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CASE REPORT

Challenges in the Treatment of Xanthoma Disseminatum: Improvement in Disfiguring Facial Lesions with Cladribine and Brief Updated Literature Review

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Abstract: Xanthoma disseminatum (XD) is a rare normolipidemic mucocutaneous xanthomatosis that falls within the spectrum of cutaneous non-Langerhans cell histiocytosis. The management of XD poses significant challenges due to the limited availability of clinical data. Here, we report a case of XD with disfiguring facial involvement that showed marked improvement following treatment with cladribine. The patient tolerated the treatment well, with no significant adverse effects observed except for a transient decrease in white blood cell count, which normalized after symptomatic treatment with appropriate oral medications. Additionally, we provide an updated review of the literature on the use of cladribine in XD. Through this case report and literature review, we aim to underscore both the potential benefits and limitations of cladribine therapy for patients with XD. Furthermore, we emphasize the critical importance of effective interdisciplinary collaboration between dermatology and oncology for the optimal management of this condition.

Keywords: xanthoma disseminatum, disfiguring facial lesions, cladribine, adverse events

Background

Xanthoma disseminatum (XD) is a rare non-Langerhans cell histiocytosis characterized by disfiguring cutaneous lesions—typically symmetrical, red-brown to yellow papules that frequently coalesce into plaques.[1] With over 100 reported cases, XD presents unique therapeutic challenges due to its frequent mucosal involvement, risk of systemic complications (including urolithiasis[2]), and potential infiltration of the central nervous system, bones, and viscera. No standardized treatment exists, and the condition often proves refractory to conventional therapies. However, cladribine, a purine analog with established efficacy in hematologic malignancies and relapsing-remitting multiple sclerosis (RRMS),[3–5] has recently shown promise in improving disfiguring facial lesions in XD.

As an antineoplastic agent, cladribine selectively targets lymphocytes by disrupting DNA synthesis and inducing apoptosis.[4] While its immunosuppressive effects are well-documented in hematologic and autoimmune disorders, its role in XD remains investigational. Cladribine can treat XD, which may be related to targeted DNA damage, energy metabolism collapse, and selective cell apoptosis. Preliminary evidence suggests clinical improvement in cutaneous manifestations, yet critical gaps persist regarding optimal dosing, treatment duration, and mitigation of adverse effects—particularly myelosuppression and opportunistic infections. This review evaluates the therapeutic potential of cladribine in XD, with a focus on its impact on disfiguring facial lesions, while providing an updated synthesis of the literature.

We report a 26-year-old woman with progressive multiple yellow-brown papules on the face, neck and axillae for 3 years, while skin biopsy of the axillary papules was consistent with the pathologic diagnosis of XD; the patient had previously used oral upadacitinib and prednisone without significant effect, so after treatment with Cladribine in our

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hospital after ruling out the relevant contraindications, the patient's skin rash and itching had significantly improved and subsided compared to before treatment.

Case Report

We report a 26-year-old woman with a 3-year history of progressive yellow-brown papules on the face, neck, and axillae (Figure 1A–C), accompanied by severe pruritus that disrupted sleep. Previous treatments, including oral acyclovir, prednisone acetate, upadacitinib, and topical triamcinolone acetonide and halometasone creams, yielded no significant improvement. Clinical examination revealed: Yellowish-red, soft papules on the forehead, periorbital, perioral, and neck regions. Yellowish-red patches in the periorbital and perioral areas. Densely distributed yellowish-red, waxy papules in the bilateral axillae, measuring approximately 2–8 mm in diameter. Some of these papules coalesced to form confluent, reticulated plaques with a smooth surface and well-defined borders. The lesions were symmetrically distributed and felt soft to rubbery on palpation. A small number of yellowish-red, soft papules on the flexural areas of the extremities and the inguinal region. No evidence of mucosal involvement was found. A skin biopsy of axillary lesions demonstrated dermal fibrous histiocytoma with abundant foam cells, consistent with XD. Immunohistochemical analysis indicated that S100 and CD1a were negative (-), while CD68 and CD163 were positive (+).

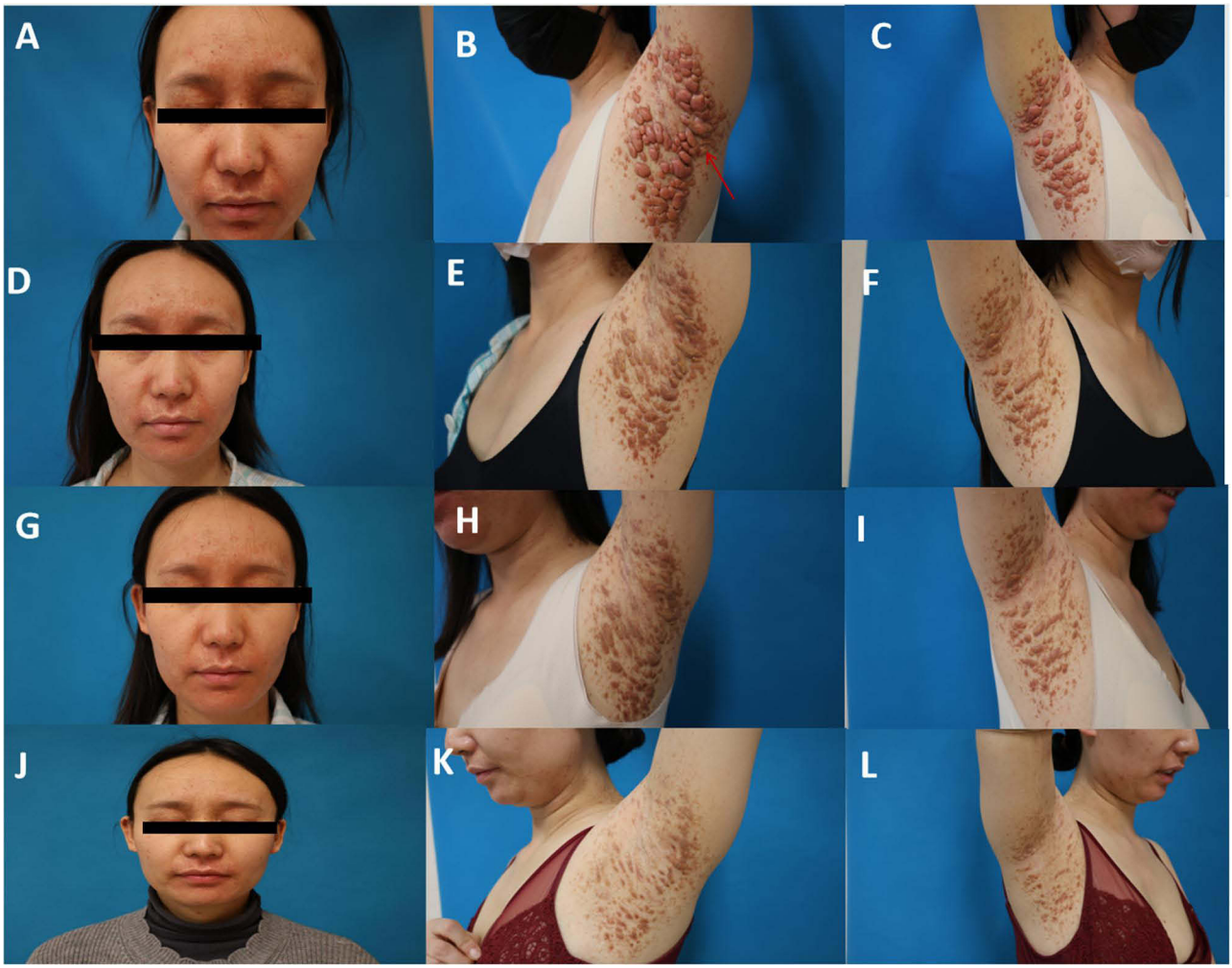

Figure 1 Clinical photographs show the progression of the patient's condition. (**A**–**C**) Before and; (**D**–**F**) after completing 3 courses of treatment; (**G**–**I**) after completing 5 courses of treatment. The location of the biopsy (red arrow); (**J**–**L**) after completing five treatment courses, two full courses of cladribine treatment were administered again three months later.

Upon admission, routine blood tests, biochemistry, and chest radiographs were unremarkable, and contraindications were excluded. The patient received cladribine at 0.14 mg/(kg·d) intravenously for 5 consecutive days per course, repeated monthly for a total of 5 courses. By the third course, the rash had decreased by approximately two-thirds, with residual lesions becoming smaller and softer, and pruritus significantly improved (Figures 1D–F). After completing 5 courses, the rash was nearly resolved, with only a few residual yellow papules in the axillae (Figure 1G–I).

During treatment, transient leukopenia, primarily lymphopenia, was observed, which resolved within 1–2 weeks post-treatment with symptomatic management. At the 3-month follow-up, a few pruritic papules recurred in the axillae and face, prompting two additional courses of cladribine treatment, which again led to the resolution of symptoms and further regression of the existing rash (Figure 1J–L). The patient remains under follow-up, with no significant adverse effects other than transient leukopenia.

Discussion

Xanthoma disseminatum (XD) is a non-Langerhans cell histiocytosis of unknown etiology, characterized by reactive histiocytosis with secondary lipid deposition within histiocytes.[6] The disease can occur at any age, including infants as young as 8 months, but is more prevalent in young individuals and males.[7] Lesions typically present as disseminated yellowish-red or brown papules or nodules, predominantly in flexural areas, which may coalesce into verrucous plaques. Mucosal involvement occurs in approximately 50% of cases, commonly affecting the oropharynx (causing dysphagia), larynx (leading to respiratory distress and airway obstruction), conjunctiva, and cornea (potentially causing blindness). Involvement of the bronchi, bronchioles, tonsils, and even cerebral xanthomas has also been reported. Severe dysphagia or dyspnea can be life-threatening due to the risk of asphyxiation. Approximately 50% of patients develop urolithiasis, despite normal lipid levels. Histopathological analysis reveals abundant xanthomatous cells, Touton giant cells, and inflammatory infiltrates.[8] Immunohistochemistry is negative for S-100 and CD1a but positive for monocyte and macrophage markers, including CD68, CD11b, CD11c, CD14, lysozyme, MAC-387, α1-antitrypsin, and factor XIIIa.[8] Electron microscopy shows no Langerhans granules in the histiocyte-like cells.

There is no satisfactory treatment for XD,[6] and the lesions can be treated by freezing, electrocautery, dermabrasion, laser and surgical excision. Some foreign studies have reported the use of cyclophosphamide, azathioprine, vincristine, methotrexate and other immunosuppressants for systemic treatment, as well as the systematic application of glucocorticosteroids, lipid-lowering drugs, nitrogen mustard phenylbutyrate and antimalarials, as well as intracutaneous injection of γ2 interferon and radiotherapy, which have been partially effective, but have failed in a large number of cases.[6,9,10] Existing case studies indicate that cladribine demonstrates superior efficacy compared to traditional therapies, with significantly higher response rates and longer duration of remission. Notably, cladribine is effective for both cutaneous and systemic manifestations, including critical visceral involvement such as tracheal stenosis, hypothalamic infiltration, and pharyngeal lesions.

As an anti-tumour drug, cladribine is mainly used for the treatment of acute leukaemia, malignant lymphoma and multiple myeloma.[11] In recent years, cladribine has shown good therapy in XD treatment.[12] A systematic review study showed that cladribine had the highest complete remission rate (CRR) of 27.1% and the lowest non-response rate of 9.1%.[5] This suggests that cladribine has significant potential in the treatment of XD. Although cladribine has shown good short-term efficacy in XD treatment.[13] The long-term efficacy and safety of cladribine needs to be further observed in order to determine the optimal therapeutic dosage and course of treatment to maximise efficacy and minimise adverse events. Currently, there are fewer long-term follow-up studies on cladribine in the treatment of XD, and in-depth studies are needed to investigate the mechanism of action of cladribine in the treatment of XD, to provide a basis for the development of new therapeutic targets, and to carry out a multicentre, randomised controlled trial to validate the efficacy and safety of cladribine in the treatment of XD; therefore, more clinical data are needed to assess its long-term effects and potential adverse events.

Current research has revealed that the treatment of XD with cladribine may be related to the following mechanisms. Cladribine, a purine nucleoside analog, exerts its therapeutic effects in xanthoma disseminatum (XD) through multiple mechanisms. Intracellularly, it incorporates into DNA to inhibit synthesis and repair, disrupts DNA break repair, and depletes NAD/ATP, ultimately suppressing cell proliferation.[14] Given the shared lineage between monocytes and

pathogenic histiocytes, cladribine selectively targets abnormally proliferating histiocytes in XD. Additionally, its immunomodulatory effects involve altering lymphocyte subpopulations,[15] as demonstrated in vitro, which may help restore immune homeostasis in XD. These dual actions—direct cytotoxic effects on histiocytes and immune regulation—underlie its clinical efficacy in XD treatment.

XD is characterized by CD68(+)/CD1a(−)/S100(−) non-Langerhans cell proliferation. Cladribine demonstrates selective activity against these cells, likely due to shared pathways with Langerhans cells (where it is effective in refractory cases).[16] Its mechanism involves targeted inhibition of abnormal proliferation with minimal impact on normal cells—possibly through apoptosis induction, as seen in other proliferative disorders like aggressive mastocytosis.[17] This selective cytotoxicity may explain its therapeutic efficacy in XD.

This study has several noteworthy limitations that warrant careful consideration. Primarily, as a single-case report with a relatively short follow-up duration, the findings inherently lack generalizability to the broader population of xanthoma disseminatum patients. Secondly, the pathogenesis of xanthoma disseminatum is not fully understood, and there is no uniform protocol for the therapeutic mechanism and standardised dosing of cladribine. Although cladribine was effective in this patient, its efficacy may not be universal due to individual variability (Table 1). Long-term follow-up studies are required to assess its sustained benefits and safety.

In the diagnosis and treatment of xanthoma disseminatum, dermatology and oncology must collaborate closely while clearly defining their respective roles and responsibilities: Dermatology is responsible for the initial diagnosis, identifying characteristic skin lesions (such as wax-drop-like papules), and confirming the diagnosis through deep skin biopsy (CD68+/CD1a- immunohistochemistry); while managing localized lesions (laser therapy/local injection); Oncology is responsible for systemic evaluation (PET-CT/bone marrow biopsy to rule out malignant tumors) and systemic treatment of progressive cases (eg, cladribine regimen).

Table 1 Cladribine-Treated XD Cases Summary Table

Study (Year)	Sex/Age, y	Treatment Cycles, No	Extent of Disease	Response	Major Side Effects	Follow-Up
Gayed MM et al[13] 2024	M/65	6	Arm, torso, contralateral arm, axilla, neck, and face.	Neck, face, and thigh lesions resolved; torso and axillary lesions flattened with residual hyperpigmentation.	Prolonged pancytopenia	Unknown
Tuan H et al,[3] 2019	M/25	5–8	Face, mucosa, conjunctiva, and skin folds (perioral, neck, axillary, inguinal, genital, perianal)	After 5–9 cladribine cycles, cutaneous and mucosal lesions significantly resolved.	No bone marrow suppression	After 52–66 months of follow-up, and to date, these patients are still in remission and have not shown any sign of relapse
	M/30		Face, mucosa, conjunctiva		No treatment-related adverse effects	
	M/5		Face, mucosa, conjunctiva, and skin folds (perioral, neck, axillary, inguinal, genital, perianal)			
Gupta V et al,[2] 2016	M/23	8	Face, neck and axillae	After 2 cladribine cycles, no new lesions developed. Existing lesions improved markedly by the 5th cycle, except peri-oral papules, which flattened significantly by the 8th cycle.	No treatment-related adverse effects	3-month the skin lesions have continued to gradually flatten, without relapse

(*Continued*)

Table 1 (Continued).

Study (Year)	Sex/Age, y	Treatment Cycles, No	Extent of Disease	Response	Major Side Effects	Follow-Up
Khezri F et al,[14] 2011	M/55	8	Bilateral arms, axillae, chest, breasts, inguinal region, and proximal thighs (anterior/posterior), and posterior neck	After 3 cycles, no new lesions developed, 50% improvement in prior cutaneous lesions	Joint pain and nightsweats	After 8 y, complete resolution with no evidence of recurrence
	M/46	5	Bilateral facial (cheeks, eyelids), ocular (limbal conjunctiva, orbits), and upper torso (chest, back, shoulders)	After 5 cycles, no new lesions developed, less inflammatory protuberant papules	No treatment-related adverse effects	3 mo after completing treatment, lesions had flattened and faded
	M/41	6	Bilateral upper limbs 、head/neck, and trunk	After 6 cycles, no new lesions developed, prior lesions much less indurated and erythematous	No treatment-related adverse effects	After 3 y, complete clearance with no new active lesions
	M/67	5	Bilateral upper limbs (arms, axillae), head/neck (scalp, periorbital, temples, cheeks, jawline), and trunk (chest, upper back)	After 4 cycles, lesions showed improvement: no new lesions; face/neck/chest lesions improved 50%; scalp/oral/lip lesions mostly resolved; arm/inguinal lesions substantially improved	No treatment-related adverse effects	After 6 mo, lesions continued to flatten and involute with no evidence of new lesions
	M/46	5	Bilateral axillae, eyelids, abdomen, pubic region, flanks, genitalia (penile corona, scrotum), and gluteal folds	After 5 cycles, no new lesions occurred; symptoms of burning and itching improved 80%; much less redness and induration of other lesions with flattening	No treatment-related adverse effects	Unknown

Conclusion

Although definitive conclusions remain premature, cladribine demonstrates potential as a safe and effective therapeutic option for xanthoma disseminatum. Further research is warranted to elucidate the duration of its clinical benefits and to determine whether its efficacy extends beyond cutaneous manifestations. Additionally, interdisciplinary collaboration is essential for the comprehensive management of XD. Future studies should focus on elucidating the therapeutic mechanisms of cladribine and optimizing treatment protocols to enhance patient outcomes.

Ethics Statement

The patient provided written informed consent for publication of this report and accompanying images. The Ethics Committee of BenQ Hospital, affiliated with Nanjing Medical University, has approved the publication of the case details.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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