Xanthoma Disseminatum

Effective Therapy With 2-Chlorodeoxyadenosine in a Case Series

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Background: Xanthoma disseminatum is a rare non-familial disease characterized by lipid deposition in skin and internal organs due to histiocytic cell proliferation, classified as a benign non-Langerhans cell histiocytosis. This chronic disease has no known established treatment. We report 8 cases of xanthoma disseminatum with treatment outcomes in long-term follow-up and provide a review of the medical literature.

Observations: We studied clinical manifestations; disease course; histopathologic and immunopathological findings; and responses to treatment in 8 consecutively seen patients with xanthoma disseminatum, including follow-up. The follow-up period ranged from 3 months to 8 years. Five patients received 2-chlorodeoxyadenosine. Therapy with 2-chlorodeoxyadenosine was effective at inducing remission and long-term control of cutaneous lesions of xanthoma disseminatum in 5 cases. Adverse effects were minimal, and treatment was well tolerated. No improvement was noted in untreated patients.

Conclusion: Among 8 cases of xanthoma disseminatum, a positive response to treatment with 2-chlorodeoxyadenosine was seen in 5 cases.


XANTHOMA DISSEMINATUM (XD) is a rare benign, non-familial condition in which lipid deposition occurs secondary to a proliferation of histiocytic cells. No known trigger for xanthomatous proliferation and deposition has been identified. Xanthoma disseminatum has been described as a reactive phenomenon rather than a neoplastic process. It is characterized by cutaneous xanthomatous lesions that usually affect the flexural regions, along with ocular, oral and pharyngeal, visceral, central nervous system, and skeletal involvement. Age at onset of XD can be as early as 8 months or as late as 85 years. The disease is more prevalent among males, with a male to female ratio of 2:1. No typical inheritance pattern or geographic distribution has been identified.

Three clinical variants have been proposed on the basis of disease progression and prognosis: a common persistent form, a less common progressive form with systemic involvement, and a rare form of self-limited disease. The disorder can be differentiated from eruptive xanthomas, malignant histiocytosis, and Langerhans cell histiocytosis through age at onset, serum lipoprotein profiles, histopathologic findings, and immunohistochemical results. Since its first description by Montgomery and Osterberg in 1938, only approximately 100 cases have been reported in the medical literature. Although the natural history of XD is usually benign, with spontaneous resolution of cutaneous lesions over 2 to 40 years, lesions in certain anatomical locations may result in substantial morbidity and death. There is no consensus regarding curative therapy for XD. Response to any form of therapy in XD has been mostly unsatisfactory. Herein, we report 8 cases of XD, 5 of which showed substantial improvement after administration of 2-chlorodeoxyadenosine (2-CdA).

REPORT OF CASES

The 8 cases are briefly described herein. Patient characteristics are summarized in the Table.

CASE 1

A 75-year-old woman had onset of purpuric xanthomatous nodules, papules, and plaques under her arm and subsequently of the axillae, anterior surface of the chest,
breasts, inguinal area, upper anterior and posterior surfaces of the thighs, and posterior surface of the neck. The patient’s lipid profile results were within the reference range. There was no internal organ involvement. Pathologic features were consistent with XD. The patient received topical treatments with dressings, but she elected to receive systemic therapy.

### Table. Clinical Summary of the 8 Cases

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Location of Skin Lesions</th>
<th>Internal Organ Involvement</th>
<th>Lipid Profile</th>
<th>Diagnosis Confirmed by Pathologic Findings</th>
<th>Treatment With 2-CdA</th>
<th>Treatment Cycles, No.</th>
<th>2-CdA Treatment Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/75</td>
<td>Arm, axillae, anterior surface of chest, breasts, inguinal area, upper anterior and posterior surfaces of thighs, posterior surface of neck.</td>
<td>No</td>
<td>Reference range</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Died of unrelated cause</td>
</tr>
<tr>
<td>2/M/55</td>
<td>Cheeks, eyelids, eye globe in a limbic distribution, orbits, chest, upper back, and shoulders</td>
<td>No</td>
<td>Reference range</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>After 3 cycles, no new lesions developed, 50% improvement in prior cutaneous lesions</td>
<td>After 8 y, complete resolution with no evidence of recurrence</td>
</tr>
<tr>
<td>3/M/46</td>
<td>Flanks, thighs, calves, chest, abdomen, back, back of thighs, arms, eyelids</td>
<td>No</td>
<td>Reference range</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>After 5 cycles, no new lesions developed, less inflammatory protuberant papules</td>
<td>3 mo after completing treatment, lesions had flattened and faded</td>
</tr>
<tr>
<td>4/M/41</td>
<td>Arms, axillae, scalp, around eyes, temples, cheeks, jaw line, neck area, chest, upper back, arm, upper and lower eyelids bilaterally</td>
<td>No</td>
<td>High cholesterol level</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>After 6 cycles, no new lesions developed, prior lesions much less indurated and erythematous</td>
<td>After 3 y, complete clearance with no new active lesions</td>
</tr>
<tr>
<td>5/M/67</td>
<td>Periocular area, cheeks, angles of mouth, neck, upper back, shoulders, anterior surface of chest, axillae, inguinal areas, perianal area, scalp, eyelids, external ear canal, sclera, conjunctiva, soft and hard palates, lower interdental papillae, subglottic lesions bilaterally</td>
<td>Pituitary stalk and gland, with diabetes insipidus and airway involvement</td>
<td>Reference range</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>After 4 cycles, no new lesions developed; face, neck, and chest area lesions improved 50%; many of scalp, oral mucosal, and lip lesions resolved; arm lesions and inguinal lesions also improved substantially</td>
<td>After 6 mo, lesions continued to flatten and involute with no evidence of new lesions; on MRI, normalization of anatomical parameters of the pituitary</td>
</tr>
<tr>
<td>6/M/33</td>
<td>Eyelids, mouth and nose area, axillae, neck, groin, antecubital fossae, popliteal fossae, wrists, ankles, buttocks, scrotum and penis, lips, buccal mucosa, palate, tongue</td>
<td>No</td>
<td>Reference range</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Unknown</td>
</tr>
<tr>
<td>7/M/46</td>
<td>Axillar, eyelids, anterior surface of abdomen, pubic area, flanks, corona of the penis, scrotum, gluteal fold</td>
<td>No</td>
<td>Reference range</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>After 5 cycles, no new lesions occurred; symptoms of burning and itching improved &gt;80%; much less redness and induration of other lesions with flattening</td>
<td>Unknown</td>
</tr>
<tr>
<td>8/M/25</td>
<td>Inferior and superior to iris of each eye, around maxillary and mandibular portions of gum</td>
<td>Pituatory stalk, adenoids, soft palate</td>
<td>High triglyceride level</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Died of self-inflicted wounds</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; NA, not applicable; 2-CdA, 2-chlorodeoxyadenosine.
no systemic treatment because of her advanced age. No additional follow-up information is available for this patient.

**CASE 2**

A 55-year-old man had acute and progressively worsening onset of yellowish lesions that began on the cheeks and progressed to involve the entire face, eyelids, globe of the eyes in a limbic distribution, orbits, chest, upper back, and shoulders. The patient's lipid profile results were within reference range. There was no internal organ involvement. The pathologic evaluation of the lesions showed a granulomatous inflammatory infiltrate composed predominantly of histiocytes with xanthomatous cytoplasm and many giant cells, extending to the mid reticular dermis and into the deep dermis. Special stains were performed, including CD68, which was positive for disease; stains for S-100 and CD1a were negative for disease, consistent with the diagnosis of XD.

Treatment was started with 2-CdA utilizing a dose of 0.14 mg/kg/d for 5 days of 1 week and repeated every month for 8 months, with a complete blood cell count conducted weekly. After three 1-month treatment cycles, no new lesions had occurred, and the patient had 50% improvement in established cutaneous lesions. Adverse effects of 2-CdA were limited to joint pain and night sweats. After 5 treatment cycles, the patient had no new lesions and had achieved additional improvement in established lesions, which were more flat and less erythematous. After 8 years of follow-up to date, the patient continues to have complete resolution with no evidence of recurrence.

**CASE 3**

A 46-year-old man had onset of disfiguring, yellow-to-orange-colored papules and plaques on the right side of his flank. He subsequently had plaques on the left side of his flank, anterior and posterior surfaces of the thighs, calves, chest, abdomen, back, and arms. The lesions spared only the face, palms, soles, and feet. Yellowish nodules developed over the arms, shoulders, and thighs. He also had involvement of the eyelids, with a granular appearance of the eyelid margin. His lipid profile findings were within the reference range. There was no internal organ involvement. Pathologic findings on a skin biopsy specimen showed changes consistent with XD.

Treatment was started with 2-CdA at a standard dose (0.14 mg/kg/d for 5 days of 1 week and repeated every month) for 8 months, with a complete blood cell count conducted weekly. After three 1-month treatment cycles, no new lesions had occurred, and the patient had 50% improvement in established cutaneous lesions. Adverse effects of 2-CdA were limited to joint pain and night sweats. After 5 treatment cycles, the patient had no new lesions and had achieved additional improvement in established lesions, which were more flat and less erythematous. After 8 years of follow-up to date, the patient continues to have complete resolution with no evidence of recurrence.

**CASE 4**

A 41-year-old man had onset of disfiguring, yellow-to-orange-colored plaque skin lesions under the arms, on the axillae and scalp, and around the eyes. The lesions were largely asymptomatic. Many new lesions were beginning to develop over the face, temples and cheeks, jaw line, neck area, chest, upper back, arms, and upper and lower eyelids bilaterally. There was no internal organ involvement. His lipid profile results showed that he had a high cholesterol level (total cholesterol level, 259 mg/dL; low-density lipoprotein level, 204 mg/dL; high-density lipoprotein level, 32 mg/dL; triglycerides level, 116 mg/dL; to convert total cholesterol, low- and high-density lipoproteins, and triglycerides to millimoles per liter, multiply by 0.0259). Pathologic findings of a skin biopsy were consistent with XD.

Treatment was started with 2-CdA for six 1-month 6 cycles (5 days of treatment in 1 week and repeated every month). After completion of the 6 cycles, xanthomatized lesions persisted—but were much less indurated and much less erythematous—in the peri-orbital areas, temples, chin, submandibular neck area, posterior surface of the neck, upper back and shoulders, and upper chest, with substantial involution of the xanthomatized lesions of the axillae, antecubital area, and groin. After 3 years of follow-up, the patient had complete lesion clearance and no new lesions of XD developed in the interim.

**CASE 5**

A 67-year-old man had onset of multiple progressive, discrete, erythematous, papular-to-nodular lesions in the periocular area, cheeks and angles of the mouth, neck, upper back, shoulders, anterior surface of his chest, axillae, inguinal areas, perianal area, scalp, eyelids, and the external ear canal. He also had xanthomatous lesions with prominent telangiectasia of sclerae, conjunctivae, and soft and hard palate; lower interdental papillae; and subglottic lesions. The patient had infiltration of the pituitary stalk and gland, with diabetes insipidus and airway involvement. Results of the lipid profile were within the reference range. Pathologic evaluation of a skin biopsy specimen showed changes consistent with XD.

Treatment was started with 2-CdA (0.14 mg/kg/d for 5 consecutive days and repeated monthly). After 4 treatment cycles, the patient had approximately 50% improvement in lesions of the face, neck, and chest areas. Many of the lesions of the scalp, oral mucosa, and lips had resolved. The underarm lesions and inguinal lesions had improved significantly. He had no new lesions develop during follow-up. After 6 months of follow-up, the lesions continued to flatten, with involution of the XD lesions and no evidence of new lesions. Follow-up magnetic resonance imaging of the pituitary showed normalization of the anatomical parameters.

**CASE 6**

A 33-year-old man had onset of progressive pink papules around the margins of his eyelids and subsequently around his mouth, nose, and axillae. The lesions then became disseminated in the flexural neck, axillae, groin areas, antecubital fossae, and popliteal fossae and at the flexures of his wrists and ankles, with lesions on the buttocks, scrotum, and penis. Subsequently, lesions developed in the nares and the mouth, involving the lips, buccal mucosa, palate, and tongue. There was no internal
organ involvement. The patient’s lipid profile findings were in the reference range. Pathologic results of a skin biopsy were consistent with XD. The patient refused any systemic treatment. No additional follow-up information is available on this patient.

CASE 7

A 46-year-old man had onset of progressive discrete and coalescing papules and nodules that ranged from violaceous to yellow and xanthomatized in the axillae and the eyelids (Figure 1); they subsequently progressed over the anterior surface of the abdomen, pubic area, flanks, corona of the penis, scrotum, and gluteal fold. There was no internal organ involvement. Results of his lipid profile were in the reference range. Pathologic findings of a skin biopsy were consistent with XD. The patient completed 5 cycles of 2-CdA treatment at 0.14 mg/kg/d for 5 consecutive days, repeated monthly. His symptoms of burning and itching improved considerably, estimated at more than 80%. He also had much less redness and induration of the other skin lesions (Figure 2).

CASE 8

A 25-year-old man had onset of progressive xanthomatous yellow papules under his eyes, inferior and superior to the iris of each eye, and around the maxilla and
mandibular portions of the gum. He had a sore throat and severe hoarseness of his voice. There was also infiltration of the pituitary stalk, adenoids, and soft palate. The patient's lipid profile results showed a high triglyceride level. Pathologic evaluation of a skin biopsy showed changes consistent with XD (Figure 3). The patient refused any systemic treatment and later died of self-inflicted wounds.

COMMENT

Xanthoma disseminatum is a rare, non–Langerhans cell histiocytic syndrome that predominantly affects young men and seems to be sporadic. No familial cases have been reported. The disease often begins insidiously but may lead to extensive morbidity. It usually presents with red-to-yellow papules and nodules, often in such flexural sites as the axillae and groin, that gradually enlarge over several years, forming confluent xanthomatous plaques. Mucous membrane involvement occurs in 40% to 60% of patients, mostly affecting the oropharynx (leading to dysphagia), larynx (dyspnea), or the cornea and conjunctiva (blindness). Involvement of nonmucocutaneous sites also occurs; 40% of patients eventually have diabetes insipidus due to meningeal involvement in the pituitary fossa. Central nervous system lesions may present with epilepsy, hydrocephalus, or cerebellar ataxia. Osteolytic bone lesions and synovitis have been described.

Histopathologic results include diffuse dermal infiltration by histiocytes and Touton giant cells, along with a sparsity of lymphocytes, plasma cells, and neutrophils. Usually, eosinophils are not a prominent component of the inflammation. Immunohistochemical evaluation shows that the histiocytes are phenotypically indistinguishable from dermal dendrocytes, most commonly expressing the surface markers CD68 and factor XIIa and lacking expression of S-100 and CD1a.11

The response to any form of treatment in XD is at best unsatisfactory. Surgical excision or laser therapy can improve physical and functional appearance, but the course of the disease is characteristically punctuated with frequent relapses. Treatment with antimitic drugs has been ineffective in many reported cases.10 Oral corticosteroids do not seem to be remittive, but may offer some palliation and possibly deter recurrence of cutaneous lesions after surgical excision. Clofibrate has been of limited benefit in a few cases. Cyclophosphamide and azathioprine have been reported to be effective in selected cases.11 Calverly et al12 described a patient with treatment failure to prednisone and vinblastine used in combination, although vinblastine was reported to be effective in another case.13 Azathioprine was reported to be ineffective for a patient with upper respiratory tract involvement.14 Stojkovic et al14 reported symptomatic improvement in an 18-year-old girl with XD and central nervous system lesions treated with a combination of corticosteroid treatment and chemotherapy. Seaton et al15 reported that cutaneous lesions remained stable during azathioprine administration, although preexisting plaques did not improve and ocular lesions progressed despite treatment. Cyclophosphamide therapy has resulted in significant resolution of cutaneous, ocular, and laryngeal lesions. In brief, although improvement has been reported with glucocorticoids, fibrates, chlorambucil, and cyclophosphamide, none of these treatments led to lasting beneficial effects in most cases.

2-Chlorodeoxyadenosine is a purine nucleoside analog resistant to deamination adenosine deaminase. Cladribine is not directly DNA toxic; instead, its mechanism of action includes inhibition of ribonucleotide reductase, DNA polymerase, and DNA. For the most part, it has been used for the treatment of lower-grade lymphoproliferative disorders and myeloid leukemias.15 Theoretically, 2-CdA could be of use for the treatment of XD because of similarities among histiocytes, the progenitor cells of XD and monococytes. It was successfully used in the treatment of an adult patient with Langerhans cell histiocytosis in 1993.15 Nevertheless, to our knowledge, there has not been a report of 2-CdA use in XD, even though it has been prescribed by individual clinicians. The toxicity profile of cladribine is well established. It has been found to be well tolerated when given in therapeutic doses. Its toxicity is mainly limited to myelosuppression and infectious disease susceptibility.16

We describe 7 men and 1 woman seen consecutively who had XD (age range, 25-75 years). Two of these patients had an abnormal lipid profile, and 2 had internal organ involvement. Five of our patients elected to receive 2-CdA therapy with a dosage of 0.14 mg/kg/d for 5 days, repeated every month for 5 to 8 cycles. After 3 to 5 treatment cycles, new lesions stopped developing in all patients, and all patients had substantial improvement in their established lesions. Treatment was well tolerated, and none of our patients showed any serious adverse effects of the medication. The follow-up period ranged from 3 months to 8 years, during which all patients treated with 2-CdA showed satisfactory remission with no development of new lesions. Of note, 3 patients in our case series refused to receive treatment with 2-CdA; 2 of these patients died of unrelated causes with no improvement in skin lesions, and follow-up on the other patient is not available.
In summary, 2-CdA induced regression of mucocutaneous lesions in XD without serious toxic effects. To our knowledge, the present report is the first on 2-CdA efficacy in this rare and severe disorder. We believe it is important to report these 8 cases with 5 treatment summaries because prior reports have failed to show efficacy of other treatment modalities.

In conclusion, 2-CdA therapy resulted in remission of XD in 5 of 8 patients. Therapy was administered easily, with minimal adverse events and no substantial immediate or delayed toxic effects. Further clinical trials are necessary to determine the role, optimal dosage, and administration route (intravenous vs oral) of 2-CdA in the treatment of XD.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Khezri, Gibson, and Tefferi. Acquisition of data: Khezri, Gibson, and Tefferi. Analysis and interpretation of data: Khezri, Gibson, and Tefferi. Drafting of the manuscript: Khezri and Gibson. Critical revision of the manuscript for important intellectual content: Khezri, Gibson, and Tefferi. Statistical analysis: Khezri. Obtained funding: Gibson. Administrative, technical, and material support: Khezri and Gibson. Study supervision: Gibson and Tefferi.

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