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**Periocular xanthogranuloma with adult-onset asthma as a rare disorder
associated with elevated IgG4 levels**

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Title:

Periocular xanthogranuloma with adult-onset asthma as a rare disorder associated with elevated IgG4 levels

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A 69-year-old man with periocular xanthogranuloma was admitted to the Hematology Clinic of Holy Cross Cancer Center in Kielce, Poland, to exclude systemic histiocytosis. He had a 5-year history of bilateral yellow swelling of the upper and lower eyelids and he reported sinusitis, nasal polyps, and adult-onset asthma occurring 3 years before the periocular infiltration. His medical history also consisted of skin lesions and eosinophilia. Physical examination showed significant swelling of the eyelids (Figure 1A), erythematous and edematous lesions on the skin of the torso and upper extremities with multiple of excoriations (scratch marks), and clubbed fingers. A complete blood count showed an elevated eosinophil count of $1.11 \times 10^9/l$. Other results, including red blood cell and platelet counts, were normal. Biochemical tests showed polyclonal hypergammaglobulinemia on serum protein electrophoresis with immunoglobulin G (IgG) levels of 21.3 g/l and immunoglobulin E (IgE) levels of 8.181 mg/l. C-reactive protein count and erythrocyte sedimentation rate were within normal range. Test results for antinuclear and antineutrophil cytoplasmic antibodies were negative.

Before being admitted to the clinic, the patient had a biopsy of the lower right orbit that showed histiocytic infiltration (Figure 1 B,C). Additional immunostaining did not show expression of CD1a and Cd207 antigens, excluding Langerhans cell histiocytosis. Magnetic resonance imaging confirmed hypertrophy of intraorbital fat tissue, bilateral proptosis, and thickening of the eyelids of both eyes (Figure 1D). To exclude systemic histiocytosis, we ordered a whole-body computed tomography scan, which showed no osteolytic lesions; liver and spleen size was normal. High-resolution computed tomography of the chest showed no changes characteristic of systemic histiocytosis. Bone marrow trephine biopsy findings were typical for normal hematopoiesis. The *BRAF* p.V600E mutation was not detected [1].

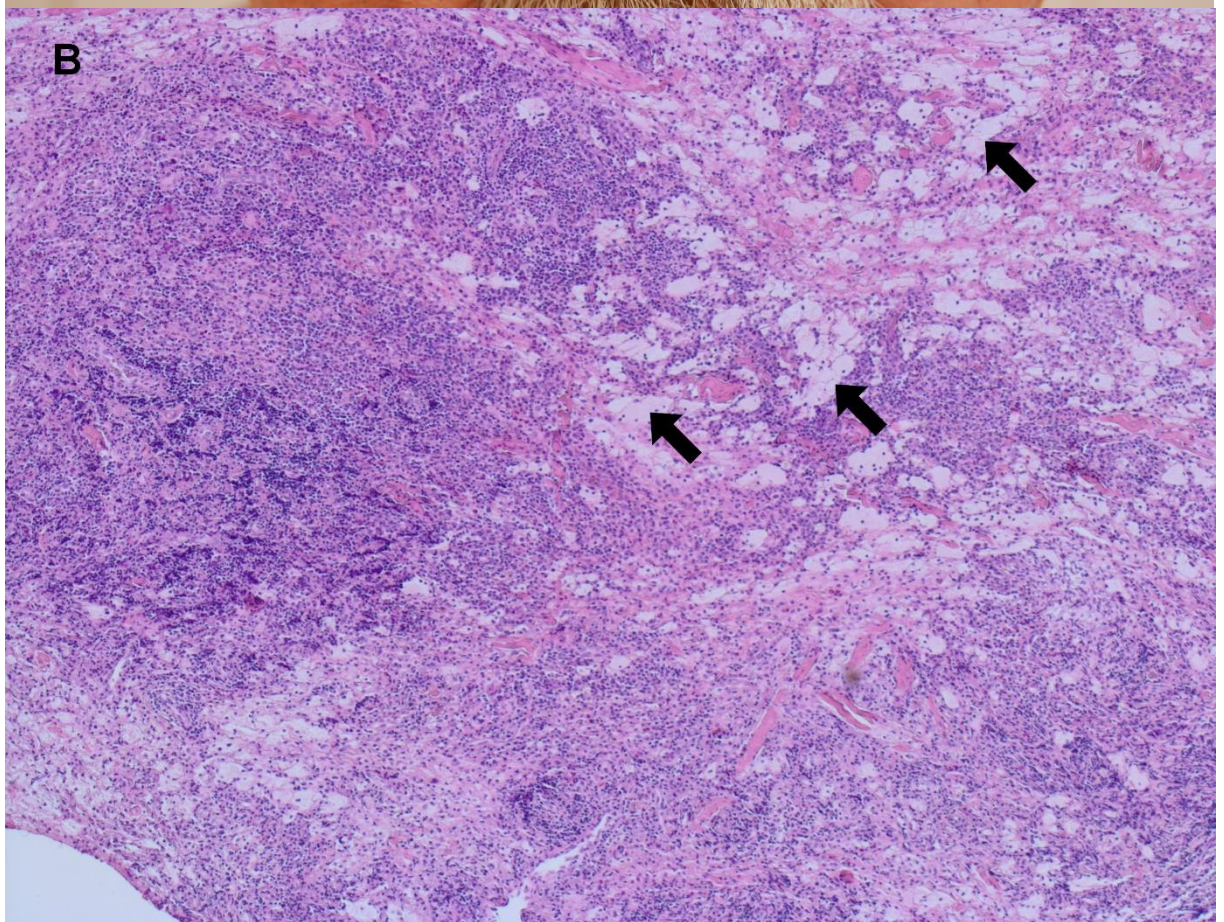
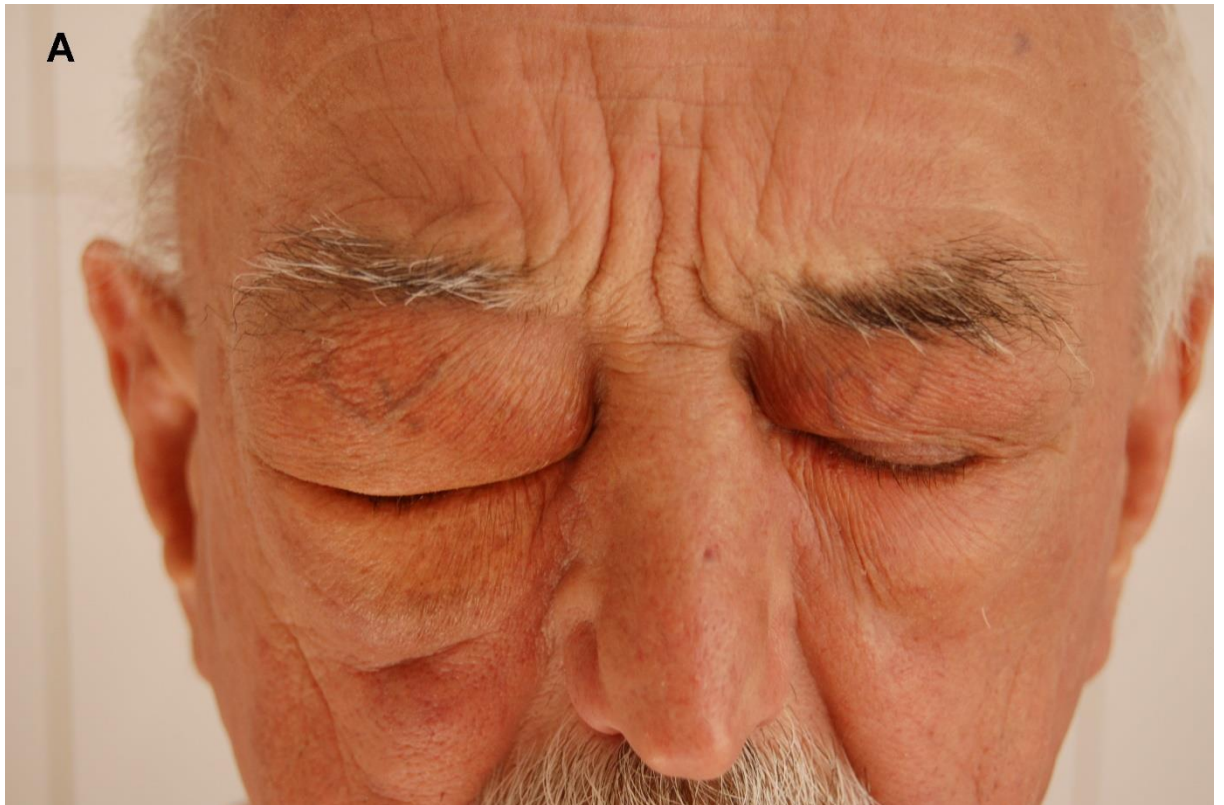
A biopsy sample of the affected skin segment (right subscapular area) showed perivascular inflammatory infiltrates consisting mainly of eosinophils, lymphocytes, and IgG4 plasmocytes

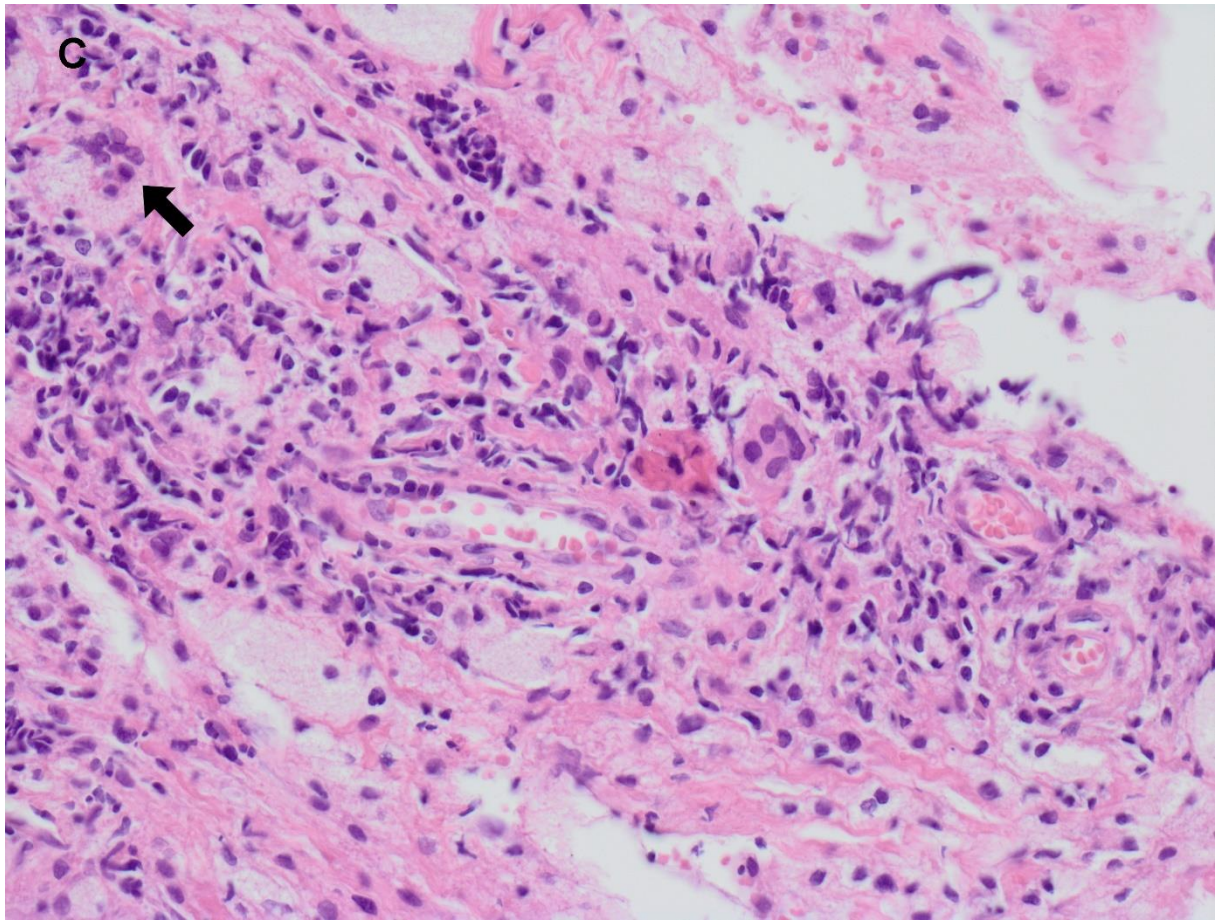
(Figure 1E). IgG4 plasmocytes were also found in previous biopsy specimens from the lower right orbit. The serum IgG4 level was significantly elevated at 3.38 g/l.

With detection of periocular histiocytic infiltration and symptoms of adult-onset asthma, nasal polyps, and eosinophilia, a diagnosis of periocular xanthogranuloma with adult-onset asthma (PXAOA) was made [2,3]. Oral prednisone was initiated at 1 mg/kg daily and gradually tapered. Simultaneously, the patient received six cycles of intravenous cyclophosphamide at 750 mg/m² every 4 weeks. Within 7 months, periocular swelling had decreased considerably (Figure 1 F,G). Serum levels of IgG, IgG4, and IgE were normalized, as was the eosinophil count. When prednisone was tapered to 10 mg daily, ocular manifestations recurred. Methotrexate was then initiated with good effect. PXAOA is a rare, nonmalignant, non-Langerhans-derived histiocytic disorder. Some cases are defined in the literature as a manifestation of IgG4-related disease (IgG4-RD) [4]. However, patients with elevated serum IgG4 levels manifest a wide array of disorders, only a small minority having IgG4-RD [5]. The differential diagnosis is complicated, but according to the American College of Rheumatology and European League Against Rheumatism draft classification criteria for IgG4-RD, the elevated serum IgG4 level in this patient was an accompanying immune dysfunction.

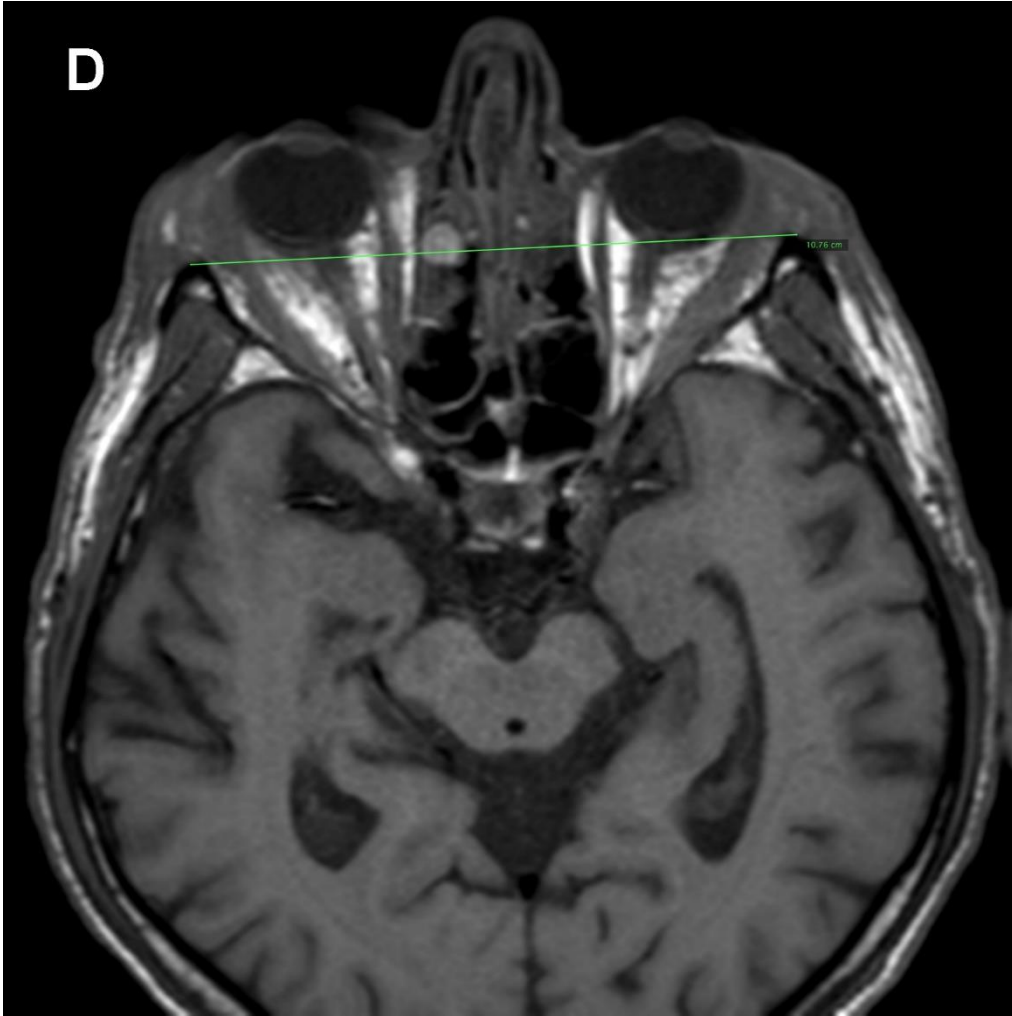
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D



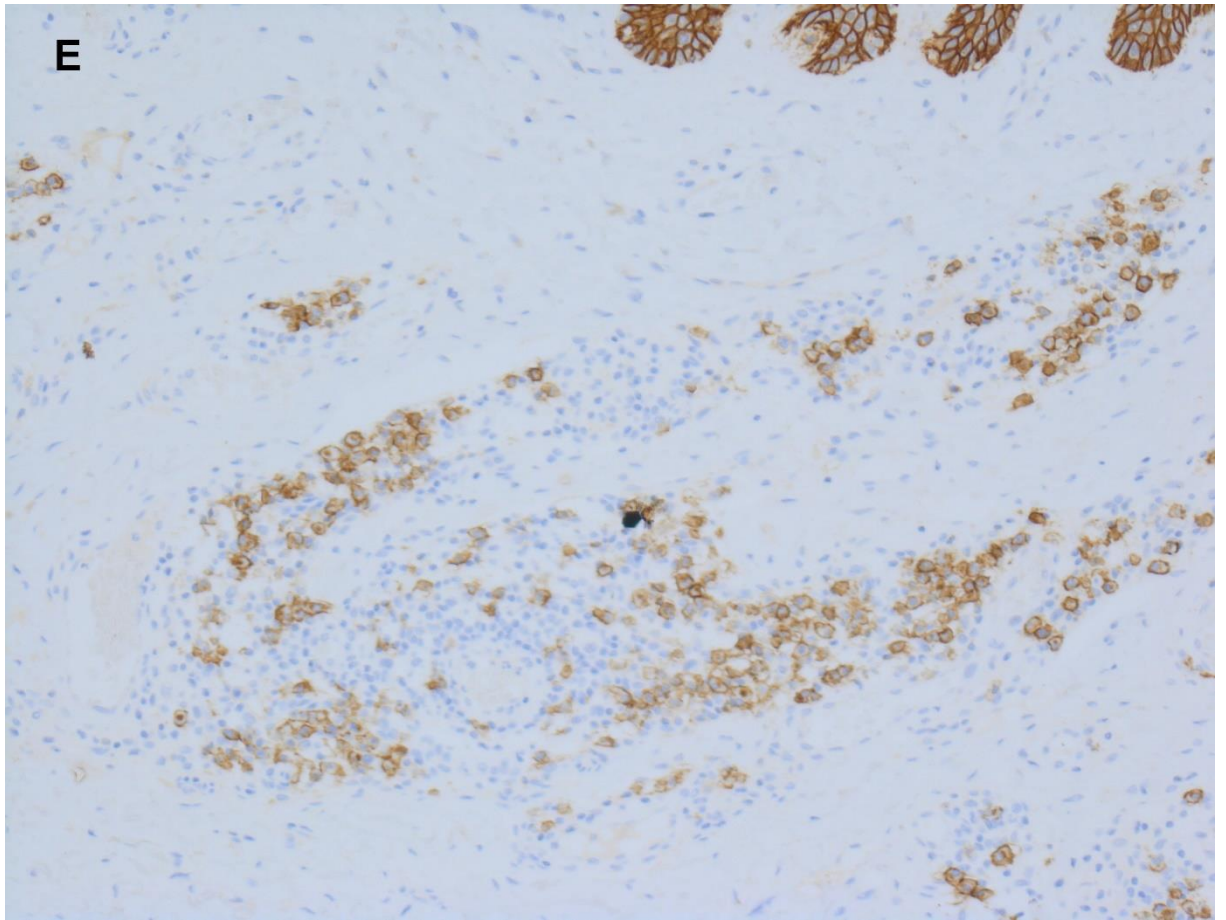




Figure 1 **A, F** – clinical photograph; bilateral, rubbery, yellow lid lesions: **A** – before treatment; **F** – after treatment. **B, C** – histopathologic analysis of biopsy specimens from right orbit: **B** – infiltrate composed of lymphocytes and foamy histiocytes (arrows); hematoxylin and eosin staining, magnification $\times 100$; **C** – multinucleated giant cells and Touton giant cells (arrow); hematoxylin and eosin staining, magnification $\times 400$. **E** – histopathologic analysis of biopsy specimens from the skin of the right subscapular area; positive immunohistochemical reaction to IgG4; magnification $\times 400$. **D, G** – magnetic resonance imaging of the head in the axial plane; ocular proptosis due to hypertrophy of the intraorbital fat tissue and thickening of

the straight lateral and straight lower muscles; green interzygomatic line was marked for the assessment of the level of proptosis: **D** – before treatment; **G** – after treatment.

The authors obtained informed consent from the patient.