LOCAL CORTICOSTEROID TREATMENT OF EYELID AND ORBITAL XANTHOGRANULOMA

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ABSTRACT

Purpose: To demonstrate the efficacy of local corticosteroid therapy for the treatment of eyelid and orbital xanthogranuloma in adults.

Methods: We performed a retrospective chart review of six patients receiving local triamcinolone acetonide (40 mg/mL) injections for the treatment of eyelid and orbital xanthogranuloma at the University of Michigan. All patients underwent diagnostic biopsy prior to treatment. The effects of this therapy on symptoms and signs of the disease were assessed.

Results: All six patients complained of eyelid swelling or nodularity, and five had yellow discoloration of their eyelids. All lesions involved the eyelids and anterior orbit, and five were present bilaterally. Biopsy revealed necrobiotic xanthogranuloma in four patients and adult-onset xanthogranuloma in two patients. Triamcinolone acetonide was administered intralesionally as series of two to 25 injections. Local control was obtained in all six cases, with the reduction of symptoms and signs of the disease in five cases. Two patients with necrobiotic xanthogranuloma developed non-Hodgkin's lymphoma. Average follow-up of patients whose treatment was not truncated by systemic chemotherapy was 52 months (range, 30 to 86 months). No complications occurred as a result of this treatment.

Conclusion: Intralesional injection of triamcinolone acetonide is an effective, safe treatment for orbital xanthogranuloma in adults. This modality avoids the side effects associated with systemic corticosteroid or cytotoxic agent therapy.

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INTRODUCTION

Three types of idiopathic xanthogranuloma occur in the eyelids and orbits of adults: necrobiotic xanthogranuloma (NXG),[1,2] adult-onset xanthogranuloma (AXG),[3,4] and Erdheim-Chester disease.[5,6] All three types of xanthogranuloma may be associated with systemic manifestations. NXG is commonly complicated by paraproteinemia and multiple myeloma or other lymphoproliferative disorders,[1,2] whereas AXG may be associated with adult-onset asthma.[3] Erdheim-Chester disease typically involves the posterior portion of the orbit and is associated with widespread systemic disease that results in death due to infiltration of vital organs.[5,6] This disorder,[7,8] like NXG[9] and AXG,[10] has been routinely treated with combinations of systemic corticosteroids, cytotoxic agents, and radiotherapy. However, NXG and AXG tend to affect the eyelids and anterior orbital tissue. The accessibility of NXG lesions to injection has prompted some to treat them with intralesional corticosteroids, yielding inconsistent results.[11,12] We describe treatment of AXG and NXG with series of local injections of triamcinolone acetonide. This therapy controls the disease while avoiding the side effects of systemic or radiation treatment.

METHODS

A retrospective review was performed on the charts of six patients who presented to the Eye Plastic and Orbital Surgery Service of the University of Michigan Kellogg Eye Center. They sought treatment for relief of symptomatic eyelid swelling and discoloration. After computed tomographic (CT) scans were obtained in five of six cases, each patient underwent diagnostic biopsy, establishing the diagnosis (Figure 1). All six patients received intralesional triamcinolone acetonide (40 mg/mL) injections given into subcutaneous and anterior orbital tissue exhibiting palpable nodularity. The medication was delivered by means of a 25-gauge needle with 20 to 40 mg given into each site of nodularity up to a total dose of 120 mg. A series of repeated injections was given at 1- to 6-month intervals until nodularity was not palpable. Visual acuity was checked before and after each series of injections. The presence and severity of nodularity, skin discoloration, ptosis, and diplopia were documented before and after treatment. Also noted were patient age, sex, laterality of involvement, associated systemic disease, and complications. Informed consent for biopsy and treatment was obtained for all patients. This study was approved by the University of Michigan Institutional Review Board.

RESULTS

A summary of the clinical data for all six patients is given in Table. Biopsy established the diagnosis of NXG in four patients and AXG in two patients. Equal numbers of men and women were affected. The average age was 53 years (range, 34 to 73 years). The average duration of symptoms prior to presentation was 29 months (range, 1.5 to 60 months).

Nodularity, swelling, or both were present in all cases. Also present were yellow discoloration (five patients), diplopia (four patients), proptosis (four patients), and ptosis (three patients). The disease process was bilateral in five of the six patients. Orbital involvement, localized primarily superiorly and anteriorly, was present in all five cases that underwent CT scanning.

Intralesional triamcinolone acetonide was delivered into regions of palpable tissue nodularity and into the anterior orbital tissues based on CT scans without adverse effects in all six patients. According to clinical findings, repeated series of injections were

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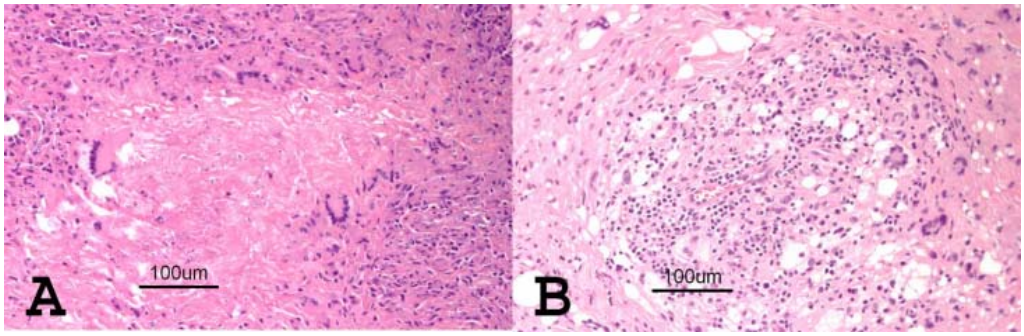

FIGURE 1

Biopsy findings of necrobiotic xanthogranuloma (NXG) and adult-onset xanthogranuloma (AXG). A, Photomicrograph of patient 2 showing typical features of NXG, namely, granulomas with histiocytes containing lipid pallisading around areas of necrobiotic collagen. B, Photomicrograph of patient 4 showing AXG findings of lipogranulomatous inflammation with Touton-type giant cells and fibrosis.

given in four patients, all of whom demonstrated dramatic improvements in their symptoms and signs (Figure 2), which were maintained in each patient during an average follow-up of 52 months (range, 30 to 86 months). Posttreatment CT scans of the two patients with AXG confirmed reduction of their periocular disease (Figure 3). Patients 2 and 4 (Table), both with NXG, developed systemic lymphoproliferative malignancies, which required systemic treatment with corticosteroids and cytotoxic agents. These patients underwent only two and one series of injections, respectively. Even with this short course, improvement was seen in one patient and stability in the other.

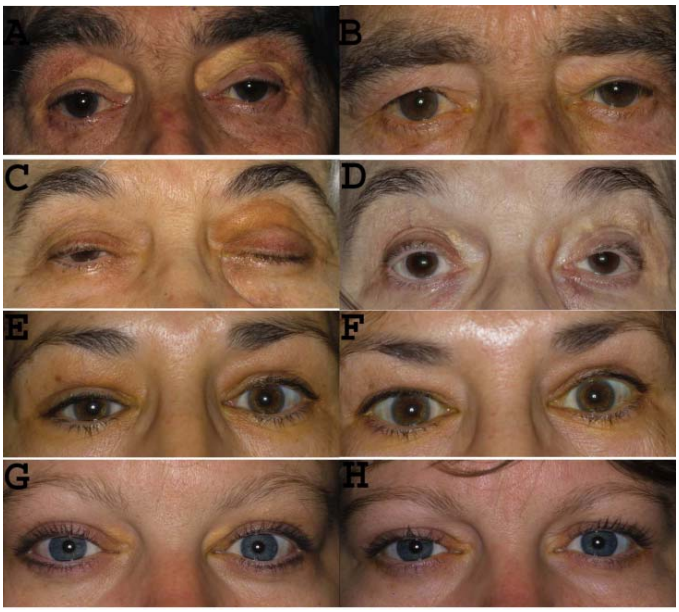

FIGURE 2

Clinical response of necrobiotic xanthogranuloma (NXG) and adult-onset xanthogranuloma (AXG) to corticosteroid injections. A, Patient 1 with bilateral diffuse NXG lesions causing eyelid fullness, discoloration, and mechanical ptosis; numerous injections of intralesional triamcinolone resulted in resolution of lesions, maintained for 84 months (B). C, Patient 3 with NXG causing severe left ptosis, discoloration, and fullness; local corticosteroid treatment markedly decreased discoloration and fullness, and ptosis was corrected surgically after 37 months (D). E, Patient 5 with bilateral upper eyelid fullness, discoloration, and proptosis present at the time of diagnosis of AXG; all these parameters showed improvement following local triamcinolone injections that was maintained for 46 months (F). G, Patient 6 with AXG causing right upper eyelid fullness, discoloration, and mechanical ptosis; intralesional triamcinolone improved all of these findings as seen at 30 months follow-up (H).

TABLE. OVERVIEW OF FOUR CASES OF NECROBIOTIC XANTHOGRANULOMA AND TWO CASES OF ADULT-ONSET XANTHOGRANULOMA

CASE NO.	AGE/SEX	DX	ASSOCIATED SYSTEMIC DISEASE	SYMPTOMS AND SIGNS	DURATION OF SYMPTOMS AND SIGNS (MONTHS)	INVOLVED SITE	ORBITAL INVOLVEMENT	TRIAMCINOLONE DOSE	NO. OF INJEC-TIONS	RESPONSE	COMPLI-CATION	FOLLOW-UP (MONTHS)
1	60/M	NXG	None	Nodularity, discoloration, diplopia, swelling, ptosis	32.0	Bilateral	Bilateral su-peroanterior	40 mg	22	Improved nodu-larity, discolor-ation, ptosis	None	86
2	54/M	NXG	NHL	Nodularity, discoloration, diplopia	1.5	Bilateral	Unknown	40 mg	2	Improved nodularity	None	3
3	73/F	NXG	MGUS	Nodularity, discoloration, diplopia, proptosis, ptosis, pain	6.0	Bilateral	Left superoanterior	30 to 120 mg	9	Improved nodu-larity, discolor-ation, diplopia	None	37
4	41/M	NXG	CLL, MDS	Nodularity, discoloration, proptosis, swelling	60.0	Bilateral	Bilateral su-peroanterior and EOM	30 mg	1	Stable	None	96 (died of CLL)
5	34/F	AXG	Eczema	Nodularity, discoloration, proptosis	24.0	Bilateral	Bilateral su-peroanterior	32 to 70 mg	3	Improved all signs	None	46
6	57/F	AXG	None	Nodularity, discoloration, diplopia, proptosis, ptosis	48.0	Right	Superoanterior	40 to 90 mg	2	Improved all signs	None	30

AXG = adult-onset xanthogranuloma; CLL = chronic lymphocytic leukemia; Dx = diagnosis; EOM = extraocular muscles; MDS = myelodysplastic syndrome; MGUS = monoclonal gammopathy of uncertain significance; NHL = non-Hodgkin's lymphoma; NXG = necrobiotic xanthogranuloma.

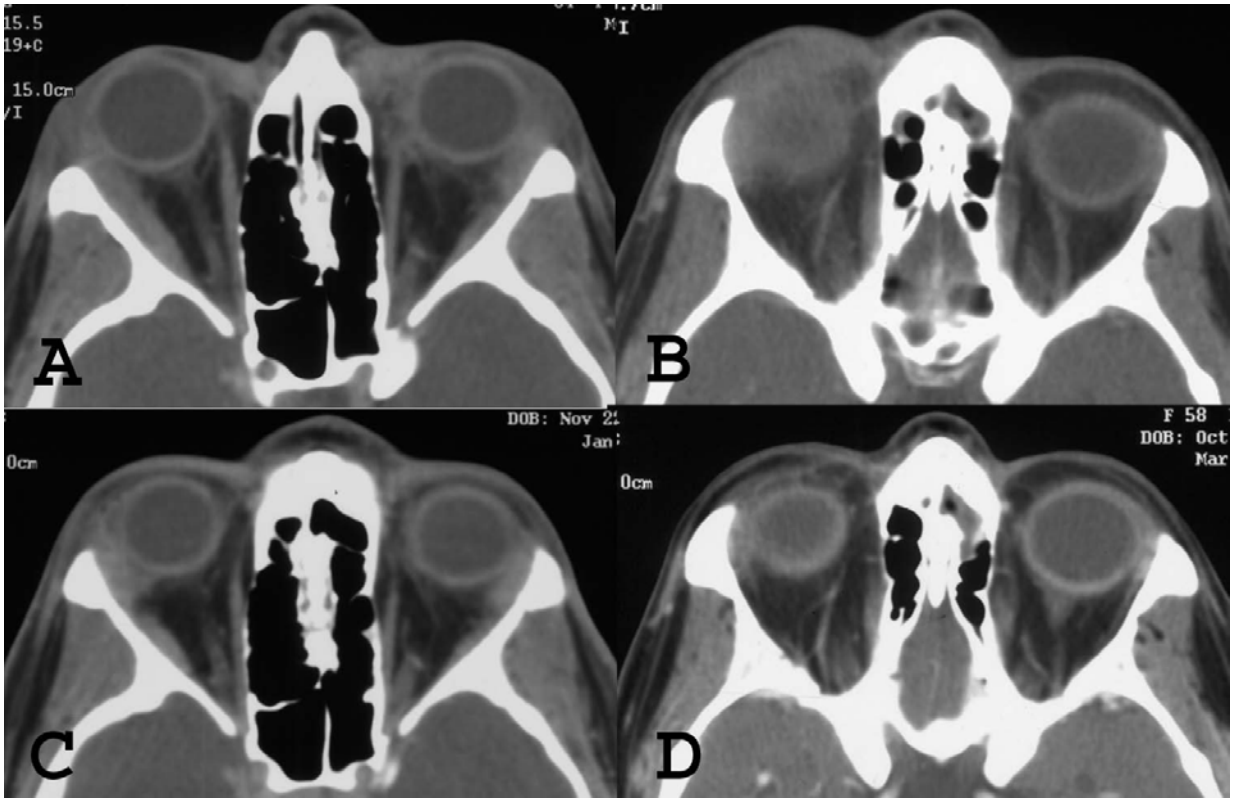

FIGURE 3

Radiographic improvement of adult-onset xanthogranuloma (AXG) lesions to corticosteroid injections. Computed tomographic scans of both patients with AXG. Pretreatment involvement of eyelid and anterior orbital tissues by diffuse, infiltrating inflammatory masses involving both eyes of patient 5 (A) and the right eye of patient 6 (B); intralesional triamcinolone injections improved the radiographic findings in both cases (C and D), respectively.

DISCUSSION

Corticosteroid injection into the eyelids and orbit has been reported as a successful treatment for numerous periocular disease processes, such as capillary hemangioma,[13] thyroid ophthalmopathy,[14] chalazia,[15] sarcoid,[16] and vernal keratoconjunctivitis.[17] More inconsistent results have been reported with sporadic use of intralesional corticosteroids for the treatment of periocular NXG.[11,12] Assessment of the efficacy of intralesional corticosteroid treatment in NXG is hampered by the lack of documentation with respect to type, dose, and depth and site of injection. In addition, the need for repeated treatment, which we found to be necessary in our cases, is not mentioned in any of the reports. We feel the consistent results obtained in our series are likely due to the use of a long-acting corticosteroid, adequate depth of injection into the involved subcutaneous and anterior orbital tissue, and the delivery of repeated injections until adequate clinical response was achieved.

In our cases, the chief symptoms and signs of nodularity, swelling, and skin discoloration all responded to local corticosteroid treatment. Of the three cases with diplopia, one resolved following therapy. One of three cases of ptosis improved following treatment, whereas two required surgical correction. All cases achieved an improved and acceptable cosmetic result.

Periocular corticosteroid injections may be complicated by central retinal and ophthalmic artery occlusion[18,19] as a result of embolization at the time of injection. Complications from local effects of the medication include eyelid necrosis,[20] persistent glaucoma,[21] and linear subcutaneous fat atrophy.[22] Adrenal suppression has also been reported.[23] In our series, none of these complications occurred.

We performed biopsies on all six patients. A tissue diagnosis is essential in these cases because each of these is associated with different, frequently life-threatening systemic diseases. The diagnosis serves as a basis for further directed systemic investigation and monitoring of the patient for these diseases so that prompt interventions may be implemented.

Intralesional corticosteroid injection is successful in controlling symptoms and signs of NXG and AXG eyelid and orbital involvement. This therapy avoids the use of systemic corticosteroids and cytotoxic agents, which are the currently accepted treatments for these disorders. In addition, this regimen avoids the complexity and expense of plasmapheresis and the significant local morbidity of radiation therapy, both of which are only partially effective.

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PEER DISCUSSION

DR STEVEN E. FELDON. The authors have nicely reviewed the topic of eyelid and orbital xanthogranuloma, a rare disease with only a few series reported in the ophthalmologic literature. They have demonstrated that local control of the disease can be achieved by corticosteroid injections into the affected sites. Elner and colleagues have made several key points that deserve emphasis. First, all xanthomatous lesions of the eyelids should be biopsied and studied histologically to distinguish adult onset xanthogranuloma from necrobiotic xanthogranuloma, though induration or ulceration of the lesion favors the necrobiotic form.[1] The former is often associated with asthma and possibly with non-malignant hematological disorders of anemia, thrombocytopenia, or eosinophilia. The latter is often associated with paraproteinemia, myeloma, and lymphoproliferative disorders. Erdheim-Chester is a lethal disease involving multiple organ systems.

The generally accepted treatment options include systemic corticosteroids, cytotoxic agents, and low-dose radiotherapy. Adding to these alternatives, this paper under discussion suggests that local injection of corticosteroids is also effective. A clear response is noted in most patients and, surprisingly, multiple injections seem to be well tolerated (22 injections in one patient). The potential complications of local radiotherapy or systemic treatment are avoided. On the other hand, local injections are certainly not a cure and should not be considered as a "therapeutic trial" for diagnosis. Biopsies are essential.

Relying solely on local treatment may lead to loss of vigilance in follow-up of potentially serious system manifestations of the disease. For instance, in their series of six patients, Jakobiec and co-workers[2] reported one case of a separate necrobiotic xanthogranuloma of the mandible and paraproteinemia 25 years after presentation. As with all local steroid injections around the orbit for any reason, there is risk of granuloma formation, fat atrophy, elevation of intraocular pressure in steroid responders, and perforation of the globe, especially with deep injections into an infiltrated orbit.

In summary, the authors have presented impressive data in their case series that local control of orbital adult xanthogranuloma and necrobiotic xanthogranuloma can be achieved with corticosteroid injections. They have correctly emphasized the differential diagnosis, the importance of biopsy, and the need to be vigilant for systemic manifestations of disease.

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DR MALCOLM R. ING. As pediatric ophthalmologists, we are also using intralesional injections of steroids frequently. About 15 years ago Dr Stuart Seiff (Shorr N, Seiff SR: Central retinal artery occlusion associated with periocular corticosteroid. Ophthalmic Surg 1986;17:229-31) reported retinal emboli following this procedure with potential for bilateral blindness. I wonder whether this risk of blindness applies to this type of tumor, versus the risk with a capillary hemangioma. What procedure does the author employ to reduce the risk of emboli? Do you use a small-bore needle such as a 30-gauge versus 25-gauge?

DR RALPH C. EAGLE JR. Dr Fred Jakobiec always emphasized that this group of conditions can be confused with xanthalasma clinically. I also am aware of several instances where general pathologists have diagnosed these lesions as xanthalasmas. In my opinion, the histopathology of orbital xanthogranuloma with adult-onset asthma and necrobiotic xanthogranuloma appear quite different. I have been impressed by the presence of focal follicular lymphoid hyperplasia in the case with adult-onset asthma. Do you think that both disorders are part of a spectrum, as been suggested, or do you think that they are separate entities? Have you tried to inject xanthalasmas?

DR DAVE J. WILSON. Have you looked at the immunophenotype of infiltrates in the lesion with the idea of seeing if rituximab may be an alternative to treatment?

DR EVELYN A. PAYSSE. I use intralesional steroid injections for larger vision threatening hemangiomas in young children and, on one occasion, a patient developed a Cushingoid appearance. I am especially interested in the patient that received 22 injections. What was the time period between the injections? What dose and type of steroid do you use? I also find that I cannot inject through a 30-gauge needle because it is a suspension. I need a 25-gauge needle

DR VICTOR M. ELNER. We reduced the risk of injection by pulling back on the syringe and placing the needle into the firmest portion of the lesion, where presumably there is a lot of fibrosis and not much vascularity. By doing this we ensure that we are not in an intravascular compartment. We inject very slowly with the agent, many times with patients' eyes open, as we ask them if they can continue to see while we are performing the injection. The needle has to be at least a 25-guage in order to avoid blockage from the triamcinolone precipitate.

In terms of a Cushingoid response, the dose is given usually at one month to six-week intervals to permit full leaching of the agent from the carrier. We determine the effect and then we give another injection if needed. Many times the areas of nodularity will disappear. We use the clinical response to determine the number of injections. Since this is distributed over time in an adult the doses in most cases are not high, so they do not get major adrenal suppression. I have no patients that developed any noticeable Cushingoid effects.

We have not performed immunophenotyping, except in cases complicated by possible lymphoma. We did diagnose monoclonal populations in two of the lesions that subsequently were shown to have a lymphoproliferative disease. We presume that perhaps antibody treatment against B cells may be helpful in patients with these lymphomas. We did not further assess the lesions in terms of the type of infiltrate within the benign portion of the lesion.

Xanthalasmas are distinct, usually cutaneous, unassociated with inflammation or necrosis, and are generally collections of histiocytes within the dermis. I could not find evidence that xanthalasmas are improved by injection, nor have I ever tried it. The lesions are generally soft, and are easily removed by conventional surgery and by the treatment of any associated hypercholesterolemia.

I think necrobiotic xanthogranuloma and adult onset xanthogranuloma are distinct diseases. Adult onset xanthogranuloma can be unilateral whereas necrobiotic xanthogranuloma is bilateral. Adult xanthogranuloma does not have the propensity for neoplastic disease and does not contain necrosis. The necrosis alone with the necrobiotic collagen would favor the concept that necrobiotic xanthogranuloma is a disease with more profound dysfunction of the connective tissue.