Adult orbital xanthogranulomatous disease and myotonic dystrophy type 2: coexistence or association?

Adult orbital xanthogranulomatous disease (AOXD) is a rare form of non-Langerhans cell histiocytosis, a proliferative inflammatory condition whose precise pathophysiology remains unknown. According to the most recent classification of the Histiocyte Society, AOXD belongs to the C group of cutaneous and mucocutaneous histiocytoses. Traditionally, it had been categorized into 4 heterogeneous subgroups: Adult-onset xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma, necrobiotic xanthogranuloma, and Erdheim–Chester disease (ECD). The revised classification proposes reclassification of ECD into the Langerhans cell (L) group based on the co-occurrence of Langerhans cell lesions in patients with ECD and the discovery of mitogen-activating protein kinase pathway rearrangements in both diseases. All subtypes share common histopathologic features.[1] Given the vast number of differential diagnoses and the rarity of AOXD, the initial diagnosis is often delayed. We describe a patient with adult-onset asthma and periocular xanthogranuloma and concomitant type 2 myotonic dystrophy (DM2).

A 31-year-old man with a 2-year history of recurrent profound and painful periorbital swelling and a 4-year history of chronic rhinosinusitis presented to the oculoplastics department for orbital biopsy (Fig. 1). At that time, the patient had been managed by a multitude of specialists including ENT, rheumatology, and neurology. The periorbital swelling responded to oral steroids. The patient's regimen at the time of presentation to our department consisted of oral dexamethasone. Because of lack of improvement with conservative measures, the patient had undergone endoscopic sinus surgery with septoplasty and turbinate reduction a year prior. The procedure was complicated by aspiration pneumonia. In addition, the patient reported having intermittent watery diarrhea and skin rashes. His previous medical history was significant for adult-onset asthma, biopsy-proven eosinophilic esophagitis, an atopic disposition, and 1 episode of septic meningitis 4 years before presentation. His blood work showed mildly elevated C-reactive protein, elevated IgE levels, neutrophilia, and hypogammaglobulinemia (IgG1 and -2) and elevated liver enzymes. Other than an indeterminate rheumatoid factor of 17 IU/mL, his extensive serologic work-up for infectious (HIV, hepatitis B, hepatitis C, tuberculosis), endocrine (parathyroid hormone, prolactin, hemoglobin A1C, thyroid-stimulating hormone), and autoimmune conditions (double-stranded DNA antibodies, antineutrophil cytoplasmic antibodies, antinuclear antibodies, extractable nuclear antigen antibodies, angiotensin-converting enzyme antibodies, thyroid peroxidise antibodies, thyroid-stimulating hormone receptor antibodies, glomerular basement membrane antibodies, anti-cyclic citrullinated peptide antibodies) was negative. Additional specific autoimmune serology panels for scleroderma, lupus, and myositis also were negative. The patient denied muscular weakness but recently underwent genetic testing for myotonic dystrophy type 2 (DM2) given his positive family history. In keeping with the autosomal dominant nature of inheritance for this disease, it was noted that his father and grandfather both had DM2. On review of clinical features, the patient did not present with any proximal or distal muscle weakness, myoclonus, muscle wasting, tremors, or any other systemic findings consistent with DM2. However, DM2 clinical features often present later in life (more commonly in the fourth decade), and this patient was only 31 years of age at presentation. Genetic testing was done and showed the characteristic CCTG expansion of the *ZNF9* gene on chromosome 3q21.3. Electromyography was within normal limits. Computed tomography and magnetic resonance imaging of the orbits demonstrated homogeneously enhancing bilateral lacrimal gland enlargement along with postoperative sinus changes (Fig. 2). In retrospect, this enlargement had been slowly progressive over the previous 6 years.

At the time of presentation to our clinic, the patient had mild bilateral lateral upper lid swelling with palpable lacrimal glands. Of note, there was no evidence of skin changes. His marginal reflex distance 1 measured 3 mm in each eye, levator function was 14 mm OD and 13 mm OS, and Hertel exophthalmometry measured 17 and 19 mm OD and OS, respectively. The remainder of his ophthalmologic examination was within normal limits. At the time of incisional biopsy of his right lacrimal gland, after intentional discontinuation of oral dexamethasone, yellowish, indurated subcutaneous lesions were noted on both upper lids. Histopathology of the right upper eyelid skin and lacrimal gland showed marked chronic inflammation with lymphoid follicles, foamy histiocytes, infiltrating lipid-laden macrophages, and Touton giant cells. The population of foamy histiocytes was CD1a negative. Immunohistochemistry showed no evidence of clonal lymphoproliferative disease, which was consistent with AOXD (Fig. 3). After confirmation of the diagnosis, the patient was started on corticosteroid-sparing immunosuppression with azathioprine (150 mg daily), and a tapering course of steroids was initiated. A debulking effect of the surgery was seen 6 weeks postoperatively. Further work-up did not reveal any evidence of plasma cell dyscrasias or lymphoproliferative malignancies.

AOXD is a rare condition that may result in severe morbidity and mortality. The clinical presentation of AOXD varies between subgroups but includes mechanical ptosis, proptosis, nonulcerated xanthomatous eyelid or orbital masses, diplopia, and decreased visual acuity.[2] The precise underlying mechanisms that lead to localized or systemic

https://doi.org/10.1016/j.jcjo.2022.11.013
ISSN 0008-4182

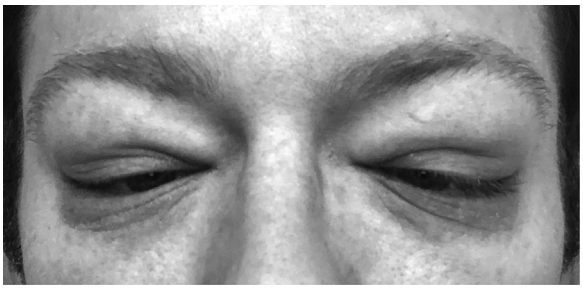

Fig. 1—Clinical appearance before initiation of steroid treatment shows bilateral periorbital swelling and medial yellowish deposits on both upper lids.

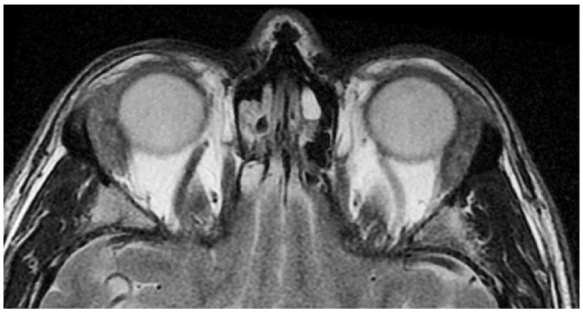

Fig. 2—Magnetic resonance imaging of the orbits with contrast material: bilateral fat-suppressed T_2 sequence with lacrimal gland enlargement and normal enhancement.

proliferation of non-Langerhans cell histiocytes remain poorly understood. One theory suggests virus-induced processes that result in reactive hyperproliferation of histiocytes (i.e., dendritic cells and macrophages) and lead to an immunologic derangement. Others postulate that these conditions represent a nonreactive idiopathic or hereditary dysregulation of the immune system. Some patients demonstrated chromosomal instability in peripheral blood cells and lesional tissue. It is unclear, however, whether these chromosomal abnormalities constitute an underlying genetic defect or are induced by the pathogenic agent (e.g., virus or environmental toxin) and simply serve as evidence of a cellular response in the context of proliferating histiocytes. More recently, rearrangements of the mitogen-activating protein kinase pathway (i.e., prototypical cancer-driving mutations) have been linked to ECD and Langerhans cell histiocytosis.[3] Whether these or similar abnormalities are also linked to the AOXD group is currently unknown. Other authors found an upregulation of diverse inflammatory markers (p-JAK2, p-STAT3, IFN-γ, IL-17, and IL-6) in AOXD tissue samples compared with normal tissues.[4] Multiple small case series describe an overlap between histiocytic disorders and various immunologic conditions, such as sinusitis, eosinophilic gastroenteritis, juvenile idiopathic arthritis, and IgG4 disease.[5,6]

DM2 is a genetic condition caused by a CCTG expansion on chromosome 3. The clinical presentation of DM2 may include myotonia, proximal and distal limb weakness or wasting, myalgia, tremors, frontal balding, cataracts, cardiac arrythmia, palpitations, dysphagia, and constipation.[7] Recent evidence suggests an association between autoimmune conditions and DM2. One study by Tieleman et al.[8] compared the prevalence of a variety of autoimmune disorders and autoantibodies in patients with DM2 and myotonic dystrophy type 1. The authors found significantly higher numbers in patients with DM28 Multiple other reports link various autoimmune conditions (e.g., Graves disease, celiac disease, myasthenia gravis, multiple sclerosis, neuromyelitis optica, and autoimmune gastritis to DM2.[9–12] Hypotheses explaining these associations include RNA-mediated processes, where cellular nucleic acid binding (CNBP) mRNA CCUG aggregates interfere with transcription and exert a toxic effect on proteins involved in inflammation. The resulting "sliceopathy" may explain the multisystem nature of the disease.[13] Another theory considers genetic linkage as a cause. Neighbouring genes on chromosome 3q13.31, for example, have been strongly related to allergic disease and rhinitis.[14] Mutations involving adjacent genes in certain DM2 patients thus may increase the susceptibility to autoimmune conditions.

Our patient expressed several complaints, and his examination showed a variety of abnormalities, which can be attributed to either of his diagnoses, some to both. In view of this symptom overlap, a possible association was questioned, and the literature was researched for existing evidence. Asthma and periorbital swelling are typically associated with AOXD. Diffuse hepatic steatosis and

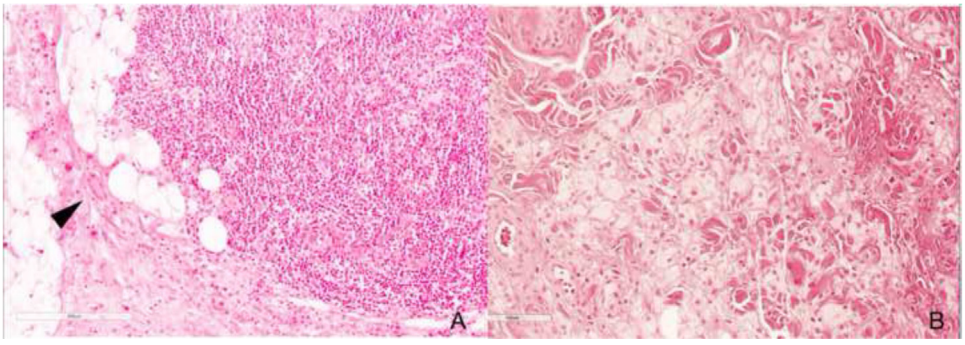

Fig. 3—Histopathology of right eyelid skin and lacrimal gland: (A) lacrimal gland tissue distorted by a proliferation of chronic inflammation, fibrosis, foamy histiocytes, and Touton giant cells (arrowhead); (B) foamy histiocytes diffusely infiltrating orbital soft tissue.

hypogammaglobulinemia are seen in patients with DM2.[15] Gastrointestinal symptoms, specifically eosinophilic gastritis, as well as an atopic or allergic spectrum of conditions, has been reported in the context of both diseases.[6,16]

This is the first reported case of AOXD with concomitant DM2. While the literature suggests that both diagnoses may have immunologic implications and similar cases linking both diseases with autoimmune conditions have been reported, no direct mechanism of causality between AOXD and DM2 can be identified at this stage. Further research is warranted to elucidate the pathogenesis of the heterogeneous group of non-Langerhans cell histiocytoses.

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Originally received Jun. 12, 2022. Final revision Oct. 5, 2022. Accepted Nov. 21, 2022.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this correspondence.

This study adhered to the Declaration of Helsinki. The UBC Clinical Research Ethics Board was contacted, and this study did not require institutional review board approval. The patient gave his consent for publication of his data and images.