SCIENTIFIC REPORT

Management of orbital xanthogranuloma with methotrexate

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Background/aims: To evaluate the efficacy of methotrexate (MTX) treatment for the periocular findings in adult-onset xanthogranuloma (AOX).

Methods: The medical records of three patients with AOX, with and without asthma, who were treated with MTX at Oregon Health & Science University, Portland, Oregon, USA were examined. Diagnosis of AOX was made by biopsy in all patients. The patients were evaluated between February 1998 and July 2006. All patients had failed prior medical and/or surgical treatment. MTX was administered at 10–20 mg/week with folate supplementation and a course of corticosteroids. Efficacy was assessed on the basis of improvement in skin discoloration, involvement of the visual axis and patients' report of inflammation.

Results: All three patients were started on MTX, but one patient discontinued treatment after 3 weeks due to nausea. With follow-up as long as 3 years, the two patients who continued treatment lost the yellow discoloration of their skin, and they reported significantly less inflammation and ptosis after treatment. Oral corticosteroids could be reduced or discontinued.

Conclusions: AOX is a rare, persistent disease that commonly involves the preseptal fat. MTX is a therapeutic option for this illness.

Adult xanthogranulomatous infiltration of the orbit and eyelids is rare, persistent, and at times associated with life-threatening diseases. Four disease entities (table 1) can cause xanthogranulomatous masses around the eye: Erdheim–Chester (EC), necrobiotic xanthogranuloma (NX), adult-onset xanthogranuloma (AOX), and adult-onset asthma and periocular xanthogranuloma (AAOX).

The diagnosis of xanthogranuloma is based on a histopathological examination that shows a non-Langerhans histiocytic infiltration with giant Touton cells and fibrosis. In NX, areas of necrosis are also seen. EC and NX are the most life-threatening diseases that cause orbital xanthogranulomas, often leading to fatal retroperitoneal fibrosis and multiple myeloma, respectively. AOX and AAOX result in xanthogranulomatous lesions limited to the eyelids and the orbit. Most commonly the masses are anterior and preseptal and only rarely involve intraconal fat. However, EC most commonly infiltrates fat posterior to the orbit.¹ The skin of the eyelids in AOX and AAOX has been described as having yellow–orange plaques. Patients rarely have visual changes, proptosis or extraocular movement disorders.^{2–4}

Very few treatment modalities have been explored for AOX and AAOX, despite the refractory and persistent nature of the histiocytic lesions. Thus far, treatment modalities have included oral prednisone, surgical resection, radiotherapy and local triamcinolone injections.^{5–6} We describe methotrexate (MTX) treatment of three patients with orbital xanthogranulomatous disease, two of whom tolerated the treatment well and responded.

METHODS AND SUBJECTS

A retrospective case review of three patients diagnosed with AOX of the eyelids and orbit from the Casey Eye Institute, Oregon, USA, was undertaken. All three patients were started on MTX and oral prednisone treatment. In two of the patients, the prednisone was tapered quickly and MTX was continued. We classified the outcome of the disease by both an objective observation of decreased swelling and a subjective report of improved symptoms.

Case 1

A 36-year-old man presented with a 1-year history of progressive swelling of his left upper lid with new-onset diplopia. The skin above the eye appeared yellowed. He had a 2-year history of adult-onset asthma treated with an albuterol inhaler as needed. The patient was noted to have lymphadenopathy in the neck, axilla and groin. A CT scan of the orbits revealed slightly irregular thickening of the extraocular muscles of the left eye, with mild inflammatory changes of the extraconal fat anteriorly and superiorly. No masses or swelling were noted in the posterior orbit, and there was no evidence of extension beyond the lids and extraconal fat. A left anterior orbitotomy and biopsy were performed. The patient's diplopia resolved. The biopsy revealed a histiocytic infiltration of the dermis and extraorbital fat. The cellular infiltration was identified as lymphocytes, plasma cells and giant Touton type cells. The cytoplasm of the cells was "foamy". There was no evidence of necrosis within the specimens and the infiltrate was identified as xanthogranulomatous. Bone scans were performed, and showed no evidence of osteosclerosis or other bony lesions. The patient had normal urinalysis and MRI of the brain, but refused serum protein electrophoresis and abdominal CT. The patient was lost to follow-up for 2 years, when he returned to the clinic with orbital skin lesions that had not resolved. He was noted to have yellowish plaques on his left lid, mild proptosis on the left with full extraocular movements and no diplopia. The patient did not note any changes in his vision, nor had any systemic complaints at that time. A referring physician had initiated a course of 40–50 mg prednisone a day for 2 months. When the prednisone was reduced to 30 mg/day, symptoms recurred. On referral, he was started on MTX 15 mg every week orally. The prednisone dose was left unchanged at 40 mg/day for 1 month after starting MTX and then tapered gradually and discontinued. The orbital swelling and discoloration decreased dramatically over the treatment period and did not recur with the tapering of prednisone. The patient reported that he felt his symptoms resolved almost completely. The patient maintained MTX treatment for three more years. He discontinued treatment following a traumatic accident that resulted in quadriplegia. The patient states that the eye symptoms have not recurred after 6 years from the beginning of treatment.

Abbreviations: AAOX, adult-onset asthma and periocular xanthogranuloma; AOX, adult-onset xanthogranuloma; EC, Erdheim–Chester; MTX, methotrexate; NX, necrobiotic xanthogranuloma

Table 1 Clinical presentation and prognosis of disease entities causing xanthogranulomatous masses around the eye

Name	Clinical Presentation	Prognosis
AOX	Symptoms are localised to the eye. This includes swelling of the eyelid, and swelling and preseptal and anterior orbital infiltration	Good. Symptoms are limited to the eye
AAOX	Adult-onset asthma begins several months before the eye symptoms. Eyelids swell and become discoloured in 95% of cases. Reactive lymphadenopathy is common. Rarely, patients suffer from lymphoproliferative diseases	Good. Patients have rare systemic involvement
EC	All patients with EC have systemic involvement including long-bone sclerosis, retroperitoneal fibrosis, diabetes insipidus and mediastinal infiltrates. Infiltrates in EC are usually intraconal	Poor. Up to 50% of patients die of EC-related illness
NX	Like AOX and AAOX, NX commonly has preseptal and anterior orbital infiltration. It is also related to multiple myeloma, lymphomas and lymphosarcoma	Poor. Patients commonly have systemic lymphoproliferative disease

AAOX, adult-onset asthma and periocular xanthogranuloma; AOX, adult-onset xanthogranuloma; EC, Erdheim-Chester; NX, necrobiotic xanthogranuloma.

Case 2

A 35-year-old woman presented with a right swollen lid and fat prolapse. She had no visual complaints at the time. A lacrimal gland biopsy was performed, which revealed an infiltration of lymphocytes, plasma cells and fibrosis replacing lacrimal gland acini. A diagnosis of chronic inflammation was made; the patient was treated with prednisone for an unknown period of time and stopped seeking care from her ophthalmologist. She underwent three more surgical procedures over the next 10 years for this swelling without relief. In 2005, pathological examination from a three-wall orbital decompression showed a mixed inflammatory infiltrate composed of lymphocytes, xanthoma cells and Touton giant cells (figs 1 and 2). No necrobiosis was noted. A diagnosis of EC was made. She was started on oral prednisone and referred to our clinic for care. At this time her visual acuity was 20/20 in both eyes, and she had no visual complaints or evidence of optic nerve compromise. Firm, non-tender masses were seen in the upper eyelids of both eyes and the lower lid of the right. Hertel measurements were 23 mm on the right and 21 mm on the left. The skin over the masses had an orange, irregular and lumpy appearance (fig 3). No other lesions were noted. The patient had a history of hypothyroidism, cholelithiasis, diabetes mellitus type 2, hypertension and symptoms of menopause. A bone scan, MRI of the brain, urinalysis, endocrinology evaluation and several blood tests were performed. The bone scan was normal. The other laboratory tests revealed no evidence of diabetes insipidus or retroperitoneal fibrosis. The masses in the eyelids did not extend into the orbit or brain. As a result, her diagnosis was changed to orbital xanthogranuloma. However, the patient's eye swelling was not resolved with surgery, and medical management of her symptoms was suggested. The patient was started on 10 mg of MTX, which was later increased to 20 mg of MTX orally a week. She was also begun on 15 mg of prednisone daily orally, which was tapered to 5 mg over 6 weeks. After 3 months of treatment, the patient has noted markedly decreased swelling in both eyes, improvement of discoloration and no more discomfort. She has remained symptom-free since the beginning of treatment 1 year ago.

Figure 1 Extraorbital fat from case 1 at 20x. Histiocytes and plasma cells infiltrate the area. Note the intracellular lipid inclusions giving a "foamy" appearance to the infiltrate.

Case 3

In 2003, a 60-year-old Caucasian man presented with a 2-year history of upper lid swelling in both eyes. He denied having had any changes in his vision, but felt that his visual field was restricted. On examination, he had 20/20 vision bilaterally and swelling in both upper lids. Before the swelling, the patient had a history of diabetes mellitus, coronary artery disease, colon cancer and appendicitis. A blepharoplasty was performed and tissue was sent for pathological analysis. Microscopic examination showed a lymphocyte and mast cell infiltrate with rare Touton giant cells. A bone scan and chest x rays were completed, which showed no evidence of osteosclerosis. There was also no history of diabetes insipidus. A diagnosis of orbital xanthogranuloma was made and treatment options discussed. The patient was started on MTX 20 mg/week but did not tolerate this secondary to fatigue. He was started on 10 mg of prednisone per day and felt that it was much more tolerable than the MTX. However, the patient was unable to drop his dosage to <10 mg without experiencing significant lid swelling. After 3 years of treatment with oral prednisone, the

Figure 2 40x magnification. Black arrow points to giant Touton cell that is the hallmark of a granulomatous infiltrate. These cells can be seen in AOX, AAOX, EC and NX.

patient does not feel that his swelling has improved. However, due to joint pain and steroid-responsive myalgias unrelated to the orbital infiltrates, the patient continues to take 10 mg of prednisone daily.

DISCUSSION

In this series, we treated two patients with orbital xanthogranuloma with weekly oral MTX. A third patient began MTX treatment but did not tolerate this well. The two patients who tolerated MTX state that their symptoms markedly improved and have not recurred since the onset of treatment. The skin masses in both patients have decreased dramatically and discolored plaques have disappeared. The patient treated only with oral steroids did not feel that his lid masses resolved. We have previously reported on one of these patients (case 1) and mistakenly identified his disease as EC at that time.⁷

Because of the exceedingly rare nature of orbital xanthogranulomas, there is no consensus on the most effective treatment of these diseases. Unlike EC and NX, AOX and AAOX have very few, if any, systemic symptoms. Patients with AAOX also have adult-onset asthma commonly well controlled with albuterol.⁴ These patients often also have associated lymphadenopathy that does not become malignant. AOX is a disease limited to xanthogranulomatous infiltrates, often around the orbit and occasionally at the limbus.⁸ Although most of the cases are limited, there was a recently reported case of periosteal infiltration in AOX.⁹

MTX is a mainstay of rheumatoid arthritis treatment. We have previously described its utility in inflammatory orbital diseases.⁷ The anti-inflammatory mechanism in MTX treatment is not well understood. The drug is a dihydrofolate reductase inhibitor. It has been suggested that it causes the enhanced release of adenosine resulting in a decreased production of inflammatory cytokines.¹⁰ The most common adverse effects of MTX therapy are nausea and fatigue. All three patients in this study noted some degree of fatigue, and patients 1 and 2 experienced nausea also. However, the nausea was mild and well tolerated by the first two patients. It is imperative to measure liver enzymes during MTX treatment, as it is metabolised by the liver and can result in hepatic fibrosis. None of the patients in this study showed any change in their liver function during the course of treatment. Despite its potential toxicity, patients receiving MTX treatment for rheumatoid arthritis actually have extended life spans compared with those with rheumatoid arthritis who do not tolerate this drug.¹¹

Adult orbital xanthogranuloma disease is a rare but persistent cause of orbital swelling and lid discomfort. According to a Medline search, only one article in the literature attempts to find a successful treatment modality for the disease process. However, this study has found that AOX responds well to MTX, if tolerated. MTX provides an excellent alternative to the local injection of corticosteroid in the treatment of this rare disease.

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