptors, statins	Cytotoxic chemotherapy, bone marrow transplantation, cladribine, corticosteroids, IFN- α , BCR-ABL/KIT inhibitor, IL-1 receptor antagonist, TNF inhibitor, and BRAF inhibitor	Local treatment: CO ₂ laser Systemic treatment: not done

BRAF, B-Raf proto-oncogene, serine/threonine kinase; *CNS*, central nervous system; *GI*, gastrointestinal; *IFN- α* , interferon- α ; *IL-1*, interleukin 1; *TNF*, tumor necrosis factor.

normally manifests as nodular lesions on the eyelids and flexures such as axillae, inguinal folds, and antecubital and popliteal fossae.³ Approximately 40% to 60% of the patients carry lesions on the mucous membranes of the upper respiratory tract.⁴ Extracutaneous manifestations involve multiple osteolytic lesions, pulmonary and central nervous system infiltration, and diabetes insipidus.^{5,6}

ECD is also a rare, disseminated form of NLCH. Recent reports suggest conflicting results of monoclonal ECD involving B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) V600E mutations in approximately 55%.⁷ It is primarily a disease of long bones presenting with medullary sclerosis radiographically, sparing epiphyses. Extraskelatal manifestations can occur in almost every organ. Cutaneous lesions include diffuse dermal or subcutaneous nodules, intertrigo-like lesions, and pigmented patches on the lips and oral mucosa.^{7,8}

Immunohistochemical results suggest NLCH cell lineage. Cutaneous lesions in our patient, similar to those of AXG, showed diffuse dermal and subcutaneous nodules without merging into plaques or forming groups. Xanthomas symmetrically involving eyelids, trunk, face, and proximal extremities of flexor surfaces, which are characteristic of XD, were not detected. The patient had multiple osteolytic lesions, which are characteristic features of XD. Extracutaneous manifestations revealed a variety of symptoms common to all 3 diseases, which prevented a clear-cut diagnosis. Characteristic features of the 3 diseases for the differential diagnosis of our patient are summarized in Table I.^{2,5-7,9} Because the patient has not shown aggressive disease progression, it is reasonable to consider our patient closer to AXG and XD than ECD. To our knowledge, no reports describing a case such as this have been published, which increased the difficulty in reaching a final diagnosis.

On our review of previous reports and articles of histiocytoses, we found that the current classification is not clear yet. On one hand, Caputo et al,⁹ in a review of unusual variants of NLCH, suggested that ECD was a variant of XD with progressive bone and visceral involvement and therefore exhibited aggressive clinical behavior. Because of similar cutaneous lesions in ECD and XD based on immunohistochemical analysis, ECD was considered as a form of NLCH.

On the other hand, Emile et al¹⁰ reported that ECD can be classified under the Langerhans cell group, not in the NLCH group, because nearly 20% of

patients diagnosed with ECD also manifest lesions of Langerhans cell histiocytosis, and both diseases show similar clonal mutations involving genes in the mitogen-activated protein kinase pathway in more than 80% of the cases. The researchers classified XD as cutaneous NLCH with a major systemic component. Also, the 2016 revision of the World Health Organization classification of lymphoid neoplasms reported ECD as a single disease entity, distinct from the other members of the juvenile xanthogranuloma family, including XD.¹¹

The Langerhans/non-Langerhans dichotomy of the classical classification of histiocytoses has been increasingly disputed.¹⁰ The challenges in classifying our patient under a single disease category raise additional questions about the current system. Whether we can define the group of disorders in histiocytoses as one disease entity that has a wide spectrum of manifestations is another subject that warrants exploration.

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