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CASE REPORT

Xanthoma disseminatum with extensive respiratory involvement effectively treated with cladribine: a case report

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ABSTRACT

Xanthoma disseminatum (XD) is a rare and benign proliferative systemic disease that usually affects the skin and mucosal membranes with variable extent. Extensive systemic involvement can be associated with higher morbidity. There is paucity in the literature describing this rare pathological entity, and the ideal management remains controversial. In this article, we report our experience with cladribine in treating a case of XD. We documented the clinical and pathological manifestations of a 24-year-old woman who was initially diagnosed with rheumatoid arthritis. She presented to our institute with respiratory compromise and was found to have XD affecting skin, mucosal membranes, joints, and bone marrow. The patient received six cycles of cladribine for 6 months, during which she showed a remarkable response in relation to the respiratory lesions. Her hemoglobin also normalized and inflammatory markers gradually decreased to reach normal values. However, her skin lesions did not respond to treatment but no new lesions appeared. With our experience with cladribine, we believe that it could be a promising treatment option for XD. However, more work has to be conducted to determine the efficacy and safety in the long term.

Key words: Cladribine, histiocytosis, non-Langerhans

Key message: Given the rarity of this understudied entity, the natural history and the ultimate treatment remain unclear. We highlight the natural history and clinical course of xanthoma disseminatum (XD) in this article. We also describe our experience with cladribine in treating XD. We believe that similar experiences should be compiled to better understand this pathology and the effective therapy options for these patients.

INTRODUCTION

Xanthoma disseminatum (XD) is a benign proliferative disorder of unknown etiology. It is classified as non-Langerhans cell histiocyte proliferation.[1]

XD was first described as a distinct entity by Montgomery and Osterberg in 1938.[2] It usually presents as coalescent yellowish papules on the face, neck, torso, and intertriginous areas. Lesions can extend further and affect the conjunctivae, oral mucosa, and respiratory tract.[1] XD usually affects skin and cutaneous tissues. However, some cases of extensive systemic involvement have been reported.[1,3] Association with diabetes insipidus was commonly described.[1,4]

Several therapeutic trials have been proposed for managing XD including but not limited to cladribine,

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cyclophosphamide, prednisone, and statins, yet the ideal treatment remains controversial.[5]

CASE HISTORY

A 24-year-old woman with a history of sinus surgery and arthritis presented with dyspnea and fatigue. She also complained of blurry vision, polydipsia, and polyuria for 6 months.

The patient was initially diagnosed with rheumatoid arthritis involving knees, ankles, and elbows 4 years ago in another private practice. Her diagnosis reportedly relied solely on clinical findings due to poor laboratory capabilities in her hometown, and she was treated with methotrexate, hydroxychloroquine, and prednisone.

Examination showed painless yellowish-brown papules measuring 1–7 mm on face, palate mucosa, eyelids, trunk, and axilla [Figure 1].

On chest examination, it was found that she had stridor and wheezing. Her optic exam showed narrowing of the visual fields in the superior temporal quadrant in both eyes.

As the skin lesions showed similarity to those encountered in dyslipidemia, a lipid profile was ordered as part of her laboratory workup. Triglycerides, cholesterol, low-density lipoprotein, and high-density lipoprotein levels were within normal limits. Her inflammatory markers were elevated. Her lab values showed microcytic iron deficiency anemia. Both rheumatoid factor and anti-cyclic citrullinated peptide were negative. Owing to the patient's complaint of excessive thirst and increased urine output, 24 h urine was obtained, measuring 4.5 L with low osmolality. In the setting of normal blood glucose and exam findings of narrowing of the visual fields in the superior temporal quadrant in both eyes, workup for diabetes insipidus was initiated. Central Diabetes Insipidus was confirmed with desmopressin testing.

Magnetic resonance imaging of the brain was negative. Coronal sections of computed tomography (CT) of head and neck showed a homogenous mass obliterating the nasopharynx [Figure 2]. CT of chest showed normal lung parenchyma, and no lytic lesions were found on chest X-ray. Upper and lower extremity X-rays were performed and were negative for lytic boney lesions.

The patient underwent pulmonary function tests, which showed fixed upper airway stenosis. Nasoscopy revealed a friable mass obstructing the choana [Figure 3]. Laryngoscopy showed fixed left vocal cord and subglottic stenosis. An attempt to bypass the stenosis was aborted due to bleeding. However, a biopsy was obtained.

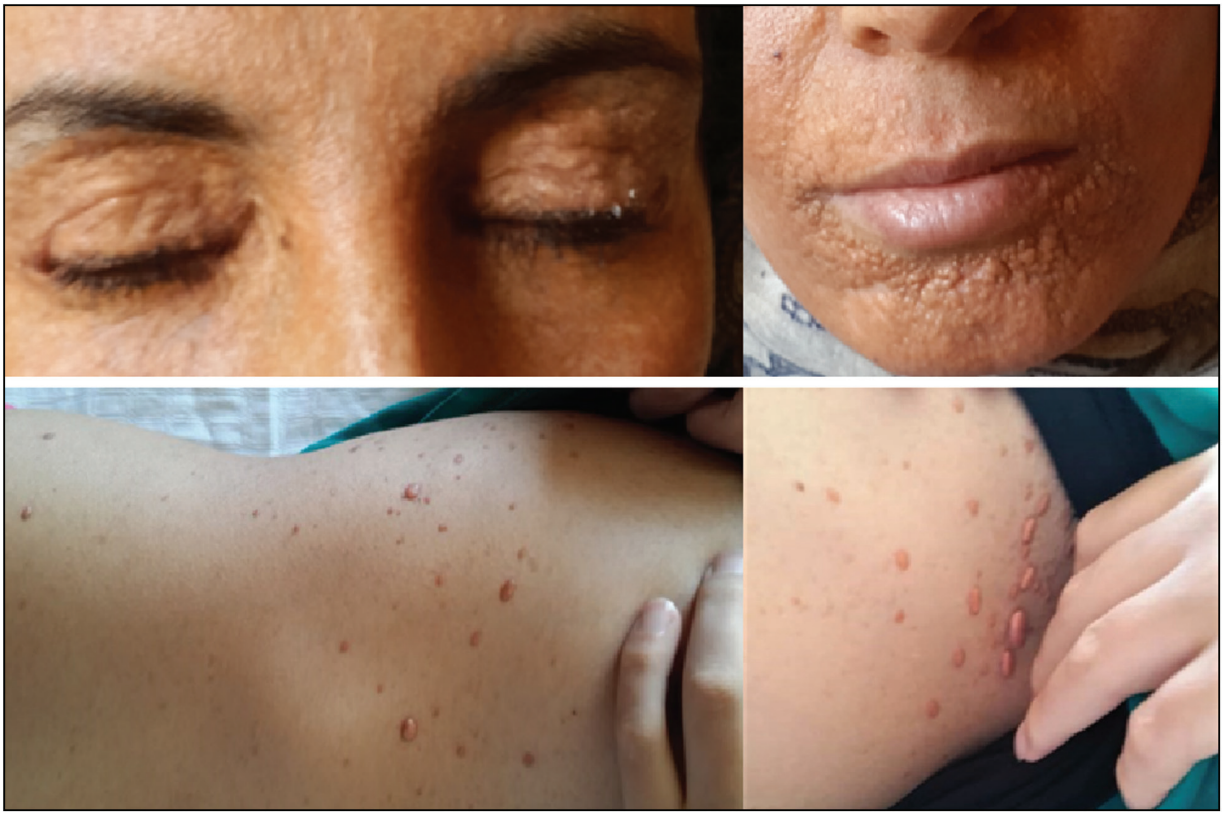

Figure 1: Skin lesions

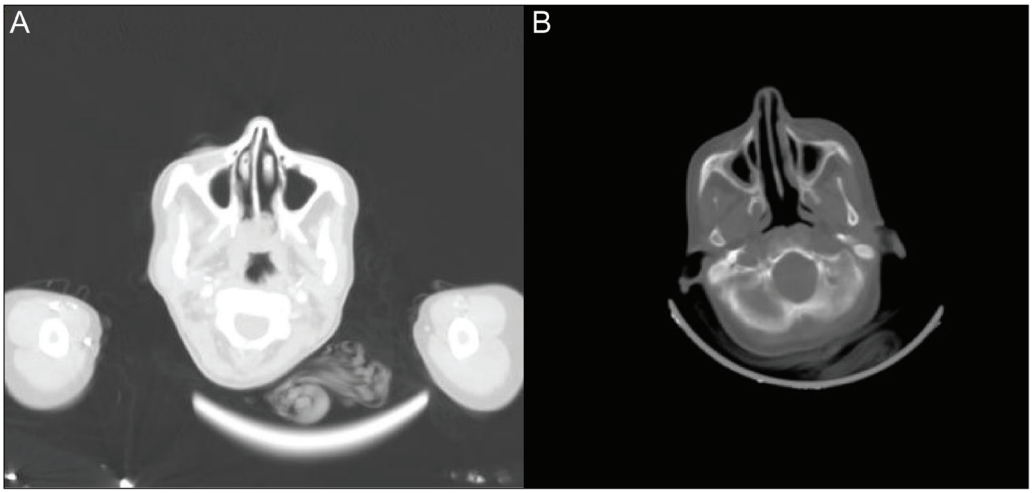

Figure 2: Axial sections of computed tomography scan showing the lesion obstructing the nasopharynx before (A) and after treatment (B)

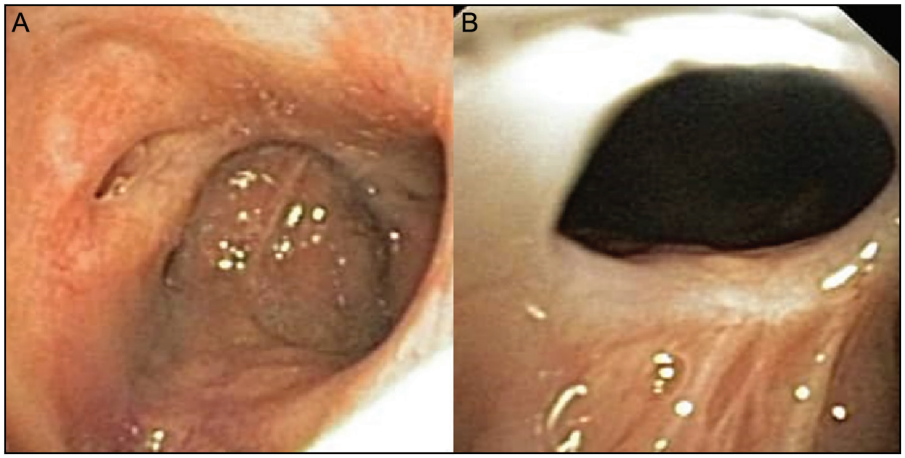

Figure 3: Endoscopic images show the mucosal lesion before (A) and after treatment (B)

Skin lesions and synovial membrane of the knee joint were biopsied. The biopsies from both skin and synovial membrane and subglottic stenosis showed proliferation of spindle cells, foamy cells, and Touton giant cells [Figure 4A]. Immune stains were positive for cluster of differentiation 68 (CD68) [Figure 4B] and negative for, S100 protein. A diagnosis of XD has been made.

The therapeutic plan included only desmopressin for the diabetes insipidus and laser therapy for her skin lesions as the patient initially refused any other treatment. However, after 3 months, the patient presented to the emergency department with weight loss, worsening dyspnea, and severe loud stridor. Urgent tracheostomy was performed to relieve symptoms. Even after the tracheostomy was performed, the patient still complained of shortness of breath. New high-resolution computed tomography showed centrilobular emphysema dominant in the upper lobes of both lungs sparing lung base. We hypothesize that this can be attributed to infiltration of the airways with XD [Figure 5].

A therapeutic trial with 0.14 mg/kg of cladribine was initiated. Cladribine was administered through 2–6 h of intravenous infusion for five consecutive days each month. The treatment was repeated for six cycles over 6 months. The patient's respiratory symptoms and joint pain gradually improved, especially after the fifth cycle. Hemoglobin, erythrocyte sedimentation rate, and C-reactive protein levels also improved as noted in Table 1. The patient received laser therapy for both skin and tracheal stenosis, which was holding the tracheostomy closure. The skin lesions did not improve; however, the tracheostomy was removed 8 months after the last dose of cladribine. The patient continued to improve 1 year after her last cladribine cycle.

DISCUSSION

XD is a benign proliferative disorder that usually presents in a stable persistent pattern. However, some reports described a progressive clinical course with extensive systemic involvement, including the central nervous system, liver, bone marrow, eyes, and joints.[1,3,5-7] The classic triad of XD

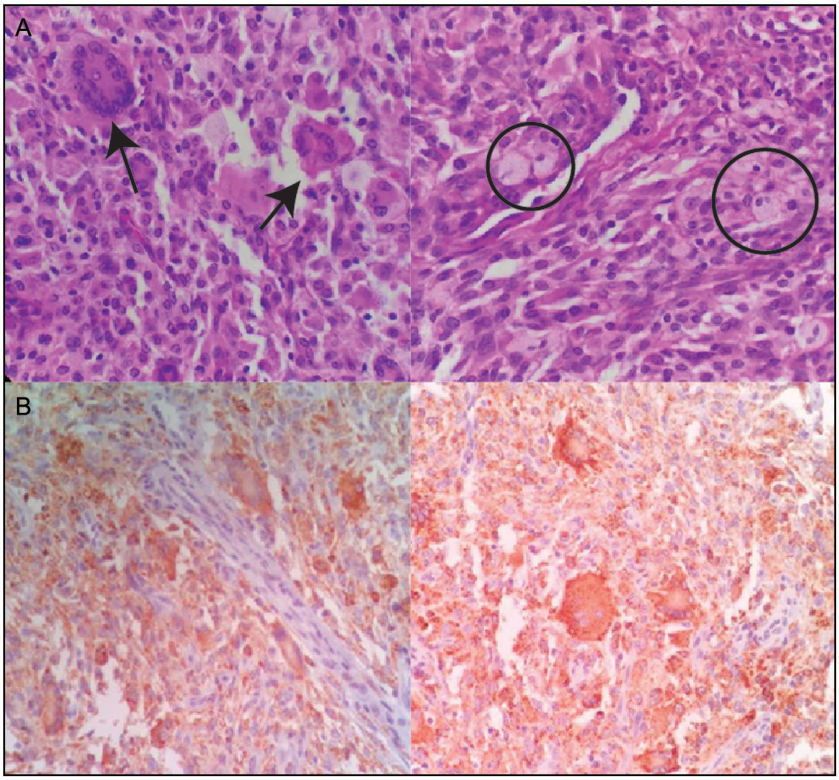

Figure 4: Skin biopsy showing (A) Touton giant cells (arrows) and dermal foam cells (in circles) and (B) CD68 positive immunostaining

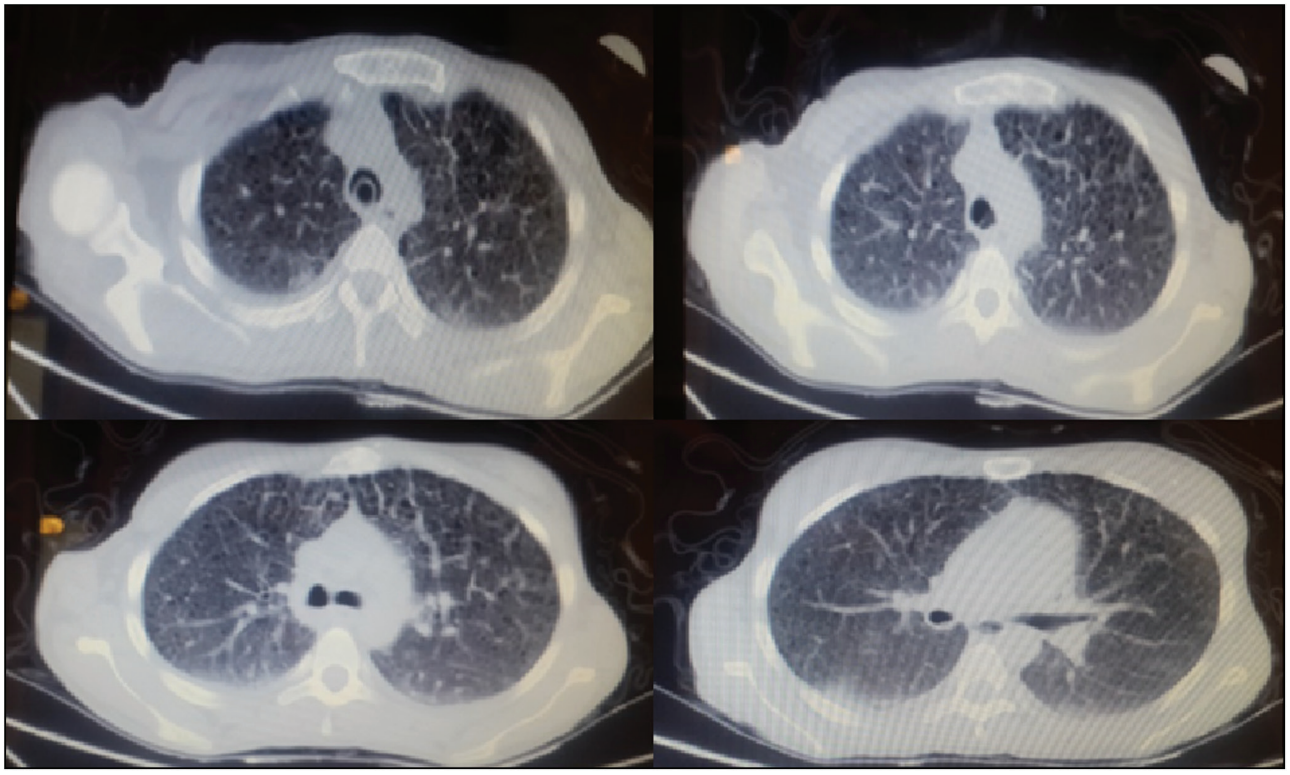

Figure 5: High-resolution computed tomography showing centrilobular emphysema dominant in the upper lobes

consists of cutaneous and mucous membrane xanthomatosis and diabetes insipidus.[4,8] Skin lesions predominantly appear on trunk, face, and intertriginous areas. As for mucosal membranes, oral mucosa and respiratory tract were most commonly involved. Respiratory manifestations include hoarseness and dyspnea.[1,4] Respiratory compromise may

Table 1: Hemoglobin, erythrocyte sedimentation rate, and C-reactive protein levels throughout cladribine cycles and at 1 year

Variable	First cycle	Second cycle	Third cycle	Forth cycle	Fifth cycle	Sixth cycle	1 year
HB (g/dL)	8.6	9.2	9.6	9	9.2	10.1	12
ESR (mm/h)	95	84	75	63	62	71	38
CRP (mg/L)	20	7.9	8.4	4.5	5.4	1.5	1.5

HB = hemoglobin, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein

become severe enough to require tracheostomy like our patient or can even lead to fatal outcomes.[9] Involvement of the central nervous system usually leads to central diabetes insipidus due to meningeal infiltration in the pituitary fossa.[5]

XD consists of foamy cells with giant histiocytes with high lipid content (Touton cells). The absence of Langerhans giant cells and epithelioid granuloma distinguishes XD from Langerhans cell histiocytosis. Immunostaining is usually positive for CD68 and negative for S100.[1,5,10]

Many treatment options for XD have been described, yet the ultimate treatment remains unclear. Adışen *el al.*[10] documented their experience with cladribine (0.14 mg/kg/day for 5 days each week, repeated every month for 7 months). The treatment was well tolerated by the patient, and the skin lesions flattened. No new lesions appeared in the 2 years of follow-up.[10]

In a case report and literature review by Campero *et al.*, various immunosuppressing agents were described with various responses. The only protocols that were effective causing complete or partial remission were vinblastine (32 cycles), cyclophosphamide, high-dose chemotherapy (carmustine, etoposide, cytarabine, and melphalan) with matched unrelated donor bone marrow transplantation, doxycycline, rosiglitazone, simvastatin, acipimox, 5–8 cycles of cladribine, cyclosporine and doxycycline, corticosteroids 1 mg/kg/day and thalidomide 100 mg/day, and anakinra (interleukin-1 receptor antagonist).[5]

Owing to cladribine's mechanism of action as a purine nucleoside analog that has been successfully used to treat myeloproliferative disorders, it could be a promising treatment option for XD due to the similarities between histiocytes and monocytes. It targets deoxyribonucleic acid (DNA) synthesis and repair by inhibiting DNA polymerase and ribonucleotide reductase.[11]

Our patient responded well to cladribine and showed a remarkable improvement despite the extent of her mucosal lesions and her poor status at presentation. Although her skin lesions did not respond to treatment, cladribine provided symptomatic relief and improved the patient's overall well-being and functional status. Also, no new skin lesions appeared after treatment.

Although we cannot rule out the possibility of spontaneous resolution, the patient's sustained and gradual improvement in relation to her treatment supports our theory. Further work has to be carried out to define the efficacy, minimal required dose, and safety on the long term.

XD is a rare infiltrative nonmalignant pathology with a variable extent and unpredictable clinical course. Till this day, the ultimate therapy has not yet been defined. Cladribine could be a promising therapy for XD, especially in cases with life-threatening lesions. Further studies are warranted to better understand its efficacy and limitations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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