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CASE REPORT

A Case of Xanthoma Disseminatum Accentuating over the Eyelids

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Xanthoma disseminatum (XD) is a rare, benign non-familial mucocutaneous disorder, which is a subset of non-Langerhans cell histiocytosis. It is characterized by mucocutaneous xanthomas in a disseminated form typically involving the eyelids, trunk, face, and proximal extremities and occurs in flexures and folds such as axillae and the groin. Mucosal involvement of the respiratory or gastrointestinal tracts may lead to hoarseness or intestinal obstruction from a mechanical mass effect. This paper outlines the case of a 47-year-old female with progressive yellow-to-brown confluent nodules and plaques of various sizes on her scalp, face, oral mucosa, neck, shoulder, axillary folds, and perianal area. Xanthomas accentuating over the eyelids and eyelashes led to partial obstruction of her visual field and interfered with blinking. Further, she suffered from xerophthalmia. The presentation of histopathological features including foamy histiocytes, inflammatory cells, and Touton giant cells in conjunction with her clinical findings indicated a diagnosis of XD. Evaluations for extracutaneous involvement including the central nervous system, respiratory tract, gastrointestinal tract, and bone resulted in nonspecific findings. Although she has been treated with surgical excisions, CO_2 laser therapy, and oral prednisolone, new lesions are still emerging. **(Ann Dermatol 22(3) 353～357, 2010)**

-Keywords-
Blinding, Field of vision, Xanthoma disseminatum, Xerophthalmia

INTRODUCTION

Xanthoma disseminatum (XD) is a rare, benign proliferative dermatologic disorder of unknown etiology[1]. It is classified as a subset of cutaneous non-Langerhans cell histiocytosis (NLCH). XD typically manifests as hundreds of discrete papules and nodules, which are red-brown to yellow in color[1]. They chiefly involve the face and trunk, and occur in flexures and folds such as the axillae and groin. XD may also involve the mucous membranes of the mouth, pharynx, larynx, conjunctiva, and cornea. Because of the asymptomatic and self-healing characteristics of NLCH, most forms do not require early and intensive treatments[1]. 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. We report on a persistent and recalcitrant form of XD in a 47-year-old woman, which lead to circumscribed blindness by obscuring her field of vision.

CASE REPORT

A 47-year-old woman presented with disfiguring yellow to red-brown colored nodules and plaques on her forehead, periocular areas, nasolabial folds, oral mucosa, chin, neck, shoulder, axillary folds, and perianal area. The papules began from both eyelids and perioral area 5 years before the presentation. They had been yellow to flesh red at first and changed to yellow to brown color with time.

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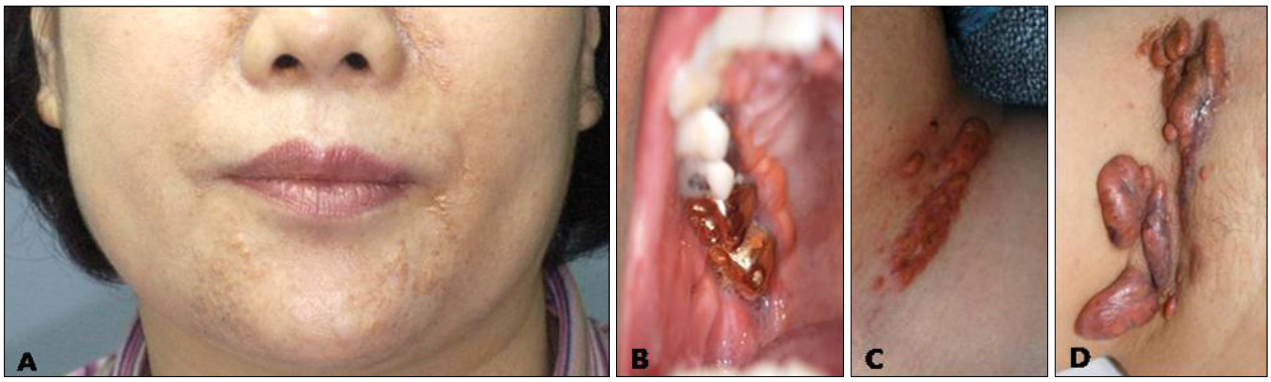

Fig. 1. Cutaneous features characterized by multiple confluent yellow to red-brown hard papules and nodules on the face (A), oral mucosa (B), neck (C), axillae (D).

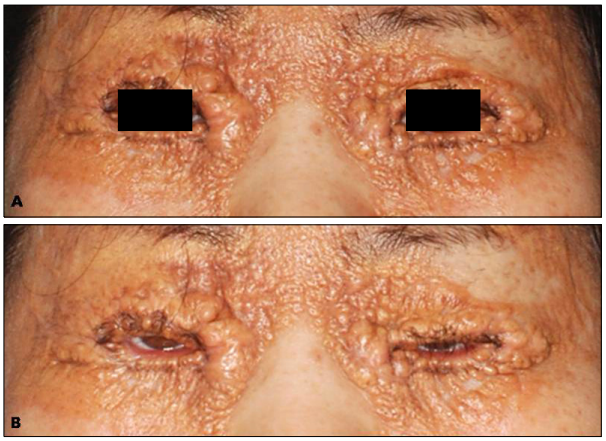

Fig. 2. Xanthoma disseminatum progressively accentuating around ocular area (A) and it hindered in closing her eyes (B).

The papules coalesced into plaques around the mouth, and new lesions had recently developed on the scalp, forehead, oral mucosa, neck, shoulders, axillae, and eventually around the anal region (Fig. 1). They grew larger and larger and were severely pedunculated, especially on the periocular area, neck, and axillae. She usually felt only itching from the newly developing papules, but they were not long lasting. She complained that multiple papules accentuating over the eyelid and eyelashes hindered the blinking of her eyes and obscured some fields of vision (Fig. 2). An ophthalmologic examination showed xerophthalmia but was otherwise normal.

She had been taking antihypertensive medications for 4 years with no other history of skin disorders. There was no drug or family history to explain her cutaneous disorder. She did not have any symptoms indicating systemic dysfunction such as polyuria, polydipsia, fever, or chills. A brain magnetic resonance image (MRI) and chest X-ray were also normal. She did not complain of any difficulty breathing despite the fact that she had similar lesions on her oral and nasal mucosa. Laryngoscopic studies of the pharynx and larynx as well as endoscopy of the gastrointestinal tract showed no signs of obstruction. She had normal values on urinalysis, fasting blood glucose, serum urea, and electrolyte tests. Thyroid- and liver-function tests, lipid profiles such as serum triglyceride, total cholesterol, and high density lipoprotein (HDL) cholesterol were also within normal ranges.

Skin biopsies taken from the axilla and inner canthus revealed intradermal infiltrates of Touton-type giant cells, foam cells, histiocytes and some other inflammatory cells (Fig. 3A, B). Immunohistochemical staining was negative for the CD1a and S-100 proteins but positive for CD68 (Fig. 3C～E). Several large pedunculated nodules on both axillae and the neck were surgically resected, and smaller lesions were removed by CO_2 laser. After surgery, she was treated with 20～40 mg of oral prednisolone once per day for 11 weeks with reduced medication for 10 more weeks for prophylactic reasons. However the lesions were recalcitrant and recurring. New lesions on the periocular areas are still emerging, and her visual field continues to narrow.

DISCUSSION

XD is a rare, benign NLCH distinguished by multiple grouped red-brown to yellow papules and nodules involving the skin and mucous membranes. The pathogenesis of NLCH is not clear[1]; however, there is some information about the epidemiology and clinical findings. First, XD usually starts before the age of 25 years in about 60% of patients[1]. Second, it is more common in males[1]. Third, XD may occur anywhere on the body including the scalp, face, trunk, and extremities[1]. It often involves the

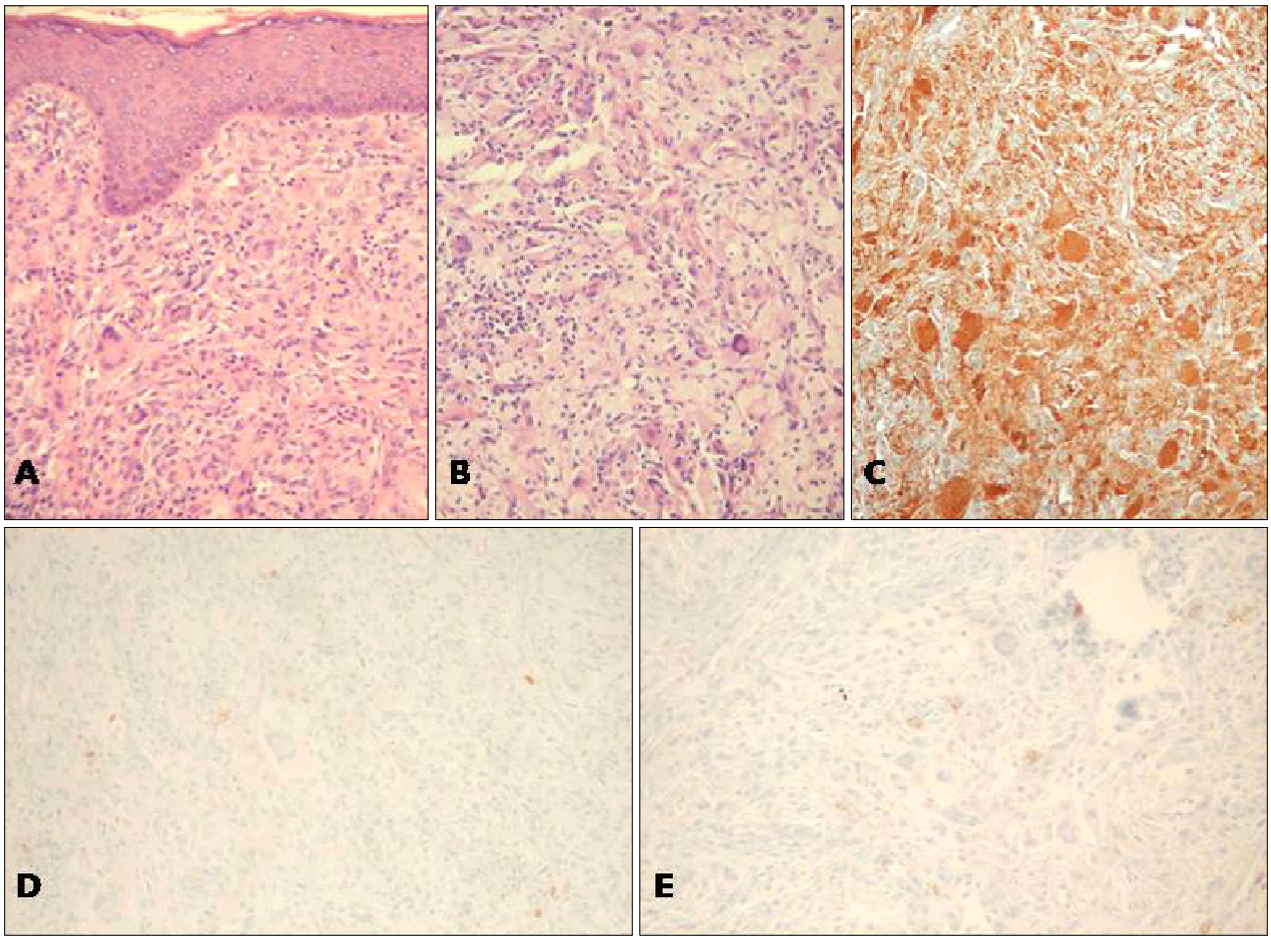

Fig. 3. Histopathologic features characterized by a mixture of histiocytes, inflammatory cells, foam cells (A: H&E, ×200), form cells and Touton giant cells (B: H&E, ×200). Immunohistochemical stainings positive for CD68 (C) and negative for S-100 (D), and CD1a (E) (×200).

eyelids and eyelashes without functional problems. About 50% of cases involve the mucous membranes of the larynx, pharynx, mouth, conjunctiva, and cornea[1]. Various symptoms are possible according to the location of xanthoma; for example, respiratory obstruction, defecation difficulty, and so on[2,3]. XD is often related with diabetes insipidus by involving the central nervous system (CNS) in about 40% of patients[4-6]. Rarely, it may be accompanied by multisystemic involvement[7].

Xanthomatous lesions in critical anatomical locations may result in morbidity and mortality. Zak et al.[8] reported intracranial involvement of XD, which resulted in death of the patient. Büyükavci et al.[9] described a case of XD with hepatic involvement, which resulted in sclerosing cholangitis. Mass effects from xanthomas can create serious problems. Ozçelik et al.[2] reported upper airway obstruction with invasion of the respiratory mucosa; Kang and Kim[3] reported gastrointestinal complications accompanied by defecation difficulties with invasion of the perianal area. In our case, there was no evidence of vital organ involvement during various evaluations. However, multiple papules accentuating in a coalesced presentation, particularly on the eyelids and eyelashes, screened her field of vision, and made it difficult for her to blink her eyes, because the papules on the eyelashes made her eyelashes stiffer.

Unlike other types of xanthomatous disorders, patients with XD usually show normal lipid profiles[10], but slightly elevated levels of serum cholesterol or triglyceride can be seen in a few patients[1]. Radiologic findings are usually nonspecific, except on a brain MRI when the XD has been associated with intracranial lesions[1]. In our patient, lipid profiles and thyroid-function test results were normal, and radiologic examinations showed nonspecific findings. As xanthomas were detected on the oral mucosa, an upper and lower gastrointestinal endoscopy and a laryngoscopy were performed, which also revealed nonspecific findings. 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[11]. 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[12]. Rough endoplasmic reticulum, fat droplets in histiocytes, and Touton giant cells can be seen on electron microscopy[13].

XD can be classified into three groups by its evolution and prognosis: a self-healing form with spontaneous resolution of lesions; a common persistent form in which lesions may never resolve; and a very rare progressive form with organ dysfunction and CNS involvement[14]. Though many subtypes among these are possible, the persistent form is the most common type. The prognosis of XD is usually good[1], although it can be worse if vital organs are involved. We considered our case as a persistent form from her poor response to systemic steroid treatment and the continuously spreading clinical course without any signs of organ dysfunction.

There are various treatments for XD, such as vasopressin, radiotherapy, cryotherapy, corticosteroids, and antiblastic chemotherapy[1], but no single treatment is universally successful (Table 1)[2,3,8,9,14-19]. For example, Büyükavci et al.[9] used mainly oral prednisolone (2 mg/kg/day) and oral

Table 1. Cases of xanthoma disseminatum published in the literature in the last 5 years

Reference	Sex/Age	Location	Treatment 1	Treatment 2	Outcome
Ozçelik et al.[2]	M/8	Mucocutaneous CNS	Tonsillectomy Adenoidectomy	Prednisolone 1 mg/kg/day Vasopressin Antibiotics	No improvement
Kang and Kim[3]	F/63	Mucocutaneous	Oral corticosteroid for several months	Several local excision with laser and TCA	No improvement
Zak et al.[8]	F/23 M/13	CNS CNS	Surgical excision Complete excision	Radiotherapy	Dead Cured
Büyükavci et al.[9]	M/12	Mucocutaneous Hepatic CNS	Oral prednisolone 2 mg/kg/day Ursodeoxycholic acid Cholestyramine Vitamins (Fat soluble: A, D, E, K)	Intranasal desmopressin Oral azathioprine 2 mg/kg/day	No improvement
Alexander et al.[14]	M/18	Mucocutaneous CNS	Nasal desmopressin High dose prednisone Dexamethasone 4 mg PO tid Intrathecal cytarabin, prednisone, etoposide	Radiotherapy Surgical resection Laminectomy	Dead
Choi et al.[15]	M/33	Mucocutaneous CNS	Cyclophosphamide 100 mg daily for 7 months Desmopressin acetate 0.4 mg daily for 7 months	CO_2 laser Electrocautary	Some improvement and new lesions Improved DI
Seaton et al.[16]	M/17	Mucocutaneous CNS	Hormone replacement Anticonvulsant Etoposide, thalidomide, topical nitrogen mustard	Azathioprine 150 mg daily for 14 months Cyclophosphamide 50～100 mg once daily for 18 months	Dramatic improvement
Savaşan et al.[17]	F/2	Mucocutaneous Hepatic	High dose steroids 30 mg/kg/day 6-mercaptopurine Methotrexate	MUD allogenic BMT (BEAM regimen) Carmustine, Etoposide Cytarabine, Melphalan	Cured
Eisendle et al.[18]	M/30	Mucocutaneous	Etoposide Interferone gamma	Combination of 3 lipid Lowering agents Rosiglitazone Simvastatin Acipimox	Partial improvement
Yusuf et al.[19]	F/32	Mucocutaneous CNS	Oral prednisolone 20 mg twice daily for 22 weeks	—	Remarkable regression
Our case	F/47	Mucocutaneous	Surgical excision CO_2 laser therapy	Oral prednisolone 20～40 mg once a day for 11 weeks	No improvement

CNS: central nervous system, TCA: trichloroacetic acid, PO: per os, DI: diabetes insipidus, MUD: matched unrelated donor, BMT: bone marrow transplantation, BEAM: carmustine, etoposide, cytarabine, melphalan.

azathioprine (2 mg/kg/day), but the patient failed to respond. Further, some have had successful results using a combination of lipid lowering agents or azathioprine and cyclophosphamide[16,18]. In some cases, treatments with oral steroids, clofibrate, and chemotherapy are effective, but it is difficult to distinguish the effect of such drugs from that of spontaneous resolution[3]. Our patient was treated with oral corticosteroid after two surgical excisions and several CO_2 laser therapies. Until recently, the disease was not well controlled. Because new lesions are still emerging, and her visual field is continuously narrowing, we are planning to use lipid lowering agents such as a series of statins and perform several surgical excisions to retain her vision.

REFERENCES

1. Carlo G, Ruggero C. Non-Langerhans cell histiocytosis. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill, 2008:1424-1434.
2. Ozçelik U, Doğru D, Akçören Z, Coşkun T, Kaya S, Göçmen A. Xanthoma disseminatum: a child with respiratory system involvement and bronchiectasis. Pediatr Pulmonol 2005; 39:84-87.
3. Kang TW, Kim SC. A case of xanthoma disseminatum presenting as pedunculating nodules and plaques. Korean J Dermatol 2007;45:290-293.
4. Wayman LL, Margo CE. Xanthoma disseminatum with bilateral epibulbar involvement. Am J Ophthalmol 2005; 139:557-559.
5. Woollons A, Darley CR. Xanthoma disseminatum: a case with hepatic involvement, diabetes insipidus and type IIb hyperlipidaemia. Clin Exp Dermatol 1998;23:277-280.
6. Varotti C, Bettoli V, Berti E, Cavicchini S, Caputo R. Xanthoma disseminatum: a case with extensive mucous membrane involvement. J Am Acad Dermatol 1991;25:433-436.
7. Calverly DC, Wismer J, Rosenthal D, deSa D, Barr RD. Xanthoma disseminatum in an infant with skeletal and marrow involvement. J Pediatr Hematol Oncol 1995;17:61-65.
8. Zak IT, Altinok D, Neilsen SS, Kish KK. Xanthoma disseminatum of the central nervous system and cranium. Am J Neuroradiol 2006;27:919-921.
9. Büyükavci M, Selimoglu A, Yildirim U, Ertekin V, Atasoy M. Xanthoma disseminatum with hepatic involvement in a child. Pediatr Dermatol 2005;22:550-553.
10. Weiss N, Keller C. Xanthoma disseminatum: a rare normolipemic xanthomatosis. Clin Investig 1993;71:233-238.
11. Walter HB, Bernhard Z. The histiocytoses. In: Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, Xu X, editors. Lever's histopathology of the skin. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2009:667-688.
12. Zelger B, Cerio R, Orchard G, Fritsch P, Wilson-Jones E. Histologic and immunohistochemical study comparing xanthoma disseminatum and histiocytosis X. Arch Dermatol 1992;128:1207-1212.
13. Yoon JS, Kim YH, Lee JH, Song KY, Park JK. A case of xanthoma disseminatum. Korean J Dermatol 1993;31:812-816.
14. Alexander AS, Turner R, Uniate L, Pearcy RG. Xanthoma disseminatum: a case report and literature review. Br J Radiol 2005;78:153-157.
15. Choi KW, Lee CY, Lee YK, Kim HS, Lee CW, Kim KH, et al. A case of xanthoma disseminatum with diabetes insipidus. Korean J Dermatol 2008;46:826-830.
16. Seaton ED, Pillai GJ, Chu AC. Treatment of xanthoma disseminatum with cyclophosphamide. Br J Dermatol 2004; 150:346-349.
17. Savaşan S, Smith L, Scheer C, Dansey R, Abella E. Successful bone marrow transplantation for life threatening xanthogranuloma disseminatum in neurofibromatosis type-1. Pediatr Transplant 2005;9:534-536.
18. Eisendle K, Linder D, Ratzinger G, Zelger B, Philipp W, Piza H, et al. Inflammation and lipid accumulation in xanthoma disseminatum: therapeutic considerations. J Am Acad Dermatol 2008;58:S47-49.
19. Yusuf SM, Mijinyawa MS, Musa BM, Mohammed AZ. Xanthoma disseminatum in a black African woman. Int J Dermatol 2008;47:1145-1147.