Two Cases of Adult-onset Still’s Disease with Orbital Inflammatory Lesions Originating from the Lacrimal Gland

Ei Bannai, Hiroyuki Yamashita, Yuko Takahashi, Haruka Tsuchiya and Akio Mimori

Abstract

Orbital inflammation has been rarely associated with adult-onset Still’s disease (AOSD). We herein describe two AOSD patients who developed lacrimal gland enlargement with inflammation spreading to the contiguous tissues in the orbit. Case 1 was a 26-year-old woman who developed bilateral eyelid swelling while taking prednisolone (22.5 mg/day) for AOSD. The swelling of the eyelid worsened after other symptoms emerged, such as a fever, a rash, and arthritis. The laboratory findings, including leukocytosis, liver dysfunction, and ferritin elevation, also suggested an AOSD flare-up. Case 2 was a 62-year-old woman who presented with left eyelid swelling. She was diagnosed with AOSD at 45 years of age but sustained remission. During admission, she subsequently developed a fever, a rash, arthritis, lymphadenopathy, and ocular hyperemia. AOSD was suspected from the clinical course. We speculate that dacryoadenitis and orbital inflammation are manifestations of AOSD.

Key words: adult-onset Still’s disease, dacryoadenitis, orbital inflammation

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Introduction

Adult-onset Still’s disease (AOSD) is a systemic inflammatory condition that typically presents with a recurring spiking fever with a concomitant salmon pink rash and arthralgia. Orbital inflammation is a rare complication associated with this disease (1-5). In this article, we report two AOSD patients who developed lacrimal gland enlargement with inflammation that spread to the contiguous tissues in the orbit.

Case Reports

Case 1

Patient 1 was a 26-year-old woman who presented with right eyelid swelling. Two years previously, she had presented with complaints of a fever, arthritis, a typical rash, and sore throat; at that time, the possibilities of infectious disease, a malignant tumor, or other rheumatic diseases were ruled out. She was diagnosed with AOSD according to the diagnostic criteria of Yamaguchi et al. and was administered 22.5 mg/day of prednisolone on admission. Biological agents were used even after a previous treatment with a tapering dose of prednisolone because recurrence had occurred. However, the third dose of infliximab induced an allergic reaction, and etanercept was ineffective and thus discontinued after several doses. Prednisolone was gradually reduced. On this admission, erythema with tenderness was present over the exterior palpebral superior region. There was no induration in the regional lymph node, extraocular motility disturbance, or chemosis. The pupil mydriasis and light reflex were normal, thus indicating the lesion to be periorbital. The left side developed identical symptoms after 11 days of unsuccessful treatment with 300 mg/day of cefcapene pivoxil. Contrast-enhanced magnetic resonance imaging (MRI) of the orbit revealed a circumscribed, enhancing mass in the bilateral eyelid consistent with the lacrimal gland extending to the anterior temporal side through the orbital soft tissues (Fig. 1A). The white blood cell count (12,100/μL), erythrocyte sedimentation rate (ESR) (21 mm/h), C-reactive protein (CRP) level (4.21 mg/dL), and ferritin level (180 ng/mL) were elevated. The eosinophil counts and...
liver enzyme levels were within the normal ranges. Negative results were noted on the assays for antinuclear antibodies (ANA), anti-dsDNA, anti-Ro, anti-La, cytoplasmic and myeloperoxidase anti-neutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor (RF). The soluble IL-2 receptor (sIL-2R), angiotensin-converting enzyme (ACE), and β-D glucan levels were within the normal ranges. A biopsy of the left upper eyelid showed the lacrimal gland infiltrated with mild lymphoid cells around the small vessels and fibroconnective tissue consistent with mild chronic inflammation (Fig. 1B). Two weeks later, the eyelid swelling worsened and the patient developed additional symptoms, including a fever, an evanescent rash, and arthritis, suggesting a diagnosis of an AOSD exacerbation with dacryoadenitis. Prednisolone (60 mg/day, body weight 53.3 kg) was commenced and dramatically improved her systemic and ocular symptoms; however, when prednisolone was tapered to 11 mg/day, partial recurrence of the bilateral eyelid swelling and tenderness was observed. The prednisolone dose was increased to 60 mg/day to induce remission and tocilizumab (TCZ) was administered for its immediate expected effect and to replace the prednisolone treatment. The prednisolone therapy was tapered in a stepwise manner, and she is currently being maintained on intravenous injections of TCZ every nine weeks.

**Case 2**

Patient 2 was a 62-year-old woman admitted after a three-week history of left eyelid swelling and tenderness without systemic symptoms. At 45 years of age, she presented with a fever, arthritis, and a typical rash, and the possibilities of infectious disease, a malignant tumor, and other rheumatic diseases were ruled out. Accordingly, she was diagnosed with AOSD based on the diagnostic criteria of Yamaguchi et al. and administered 60 mg/day of prednisolone as steroid therapy, which lead to remission. Her condition was stable without medication for the previous 5 years. She had additionally received 1-methyl-2-mercaptoimidazole treatment for Basedow’s disease, which was diagnosed at 49 years of age. A physical examination showed left peri orbital erythema and edema, but no proptosis and normal ocular movements. In the laboratory evaluation, no specific abnormalities were found, including those for the levels of RF, ANA, cytoplasmic and myeloperoxidase ANCA, CRP, and liver enzymes, and the results of the white blood cell count, ESR, and thyroid function were normal. Fundoscopy showed healthy optic discs. Contrast-enhanced MRI (Fig. 2A) revealed left lacrimal gland and peri orbital soft tissue swelling with strong contrast enhancement extending into the temporal occipitofrontalis muscles, rectus superior muscles, and the enthesis of the levator palpebrae superioris muscles. The contrast was also slightly enhanced in the sclera. Fluorodeoxyglucose-positron emission tomography (Fig. 2B) showed the highest uptake in the left lacrimal gland, suggesting that the inflammation spread from the main lesion to the contiguous tissues. Two weeks of ceftriaxone treatment failed to improve her symptom, and a subsequent naproxen administration was also unsuccessful in treating her symptom. One month after this admission, the patient developed a fever of >39°C, a salmon-pink rash, bilateral gonitis, and left cervical lymphadenopathy. Complete ptosis suggested that the inflammation extended to the levator palpebrae superioris muscles (Fig. 2C). Ocular hypemacia developed, and episcleritis was diagnosed on an ophthalmological examination. The laboratory data revealed leukocytosis (peak: 7,520/μL), elevated hepatic enzyme levels (aspartate aminotransferase level: 64 U/L, alanine transaminase: 28 U/L), increased CRP (7.41 mg/dL) and ferritin (1,731 mg/dL) levels, and mild thrombocytopenia (platelet count: 98,000/μL). A biopsy of the left eyelid showed a lymphoplasmacytic infiltration and fibrosis (Fig. 2D). Immunostaining of the cervical lymph node specimen did not
female-to-male ratio was 2:3, and the ages ranged from 2 to 23 years. Furthermore, 2 cases were AOSD (1, 5) and the remaining 3 (2-4) were JIA. In three cases, the orbital disease simultaneously occurred with AOSD/JIA, whereas in the other cases, the ocular symptoms emerged with an AOSD/JIA flare-up. Three cases presented with symptoms in both eyes; however, these symptoms may also occur unilaterally. A histopathological evaluation in one case indicated non-granulomatous chronic inflammation. In all the cases, prednisolone was administered to control the symptoms, however, the dose ranged from 10 mg on alternate days to 1 g of methylprednisolone pulse per day.

Dacryoadenitis, which is the most common form of idiopathic orbital inflammation, has thus far never been reported in association with AOSD. In the absence of definite causes, localized inflammation in the first case and generalized inflammation which presented as dacryoadenitis in the second case were found to be associated with AOSD.

The diagnostic biopsy results indicated no granuloma or necrotic and leukocytoclastic vasculitis, or fibrotic degeneration, thus ruling out sarcoidosis and vasculitis, including granulomatosis with polyangitis and eosinophilic granulomatosis with polyangiitis. No IgG4-positive plasma cells were found, ruling out a role for IgG4-mediated fibroinflammatory disease. Tuberculous and syphilitic dacryoadenitis typically occur concomitantly with periostitis of the palpebral orbital bony rim and lead to osteolysis, which was not diagnosed in either cases (6). Furthermore, other infections

detect IgG4-positive plasmacytes. Extensive investigations, including a repeat blood culture and bone marrow aspiration, failed to disclose a specific infectious or neoplastic disease. AOSD was diagnosed, and an apparent resolution of her ocular and systemic symptoms was achieved after administering 35 mg of prednisolone (body weight 70.4 kg) daily. She has continued receiving prednisolone (3 mg/day) without any flare-ups.

Discussion

AOSD/Juvenile idiopathic arthritis (JIA) can be complicated with a clinical and radiographic finding of idiopathic orbital inflammation and may involve any structures in the orbit and clinical symptoms include proptosis, ptosis, extraocular motility disturbance, pain, erythema, and chemosis. Five cases of orbital inflammation associated with AOSD/JIA have been reported since the initial report on a peripheral orbital inflammatory pseudotumor at the onset of AOSD/JIA with serositis (1). Subsequently, a postseptal pseudotumor was described, which was rarely complicated with lytic bone lesions, uveitis, or keratopathy (2). Trochleitis, an unusual form of orbital inflammation localized to the superior oblique tendon and trochlea complex, was also described (3, 4). Additionally, preseptal cellulitis was also found to be involved (5). In the five previous cases, the female-to-male ratio was 2:3, and the ages ranged from 2 to 23 years. Furthermore, 2 cases were AOSD (1, 5) and the remaining 3 (2-4) were JIA. In three cases, the orbital disease simultaneously occurred with AOSD/JIA, whereas in

Figure 2. The findings indicated orbital inflammation in patient 2. A: An orbital enhanced magnetic resonance (T2WI) image showing a diffuse enlargement of the left lacrimal gland and subcutaneous tissue swelling in the eyelid. B: An axial flurodeoxyglucose positron emission tomography image showing an oblong anterio-posterior enlargement of the left lacrimal gland with the highest contrast enhancement. C: The patient presented with left ptosis and pain, as well as erythema with edema in the lateral upper eyelid. D: A histological evaluation of the lacrimal gland specimen revealed lymphocytes and plasma cells with neutrophils infiltrating the region around the small vessels along with fibroconnective tissue, suggesting post-inflammatory changes (Hematoxylin and Eosin staining, 400×).
of the lacrimal gland, such as those caused by bacilli and *Aspergillus*, or mucormycosis do not usually occur simultaneously with the bilateral symptoms or as an acute onset.

Imaging plays an important role in elucidating the involved structures and gives indications about the underlying etiology behind orbital inflammation. It is not easy to differentiate from neoplasm or malignant lymphoma, whereas a previous report has stated that lacrimal enlargement in both the orbital and palpebral lobes is a feature of inflammatory disease in contrast with an epithelial neoplasm, which typically involves only the orbital lobes. Furthermore, a compressed oblong shape of the enlarged lacrimal glands suggests an inflammatory process, as opposed to rounded enlargements typical of an epithelial neoplasm or lymphoma (7). Nevertheless, a diagnostic biopsy should be performed positively as other pathologies affecting the orbit must be ruled out.

Our patients promptly responded to corticosteroid therapy, as did the patients in the previous reports. Spontaneous resolution or supportive treatment with acetylsalicylic acid alone has been shown to arrest the disease in some patients. Thus, an initial observation with supportive treatment for the pain should also be considered (8, 9). However, a more intensive regimen including biological agents for recalcitrant disease may be required to control recurrence in the course of reducing corticosteroids. Gutmark et al. reported the effective treatment with anakinra to an AOSD patient with recurring trochleitis (4), and we succeeded in administering TCZ in the second case in the present study. In recalcitrant conditions, corticosteroids alone cannot control the exacerbations, and biological agents may be curative.

The reason dacryoadenitis occurs in AOSD remains ambiguous, whereas in Crohn’s disease, for instance, it is speculated to be due to antigenic overlaps between the bowel and lacrimal tissues (10). Alternatively, some antigens may hematogenously localize to the lacrimal gland and incite a T-cell response that follows a granulomatous reaction pattern (11).

In conclusion, the lacrimal gland may be an inflammatory target and is affected before the full manifestations of AOSD due to systemic inflammation. Therefore, a careful follow-up is necessary if a patient with AOSD develops symptoms which suggest the presence of an orbital lesion, even if in remission. The accumulation of such cases will reveal the etiology of AOSD and thus lead to the establishment of optical therapy for this form of AOSD.

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References