Cutaneous and laryngopharyngeal papules of xanthoma disseminatum successfully treated with 2-chlorodeoxyadenosine

Naomi F. Briones, BS, MAT,[a] Norman D. Hogikyan, MD,[b] Douglas R. Fullen, MD,[c] Samuel M. Silver, MD, PhD,[d] and Thy Thy Do, MBBS[e]
Ann Arbor, Michigan

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INTRODUCTION

Xanthoma disseminatum (XD) is a rare, non–Langerhans cell histiocytosis characterized by a clinical triad of cutaneous xanthomas, xanthomas of mucous membranes, and diabetes insipidus.[1] Laboratory values, including serum lipid levels, are usually normal. Mucous membrane involvement is seen in 40% to 60% of patients, most commonly in the oropharynx and larynx.[2] Although benign, extensive skin lesions can be unsightly, and systemic involvement can lead to hoarseness, dysphagia, and diabetes insipidus and can result in increased mortality when critical organs are involved.[3] Attempted treatment modalities range widely and with varied success, using cyclophosphamide,[2] lipid-lowering agents,[4] CO_2 laser[5] and 2-chlorodeoxyadenosine (2-CdA) also known as *cladribine*.[6] Here we report a case of XD presenting with skin and symptomatic laryngopharyngeal lesions, with striking resolution after treatment with 2-CdA.

Abbreviations used:

2-CdA: 2-chlorodeoxyadenosine
XD: xanthoma disseminatum

CASE REPORT

A 55-year-old man presented to the Department of Dermatology at Michigan Medicine for further evaluation of mildly pruritic skin lesions of 3 months' duration. The patient had a prior biopsy showing xanthogranuloma and a previous laboratory workup showing normal complete blood count, lipid panel, serum and urine protein electrophoresis, and brain magnetic resonance imaging. His medical history was notable for a benign fibrous histiocytoma excised from his left orbit in 2013 and basal cell carcinoma.

On clinical examination, there were innumerable yellow-brown papules in the perioral distribution on the neck (Fig 1, *A*), upper chest, and back. There were also several yellow papules on the upper cutaneous lip and at the junction of the lower mucosal lip and gingiva (Fig 1, *B*). Repeat laboratory evaluation was unremarkable aside from a high-density lipoprotein value of 37. The patient underwent a confirmatory punch biopsy, which found a xanthomatous histiocytic dermal infiltrate with frequent Touton giant cells, consistent with XD (Fig 2).

The patient's review of systems was significant for a 3-year history of nonproductive cough and dysphonia. Of interest, he is a professional singer and very cognizant of his vocal capabilities. A laryngology consultation identified husky vocal quality and an abnormal voice-related quality of life[7] score of 72.5/100. Laryngeal and pharyngeal endoscopy including videostroboscopy found multiple submucosal papules in the posterior nasopharyngeal wall (Fig 3, *A*) and laryngeal surface

From the University of Michigan Medical School[a] and the Departments of Otolaryngology,[b] Pathology,[c] Internal Medicine,[d] and Dermatology,[e] University of Michigan.
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Correspondence to: Thy Thy Do, MBBS, Clinical Assistant Professor, University of Michigan, Department of Dermatology, 1910 Taubman Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109. E-mail: thythydo@umich.edu.

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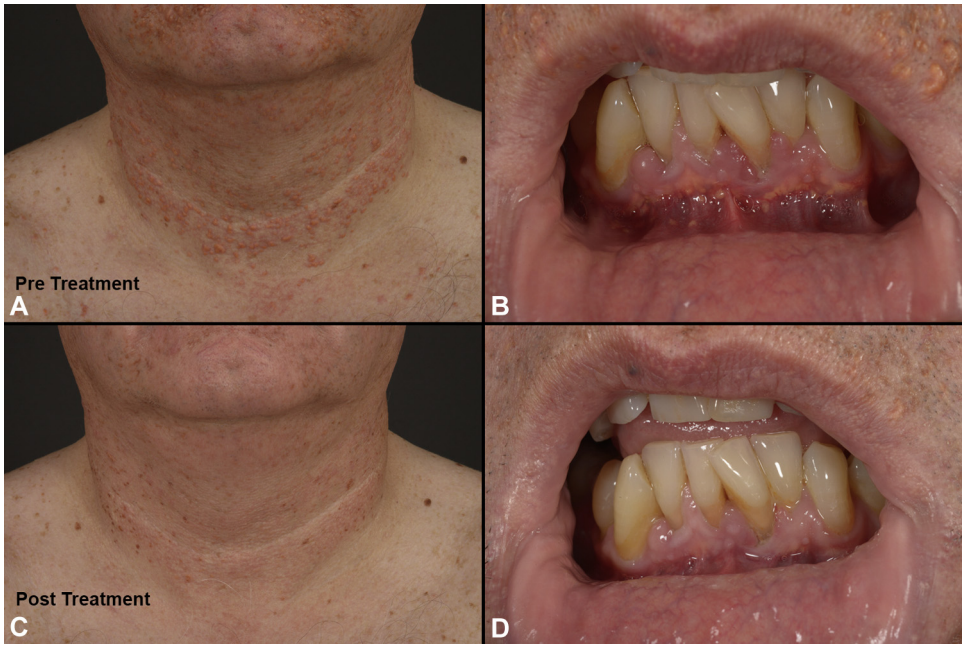

Fig 1. XD: cutaneous and laryngopharyngeal lesions before and after treatment with 2-CdA. **A**, Anterior neck pretreatment. **B**, Upper cutaneous lip and junction of the lower mucosal lip and gingiva pretreatment. **C**, Anterior neck 5 months posttreatment. **D**, Upper cutaneous lip and junction of the lower mucosal lip and gingiva 5 months posttreatment.

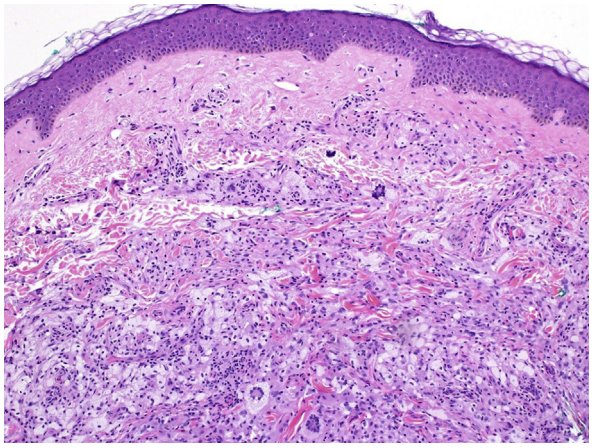

Fig 2. XD: xanthomatous histiocytic dermal infiltrate with frequent Touton giant cells in punch biopsy of skin. (Hematoxylin-eosin stain; original magnification: x100.)

of the epiglottis (Fig 3, *B*) and a prominent papule on the right anterior true vocal fold (Fig 3, *C*).

Given symptomatic and extensive cutaneous and laryngopharyngeal involvement, the patient was referred to the hematology-oncology department to discuss treatment with 2-CdA, which has been used to successfully treat cutaneous and central nervous system lesions.[6] The treatment is given as a 5-day continuous infusion as an outpatient and repeated monthly for 6 to 8 months. Our patient received 3 cycles of 2-CdA therapy, which was stopped earlier than planned because of thrombocytopenia and had excellent response with complete resolution of his throat symptoms and near-complete resolution of his skin symptoms (Fig 1, *C*), upper cutaneous lip and gingival symptoms (Fig 1, *D*), and laryngopharyngeal lesions (Fig 3, *D-F*). His voice-related quality of life score normalized to 100/100 3 months after treatment. Remarkably, the patient continued to respond to the chemotherapy for months after discontinuation of therapy. At 10 months' follow-up, he had resolution of his skin and laryngopharyngeal lesions and resolution of his thrombocytopenia. Additionally, he continues to sing professionally and is no longer troubled by cough, dysphonia, or skin lesions.

DISCUSSION

This man presented with extensive cutaneous and laryngopharyngeal lesions consistent with XD, a rare normolipemic histiocytosis. The precise etiology of XD is unknown but is commonly attributed to an inciting inflammatory process followed by xanthomatous deposition.[8] The disease can affect people of any age with a male/female ratio of 2:1-4:1, and it typically follows a chronic, benign course that can persist indefinitely or spontaneously resolve.[9] The disease is often associated with diabetes insipidus, which can be mild or transient in nature.[10] Besides

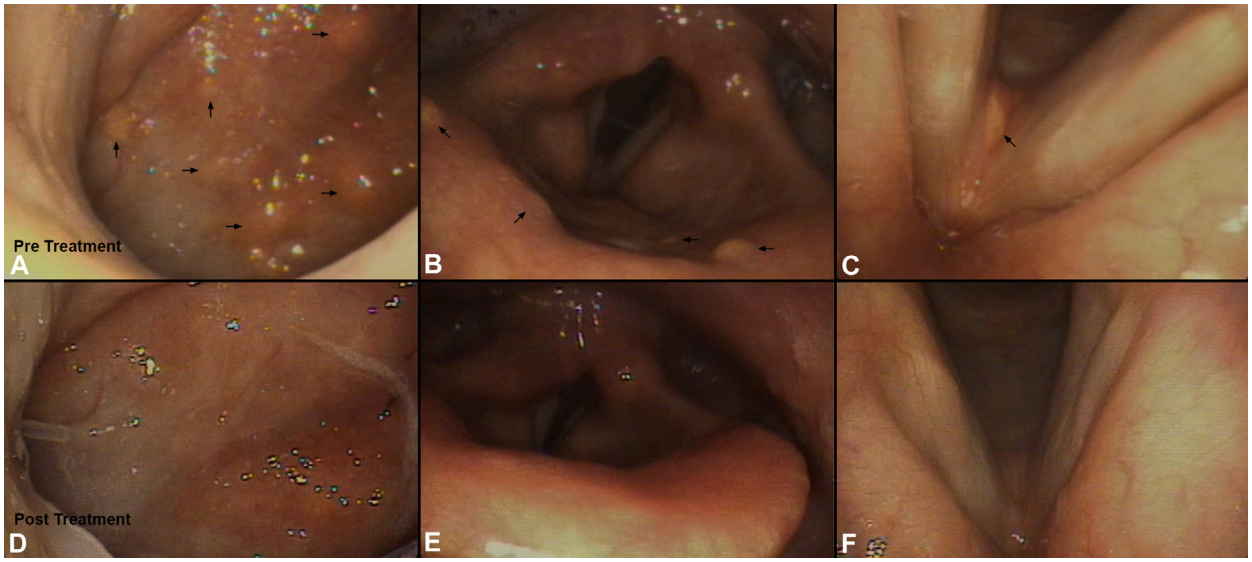

Fig 3. XD: laryngopharyngeal lesions before and after treatment with 2-CdA. **A**, Posterior nasopharyngeal wall lesions pretreatment (*arrows*). **B**, Supraglottic larynx with lesions on laryngeal surface of epiglottis pretreatment (*arrows*). **C**, Glottic larynx with lesion on right anterior true vocal fold pretreatment (*arrow*). **D**, Posterior nasopharyngeal wall 10 months posttreatment. **E**, Supraglottic larynx 10 months posttreatment. **F**, Glottic larynx 10 months posttreatment.

the skin, central nervous system, and larynx, other organs may be involved, including gastrointestinal tract, musculoskeletal, hepatobiliary, bone marrow, and respiratory tract—the latter can lead to respiratory failure and death.[4]

Treatment modalities used in cases of XD have included cyclophosphamide,[2] lipid-lowering agents,[5] and 2-CdA[6] with varying success. Laryngeal lesions specifically have been successfully treated to varying degrees with cyclophosphamide[2] and CO_2 ablative laser.[5] To our knowledge, however, this is the first report of laryngopharyngeal lesions of XD with complete resolution after cladribine therapy.

Given the possibility of widespread disease in a single patient with XD, surgical and laser modalities of treatment for targeted lesions may have limited therapeutic effects. In cases with more diffuse presentation including the skin and laryngopharynx, systemic therapies such as 2-CdA may prove to be particularly important, in as short as 3 cycles, and continued response is observed even after discontinuation of therapy.

Dermatologists play a key role in recognizing the distinctive skin manifestations of XD. Once diagnosed, other features of the disease, such as mucous membrane involvement of the respiratory tract or diabetes insipidus, may present over time. Thus, a multidisciplinary approach to care in coordination with departments such as otolaryngology, endocrinology, and hematology-oncology, is important for comprehensive management.

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