Xanthoma Disseminatum: Case Report and Mini-Review of the Literature

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SUMMARY Xanthoma disseminatum is a non-familial disorder of non-Langerhans cell origin or a class II histiocytosis with unknown etiology, with just over 100 cases reported in the literature. Because of the rarity of this disease, there is no established treatment. We studied clinical manifestations and different treatments of xanthoma disseminatum from a series of cases, including our own patient.
We studied 15 articles on treatment of xanthoma disseminatum. Local treatment with cryotherapy, radiotherapy, surgery, and carbon dioxide lasers have been attempted with various results. Systemic medication with peroxisome proliferator-activated gamma receptors, statins, fenofibrate, chlorodeoxyadenosine, cyclophosphamide, doxycycline, and cyclosporine have also been reported, but none have proven particularly successful.
Xanthoma disseminatum is usually benign and is often self-limiting.
If the lesions are accessible to surgery, that is likely to give the best results. However, if the lesions are not accessible for surgical removal then carbon dioxide laser treatment may be considered. The choice of oral treatment should be made on the basis of the patient's condition, since none of them have proven particularly effective. Expectant management is justifiable as long as the lesions are limited to the skin.

KEY WORDS: cyclosporine, doxycycline, histiocytoses, non-Langerhans cell, therapy, xanthoma disseminatum

CASE REPORT

A 61-years old man presented with a two week history of pink-brown papules on the trunk and arms. He denied any ocular symptoms, dyspnoea, polydipsia, polyuria, or neurologic symptoms.

He had taken no medication. No family history of a similar skin eruption could be elicited.

On examination there were multiple, round to oval, pink-brown papules with size ranging from 0.1 to 0.5 cm in diameter (Figure 1 and 2) The lesions were predominantly located on the upper-back and in the abdominal region. Scattered lesions were observed on the arms, and some papules had coalesced into small plaques. There was no involvement of the oral mucosa.

Skin biopsy of the lesion revealed a dermal infiltrate comprising lymphocytes, foamy histiocytes, and a few multinuclear giant cells (Figure 3).

Immunohistochemical analysis revealed positive labeling of the histiocytes and multinucleated giant cells with antibodies against CD68 (Figure 4). A stain-

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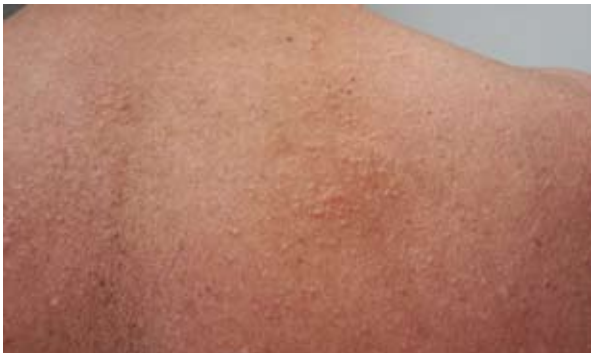

Figure 1. Lesions of xanthoma disseminatum on the upper-back of our patient revealing multiple pink-brown papules, of which some coalesced into small plaques.

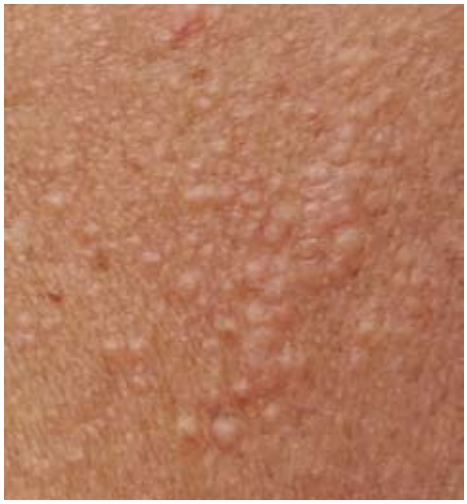

Figure 2. Close-up of xanthoma disseminatum lesions on the upper-back of our patient.

ing with LCA (leucocyte common antigen) was positive for lymphocytes and histiocytes and negative for S-100 and C-KIT markers. Based on the clinical and histopathological results we diagnosed xanthoma xisseminatum (XD).

Radiographic investigation was performed to exclude any internal manifestation of xanthoma disseminatum that could be fatal. Chest X-ray imaging was normal. Computed tomography (CT) investigation of the abdomen, on the other hand, revealed multiple enlarged lymph nodes in the mesenteric adipose tissue, as well as sigmoid diverticulosis. However, both findings were considered to be benign and nonspe-

Table 1. Summary of results of systemic treatment and demographic data of patients with xanthoma disseminatum from the published case series and reports

Case	Sex	Age Of onset, years	Duration of follow-up, years	Mucous membranes involved	DI	Other systemic involvement	Treatment	Clinical course	Remark	Ref. No.
1	M	32	3	No	Yes	No	PPAR-γ, statins, fenofibrate	Partial remission	DI treated with cyclophosphamide and desmopressin with improvement but no effect on XD cutaneous lesions.	19
2	F	59	2 ¾	Buccal mucosa, soft palate, tongue	No	No	Rosiglitazon, simvastatin, acipimox	Partial remission	Initially treated with glucocorticoids and cyclophosphamide with no success.	20
3	M	30	2	*Nasopharyngeal, conjunctiva, buccal mucosa*	No	Bone	Rosiglitazon, simvastatin, acipimox	Partial remission	Previous treatments with etoposide and subcutaneous interferon gamma were ineffective.	21
4	M	N= 5: 41-67	¼ - 8	Soft palate: N=1, eye: N=5	Yes N=1	Pituitary stalk: N=1	2-Chlorodeoxy-adenosine	Complete resolution: N=2	Number of treatment cycles: 5-8	22
5	M	10	1 ½	Ocular, laryngeal	Yes	Pituitary, central nervous system	Cyclo-phosphamide	Partial remission	XD with extensive systemic involvement at young age.	23
6	F	29	1 ½	Conjunctiva, *naso-pharyngeal*	No	No	Doxycycline	Regression	Leaving anetodermicscars.	24
Our case	M	61	½	No	No	No	Doxycycline, cyclosporine	Partial remission	No response to doxycycline.	-

DI= Diabetes insipidus

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cific. Single photon emission computed tomography (SPECT) / CT bone scans and a nuclear magnetic resonance (NMR) brain scan were both normal.

Laboratory data revealed hyperthyroidism in novo and a pre-existing leukopenia. The levels of cholesterol, triglycerides, and low density lipoprotein (LDL) were all within normal limits. Urinalysis revealed no abnormalities. The patient received treatment with thiamazol for hyperthyroidism.

Initial treatment for xanthoma disseminatum was doxycycline (200 mg per day). However, after one month of observation there was still no sign of improvement. Consequently we substituted doxycycline with cyclosporine (300 mg per day) in split doses. The treatment was given for six weeks and then stopped due to the lack of improvement. We then opted for expectant management, since the disease was tending towards stabilization with no sign of new lesions. Approximately five months after the onset of the disease, some lesions started to spontaneously disappear.

DISCUSSION

We reported the case of a 61-years-old man with xanthoma disseminatum, who achieved partial remission after subsequent treatments with doxycycline and cyclosporine.

Xanthoma disseminatum (XD) is a non-familial disorder of non-Langerhans cell origin or a class II histiocytosis with unknown etiology (1,2). This extremely rare condition was first described by Montgomery and Osterberg in 1938. Only 100 patients had been described in the literature to date (2).

The average age of disease onset is over 40 years (3). The male to female ratio is 2.4:1 (4).

Primary skin manifestations of XD include multiple red-yellow papules and nodules, most commonly in the flexural sites. However, large plaques with raised and indurated borders and some papules around the plaques have also been described by Hisanaga *et al*. (5).

In 40-60% of the patients with XD the mucous areas are also infected, which can cause significant morbidity and mortality (6). For instance, localized mucous lesions in the oropharynx, larynx, and cornea can lead to dysphagia, dyspnoea, and obstructive blindness respectively (7). If functional anatomic sites are not affected by XD lesions, then the natural history of this disorder may be benign rather than fatal (6). Nonetheless it is important to note that XD does not always affect the skin exclusively. At least two case reports described four XD patients with central nervous system involvement (8,9). One 23-year-old woman died of progressive XD lesions in the brain stem and proximal spinal cord. A few cases have also been reported where XD lesions in the pulmonary tract with involvement of the small-sized bronchi caused a fatal outcome (10,11).

Diabetes insipidus (DI) may also develop as a result of meningeal lesions in the pituitary fossa. This occurs in 40% of the patients (7).

On the basis of the clinical course of the disease, three clinical patterns can be distinguished. The persistent form is the most common variant, followed by the progressive form with systemic involvement, and a self-limited form with spontaneous resolution after many years (3). Treatment is symptomatic, and a curative regimen has not yet been discovered. However, experimental medications have been reported to cause partial or complete remission in some patients (9).

Many approaches to local treatment of XD have been attempted with various results.

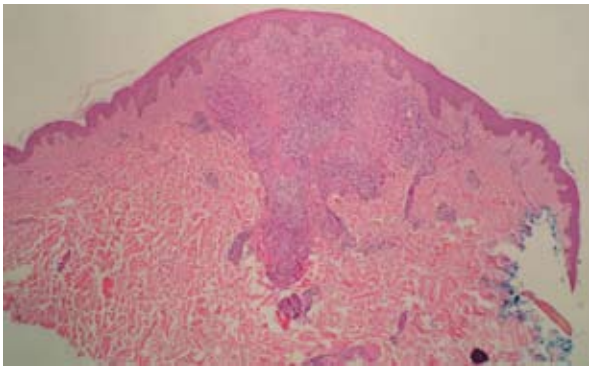

Figure 3. Histopathologic features characterized by a mixture of lymphocytes, histiocytes, foam cells, and several giant cells (C: H&E, ×40).

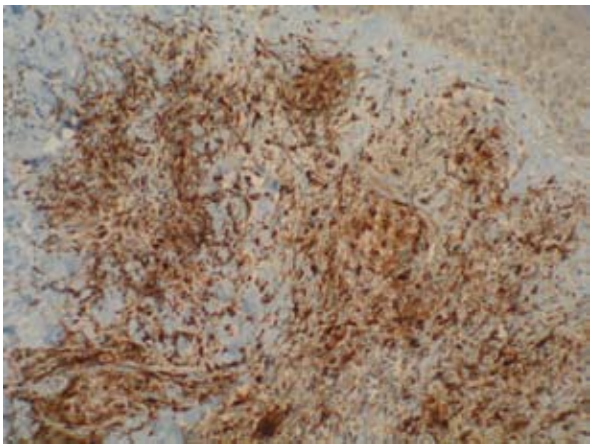

Figure 4. Immunohistochemical staining positive for CD68 in histiocytes and giant cells (D: IHC, ×200).

In the past radiotherapy (RT) of the face and neck has been tried to control advancement of the disease around the pharynx, larynx, and trachea (12). The effectiveness of RT is unclear due to the limited number of cases. Mahrel *et al*. found no improvement in an adult male with pituitary XD lesions who was treated with RT and steroids (13). In another report, cutaneous XD lesions in the neck and face region were treated with no results (14). However, Moloney reported one case of successful disease control in a patient who received Cobalt RT (15). Alexander *et al*. concluded in their recent case report that RT has a role in palliating local symptoms and in stabilizing disease progression when critical structures were involved and lesions were not amenable to surgical intervention (16). If the lesions are accessible to surgery then it appears to give the best results (3,12). Cryotherapy for localized lesions has not been successful (17). In a recent case study Carpo *et al*. achieved excellent results with a carbon dioxide (CO_2) laser in a 15-year-old girl with widespread XD lesions (18). The advantages of the CO_2 laser are that multiple lesions can be treated in one session, which is well tolerated by the patient, as well as precise vaporization of lesions and minimal postoperative pain and edema. Other treatments of cutaneous lesions include dermabrasion, electrocoagulation, and intralesional steroid injections (18). However, the effectiveness of these therapeutic modalities could not be confirmed due to the lack of clinical data.

Use of numerous systemic medications has been reported in attempts to manage the disease. However, none have proven particularly successful. Table 1 summarizes the results of published case series.

A recent case study reported a successful improvement of more than half the lesions using a combination of three lipid lowering agents: Peroxisome proliferator-activated receptor gamma (PPAR-γ), statins, and fenofibrate (19). However, a complete remission was never achieved during a follow-up period of three years. It is important to note that this patient had normal lipid levels, which is commonly found in XD patients in contrast to other xanthomatous disorders (19). Similar results with anti-cholesterol drugs were supported by two other case reports (20,21).

In one case series report, five patients underwent remission of XD lesions after receiving 2-Chlorodeoxyadenosine (2CdA) treatment. Complete clearance of lesions was observed in two patients after a follow-up period of three and eight years (22).

Seaton *et al*. proposed cyclophosphamide as a potential treatment for the more aggressive form of XD, as this resulted in a dramatic resolution of lesions in one XD patient with extensive mucocutaneous, ocular laryngeal, pituitary, and central nervous system involvement (23).

One case study reported a spectacular improvement and complete clearance of lesions with oral doxycycline treatment. (24) After the therapy was stopped there was no recurrence in the following six months.

However, the results of the above-mentioned case could not be replicated in our patient: there was no sign of improvement whatsoever after treating the patient with doxycycline for one month. We then initiated treatment with cyclosporine. This immunosuppressive agent inhibits T-cell activation and is considered to be a potential therapy for systemic juvenile xanthogranuloma, which is a non-Langerhans cell histiocytosis condition pathologically similar to XD (25). Although the lesions still persisted after six weeks, the disease tended towards stabilization and no other new lesions appeared during the treatment. The treatment was then stopped, and we opted for an expectant management for the following reasons: Firstly, our patient had XD that was only limited to cutaneous lesions without systemic involvement and thus not life-threatening. Secondly, the lesions tended towards stabilization during treatment with cyclosporine. Although cyclosporine may have played a role in the recovery, clinical response to treatment must be interpreted with caution since XD has the potential to stabilize or even undergo spontaneous resolution in its natural course, as mentioned before.

Five months after the onset of the disease lesions started to disappear. which led us to conclude that our patient had most likely suffered the self-limited form of XD, which may be affected by cyclosporine.

CONCLUSION

In this article, we presented our experience with cyclosporine in the treatment of XD. We believe that if the lesions are accessible to surgery, then surgery probably constitutes the best treatment. However, if the lesions are too extensive for surgical removal, then a CO_2 laser can be considered. We believe that expectant management is justifiable in XD patients as long as the lesions are limited to the skin and do not affect vulnerable mucous areas or internal organs that can be potentially life-threatening. Nevertheless, XD is usually benign and is often self-limiting.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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