CASE REPORT

Clinical manifestations and treatment of adult-onset asthma and periocular xanthogranuloma

Rodrigo Cavallazzi MD1, Amyn Hirani MD1, Tajender S Vasu MD1, Robert C Sergott MD2, Jurij R Bilyk MD2, Ralph C Eagle MD2, Sandra Weibel MD1


BACKGROUND: Adult-onset asthma and periocular xanthogranuloma is an uncommon and recently described disease. Little is known about the condition because only a few case reports and series are available.

OBJECTIVE/METHODS: To describe the clinical manifestations, lung physiology, and response to systemic treatment of three patients with adult-onset asthma and periocular xanthogranuloma, followed by a review of the literature.

RESULTS: Three men, with an age at diagnosis ranging from 48 to 51 years, presented with right periorbital swelling, asthma and chronic rhinosinusitis. The patients' lung physiology was consistent with airway obstruction. Diagnosis was established by periorbital biopsy. All patients received oral corticosteroids for their periorbital swelling, without significant clinical response. Two patients received oral methotrexate, with nearly complete resolution of periorbital swelling. A third patient received oral azathioprine, without clinical response. The three patients had improvement of their asthma with inhaled steroids/long-acting bronchodilator, and immunosuppressive medication.

CONCLUSION: A triad consisting of periorbital swelling, asthma and chronic rhinosinusitis should raise the suspicion of adult-onset asthma and periocular xanthogranuloma. Oral methotrexate should be considered as an alternative to corticosteroids in the treatment of this disorder.

Key Words: Adult; Asthma, Glucocorticoids; Methotrexate; Orbital diseases; Xanthomatosis

Xanthogranulomatous diseases are non-Langerhans cell forms of histiocytosis, and in adults include Erdheim-Chester disease, adult-onset xanthogranuloma, adult-onset asthma and periocular xanthogranuloma, and necrobiotic xanthogranuloma (1,2). The common features of all these diseases are the presence of foamy histiocytes and Touton giant cells. The occurrence and type of systemic manifestations are important for differentiating these conditions because histological findings are similar (1).

While Erdheim-Chester disease causes diffuse infiltration of organs and bones, and presents mainly with bone pain (3), adult-onset asthma and periocular xanthogranuloma is characterized by orbital and eyelid lesions, asthma symptoms and immune dysfunction (1). Adult-onset xanthogranuloma presents solely with periorbital symptoms. Necrobiotic xanthogranuloma manifests as discrete, slowly developing, red skin lesions that consist of nodules and plaques, with a tendency to ulcerate. They predominantly affect the face (4).

The focus of the present article is adult-onset asthma and periocular xanthogranuloma. We decided to report on the cases seen in the Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University (Philadelphia, USA), because adult-onset asthma and periocular xanthogranuloma is an uncommon and poorly recognized disease – the few case reports and series found in the literature do not describe lung physiology and, other than corticosteroids, experience with the systemic treatment of this condition is scarce.

CASE PRESENTATIONS

Three cases of adult-onset asthma and periocular xanthogranuloma are reported, followed by a review of the literature pertaining to this disease. Asthma severity was classified according to guidelines published in an expert panel report in 2007 (5).

Table 1 summarizes clinical information, treatment and outcomes of the three patients in the present study, with pulmonary function test data presented in Table 2.

Patient 1
A 51-year-old Caucasian man presented with a four-year history of right periorbital swelling. The swelling was painless, with no diminished or double vision reported. Three years previously, the patient underwent a right periorbital biopsy that revealed benign lymphoid hyperplasia. After biopsy, he received oral methylprednisolone for three weeks, which resulted in a partial reduction of swelling. However, the swelling rapidly recurred once methylprednisolone was tapered. Concomitant
with periocular manifestations, he developed severe asthma and chronic rhinosinusitis symptoms. The patient's medical history was significant for type 2 diabetes mellitus and high blood pressure. He was a former smoker with a 30 pack-year history who quit five years previously. A physical examination was remarkable for the presence of a swollen, rubbery, right upper eyelid, without tenderness. The patient's vision was 20/20 on the right and 20/25 on the left, with no afferent pupillary defect or extraocular motility impairment. Serum protein electrophoresis and immunoglobulin (Ig) quantitation were normal. Laboratory results showed an absolute eosinophil count of 640 cells/µL (8.2%). He had a positive skin test to common allergens. The initial pulmonary function test was consistent with airway obstruction, with significant response to bronchodilators (Table 2). A repeat right lacrimal gland biopsy was performed at our institution that revealed xanthogranulomatous inflammation with Touton giant and histiocytic cells. He received oral methotrexate, started at 5 mg once weekly and gradually increased to 20 mg once weekly, and inhaled fluticasone 250 µg with salmeterol twice a day. After initiation of both methotrexate and inhaled steroid/long-acting bronchodilator, the patient had nearly complete resolution of his right periorbital swelling and his asthma was well controlled. While the asthma symptoms had subsided by the time of his follow-up visit three months after initiation of therapy, resolution of the periorbital swelling took longer than 1.5 years.

Patient 2
A 48-year-old Caucasian man presented to the outpatient clinic with a one-year history of right eye redness. Initially, the patient was diagnosed with allergic conjunctivitis and treated with azelastine ophthalmic solution. Subsequently, he noticed right periorbital swelling and binocular diplopia. He was treated with oral corticosteroid without improvement of the swelling. He admitted to asthma, chronic rhinosinusitis and nasal polyps (all three conditions diagnosed 10 years previously and treated with inhaled steroids), as well as type 2 diabetes mellitus. The patient had daily asthma symptoms of moderate severity. He reported being a former smoker with a 24 pack-year history who quit nine years previously. Physical examination revealed redness over the lateral portion of the right upper eyelid, without tenderness. The patient’s vision was 20/40 on the right and 20/20 on the left, with no afferent pupillary defect. Extraocular motility was preserved but he developed diplopia on left end gaze. A pulmonary function test initially demonstrated airway obstruction, with significant bronchodilator response (Table 2). He had a positive skin test to common allergens. Laboratory investigation showed an absolute eosinophil count of 650 cells/µL (9.5%). A computed tomography scan of the orbits revealed enlargement of the extraocular muscles on the right side (Figure 1). He underwent biopsy of the anterior orbital tissue, the result of which was nearly complete resolution of the extraocular muscles on the right side (Figure 1). He underwent biopsy of the anterior orbital tissue, the result of which was nearly complete resolution of the extraocular muscles on the right side (Figure 1). He underwent biopsy of the anterior orbital tissue, the result of which was nearly complete resolution of the extraocular muscles on the right side (Figure 1). He underwent biopsy of the anterior orbital tissue, the result of which was nearly complete resolution of the extraocular muscles on the right side (Figure 1). He underwent biopsy of the anterior orbital tissue, the result of which was nearly complete resolution of the extraocular muscles on the right side (Figure 1).
Patient 3
A 51-year-old Caucasian man presented to the outpatient clinic with a five-year history of right periorbital swelling. He received oral methylprednisolone for the swelling, with no improvement. He reported mild asthma, chronic rhinosinusitis and nasal polyps that initially manifested at the same time as the onset of periorbital swelling. The patient’s medical history was also significant for chronic hepatitis C and type 2 diabetes mellitus. He was smoker with a 30 pack-year history, but quit 10 years previously. Physical examination revealed preseptal swelling in the right upper eyelid. The patient’s vision was 20/20 in both eyes, and there was no afferent pupillary defect or extraocular motility impairment. Serum protein electrophoresis was normal. There was no peripheral eosinophilia. He had a positive skin test to common allergens. Pulmonary function tests initially revealed airway obstruction with significant bronchodilator response (Table 2). He underwent biopsy of the anterior orbital tissue, the results of which showed Touton giant and histiocytic cells consistent with xanthogranulomatous inflammation (Figure 2). Because he had previously received oral corticosteroid without response, and chronic liver disease is a relative contraindication for methotrexate, he received oral azathioprine at 25 mg twice a day. He also received inhaled beclomethasone 160 µg twice a day. His clinical response to azathioprine was not significant; however, his asthma was well controlled.

DISCUSSION
In 1993, Jakobiec et al (6) reported on six patients who presented with periorbital manifestations and histological findings similar to Erdheim-Chester disease; however, a striking feature of that group of patients was that five had adult-onset asthma that started at approximately the same time as the periorbital manifestations in at least three patients. Equally noticeable was that their patients lacked the systemic manifestations commonly seen in Erdheim-Chester disease. The authors designated these cases as periorbital xanthogranulomas associated with adult-onset asthma, and proposed that they may represent a separate clinicopathological entity. Recently, Sivak-Callcott et al (1) have used the term adult-onset xanthogranuloma to label patients who present solely with a xanthogranulomatous lesion, while the term adult-onset asthma and periorbital xanthogranuloma denotes a syndrome in which a xanthogranulomatous lesion is associated with asthma and, often, reactive lymphadenopathy and increased IgG levels.

The majority of patients with adult-onset asthma and periorbital xanthogranuloma are diagnosed in their fourth or fifth decade of life; however, age at diagnosis varies broadly (6-8). The disease involves both sexes, although it has been reported with higher frequency in men (2,7-9). It is unknown whether there is a race or ethnic group category predilection.

The main clinical presentations are peribulbar swelling that is often painless and slow growing, and erythematous or yellow plaques on the eyelids (2,6). There have been reports of unilateral and bilateral periorbital involvement (6). In some instances, although signs and symptoms are unilateral, imaging studies demonstrate bilateral disease. Furthermore, some patients initially present with unilateral disease and later manifest bilateral involvement. Diplopia, a less common symptom, can be present when the disease affects the extraocular muscles (7). The swelling is firm, rubbery and usually located in the preseptal and anterior orbital areas (1,6,10). In addition to eyelid swelling and plaques, physical examination can disclose proptosis, ptosis and extraocular motility limitation (11,12).

Asthma tends to appear at approximately the same time as the periorbital manifestations (6). However, this is not always the rule because one of our patients had asthma for nine years before the onset of periorbital symptoms. Pulmonary function testing of our patients showed airway obstruction, with significant response to bronchodilators. Chronic sinusitis and nasal polyps have been reported in some cases (2,6,9). All patients in our series had chronic rhinosinusitis, with two having nasal polyps; however, none of our patients had a history of adverse reactions to acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs. The pathogenesis of asthma with this condition is unclear but the probable role of eosinophil recruitment and activation is highlighted by reports of both peripheral eosinophilia and eosinophilic tissue infiltrate in the peribulbar biopsy (6). The accumulation of non-Langerhans histiocytes in the peribulbar tissue implies an activation of the mononuclear phagocytic system, and it is known that dendritic
cells located in the airway epithelium and submucosa are important in initiating and maintaining immune responses to inhaled allergens (13). Reactive lymphadenopathy and increased IgG levels noted in some patients indicates that a systemic immunological derangement is present (1), which is likely to upregulate the immune and inflammatory reactions involved in the pathogenesis of asthma. Skin test positivity to common allergens also reveals a predisposition to IgE-mediated reactions in these patients. Other potential disease associations include diabetes mellitus and lymphoplasmacytic sclerosing pancreatitis (6,7,9).

In the appropriate clinical scenario, the diagnosis of adult-onset asthma and periocular xanthogranuloma is established when a periorbital biopsy reveals the characteristic histological findings: non-Langerhans, lipid-laden histiocytes, Touton giant cells and lymphoid aggregates with germinal centres (1,6). Features on electron microscopy and immunohistochemistry aid in the differentiation of non-Langerhans from Langerhans cells. For example, while Langerhans cells are identified by the presence of intracytoplasmic Birbeck granules and positive reaction to S-100 protein and CD1a, non-Langerhans cells are characterized by the expression of different surface markers (blood-clotting transglutaminase Factor XIIa, CD68, Mac387 and vimentin) and the absence of Birbeck granules (12).

It is not uncommon for patients to be seen by several physicians and undergo more than one peri orbital biopsy before the diagnosis is established (2). The time from onset of symptoms to diagnosis in our patients ranged from one to five years. Clinically, the differential diagnosis includes other histiocytic disorders with periorbital involvement as well as conditions that cause orbital space-occupying masses such as malignancy and sarcoidosis (14). Case reports and the present series have indicated that the periorbital manifestations of adult-onset asthma and periocular xanthogranuloma are frequently confused with xanthelasma and Graves’ disease (6,8). In a patient with periorbital swelling, the presence of asthma, chronic rhinosinusitis or nasal polyps most likely infers a diagnosis of adult-onset asthma and periocular xanthogranuloma.

Due to the rare nature of this disease, therapeutic strategies are based on anecdotal experience. Local forms of treatment include surgery, radiation and intralesion corticosteroid administration. Systemic treatment includes oral forms of corticosteroid, methotrexate and other cytotoxic medications. Oral corticosteroids as a steroid-sparing agent in patients unable to be tapered off corticosteroids.

REFERENCES

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