Journal of Rheumatic Diseases
Vol. 20, No. 4, August 2013
http://dx.doi.org/10.4078/jrd.2013.20.4.243

□ Case Report □

A Case of Adult-Onset Still's Disease Presenting with Periorbital Edema

Da-Lim Yoon, Seohyun Lee, So Young Park, You Jae Kim, Bon San Koo, Min Wook So, Yong-Gil Kim, Chang-Keun Lee, Bin Yoo

Division of Rheumatology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology that is characterized by high-spiking fever, arthralgia, sore throat, and skin rash. The typical rash of AOSD is an evanescent, salmon-colored erythema, which is considered to be the major diagnostic criterion. Recently, other cutaneous manifestations of AOSD, such as persistent plaque and urticaria, have been reported. Here, we report a rare case of AOSD presenting with periorbital swelling and erythema. A 47-year-old woman was presented with periorbital swelling, erythema, high fever, arthritis, and a sore throat. One year prior to admission, she was diagnosed with AOSD based on the diagnostic criteria of Yamaguchi. The patient's periorbital swelling and erythema may not have been associated with periorbital cellulitis because they did not respond to antibiotics but did improve after treatment with steroids. Considering all of her signs and symptoms with a history of AOSD, periorbital lesion was suspected as atypical cutaneous manifestation of AOSD.

Key Words. **Adult-onset Still's disease; Cellulitis; cutaneous manifestation**

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology that is characterized by high-spiking fever, arthralgia, skin rash, and other systemic presentations. Its clinical manifestations are diverse and its prevalence is very rare, thereby making its diagnosis difficult (1). The typical AOSD skin rash consists of evanescent, salmon-colored, maculopapular lesions that usually appear during fever. These lesions are of great diagnostic value, especially in cases where the fever is of unknown origin. However, the other cutaneous manifestations of AOSD are not considered to have any diagnostic significance and are usually misdiagnosed as another condition (e.g., bacterial or viral infections, drug eruptions, hematological malignancies, or collagen vascular disease). Recently, other cutaneous manifestations of AOSD and their diagnostic importance have been reported (2). Here, we report an unusual case of AOSD that presented with periorbital swelling and erythema.

Case Report

A 47-year-old woman was admitted to our hospital due to a 2-week history of periorbital swelling. One year prior to this admission, she presented with an episode of high fever associated with arthritis and maculopapular rashes on her trunk and limbs. At that time, she was diagnosed with AOSD based on the diagnostic criteria reported by Yamaguchi (1); high fever $>39^{\circ}C$, arthritis, skin rash, leukocytosis with neutrophilia, sore throat, negative rheumatoid and antinuclear factors, and the exclusion of other infections. After diagnosis, she was started on oral methylprednisolone at a dosage of 24 mg/day for six weeks. Within one week of steroid use, her high fever, arthralgia, and skin rash had improved. Over the next year, the methylprednisolone dose was slowly tapered to 2 mg/day without any recurrence. Other disese-modifying antirheumatic

＜Received : May 11, 2012, Revised (1st: June 15, 2012, 2nd: August 3, 2012), Accepted : August 9, 2012＞
Corresponding to : Chang-Keun Lee, Division of Rheumatology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea. E-mail : cklee@amc.seoul.kr

pISSN: 2093-940X, eISSN: 2233-4718

drugs had not been prescribed.

Two weeks ago, the patient developed swelling of both eyelids and visited the department of ophthalmology at our hospital. At that time, she had no other systemic symptoms. The records of her previous laboratory tests showed that her white blood cell (WBC) count, neutrophil ratio, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level were within normal ranges, but her liver enzyme levels were slightly elevated (aspartate transaminase [AST]: 47 IU/L; alanine transaminase [ALT]: 75 IU/L). A slit-lamp examination and dilated fundus examination revealed no abnormal findings. After examination by the ophthalmologist, she was clinically diagnosed with preseptal cellulitis and prescribed ceftriaxone for two weeks. However, her symptoms failed to improve, and she was admitted again for further evaluation.

On her second admission, her body temperature was 36.1°C and her other vital signs were stable. However, her acute symptoms had progressed and were accompanied by generalized myalgia, febrile sensation, sore throat, palpebral edema and pain, and swelling of the left parotid gland (Figure 1A). Physical examination revealed tenderness in both eyes and around the left parotid gland. Repeated examination of her visual acuities and fundus showed no abnormalities. Her breathing was clear and her heart beat was regular. There was no evidence of lymphadenopathy or hepatosplenomegaly. Neither joint nor skin abnormalities were observed. Laboratory analysis revealed a WBC count of 5,200 cells/mm^3 (85.6% neutrophils), elevated liver enzymes (AST: 110 IU/L; ALT: 101 IU/L), and high CRP (6.78 mg/dL). Her serum ferritin level was markedly elevated (12,588.6 ng/mL). Renal functions and her coagulation profiles were normal. Blood cultures showed no evidence of bacterial infection. No abnormalities were observed on chest radiography. Orbital computed tomography (CT) showed periorbital soft tissue swelling and heterogeneous enhancement around both eye sockets (Figure 2A). Neck CT showed diffuse swelling of the left parotid gland with periglandular infiltration (Figure 2B).

A fever of above 38°C was measured 3～4 times daily even after her hospital admission. On the basis of the CT findings of the eyes and neck, preseptal cellulitis and accompanying parotitis could not be ruled out, so an antibiotic regimen of ceftriaxone and nafcillin was maintained. However, two days after admission, multiple erythematous patches were found on her entire body along with urticaria, and the patient complained of arthralgia in her fingers and knees. These were symptoms were suspected of being antibiotic-induced allergic reactions, so the antibiotics were changed to levofloxacin and clindamycin. However, none of her symptoms had improved by the fourth day of hospitalization. Laboratory analysis performed after the fourth day of admission revealed a newly appeared thrombocytopenia (26,000 cells/mm^3), aggravated liver

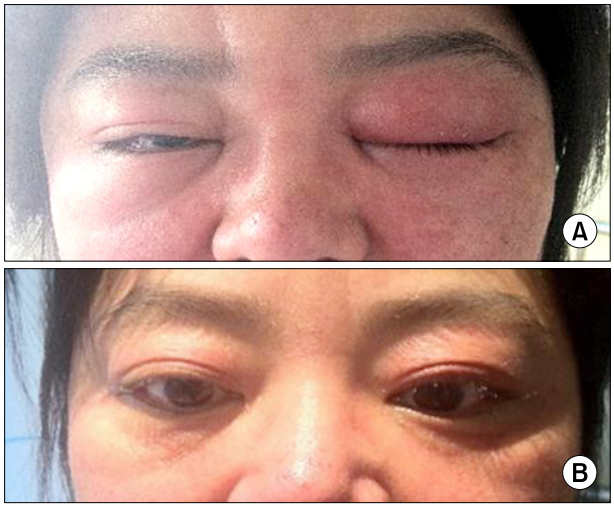

Figure 1. (A) Cellulitis-like periorbital swelling of both eyelids. (B) Improvement was noted after 5 days of steroid treatment.

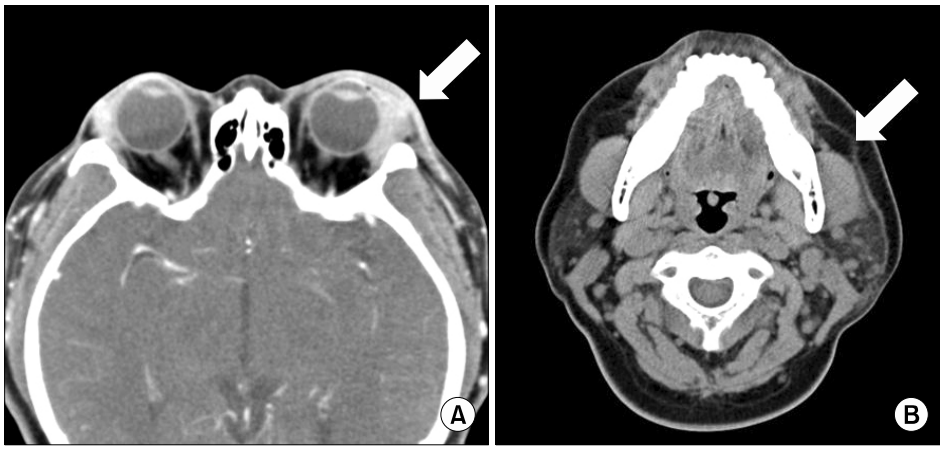

Figure 2. (A) Orbit CT scan showing left-side dominant periorbital soft tissue swelling and heterogeneous enhancement (arrow). (B) Neck CT showing diffuse swelling of the left parotid gland with periglandular infiltration (arrow).

function (AST: 2,395 IU/L; ALT: 851 IU/L; total bilirubin: 2.2 mg/dL), and decreased fibrinogen level (97 mg/dL). However, her WBC count, neutrophil ratio, hemoglobin level, ESR, and coagulation profile were within normal ranges. Triglyceride level was not checked. Repeated blood cultures did not indicate bacterial infection.

The patient's symptoms deteriorated even after continuous antibiotic therapy. Furthermore, the patient complained of a high-spiking fever, skin rash, and arthralgia, which were similar to her symptoms at the time of AOSD diagnosis one year prior. Considering all of her signs, symptoms, and her history of AOSD, atypical cutaneous manifestation of AOSD was suspected. The patient was treated using intravenously injected methylprednisolone (1 mg/kg) starting on the fourth day of hospitalization. After the next day, a steroid injection was administered, and the patient's fever, skin rash, and arthralgia rapidly improved. After five days of steroid treatment, her clinical symptoms, including the swelling of both eyelids, dramatically improved (Figure 1B). Furthermore, her thrombocytopenia (248,000 cells/mm^3), liver enzyme levels (AST: 119 IU/L; ALT: 296 IU/L: total bilirubin: 1.0 mg/dL), and other indicators of inflammation, including ESR (3 mm/hour) and CRP (0.86 mg/dL), were normal. The patient was discharged from the hospital with a prescription for oral methylprednisolone (40 mg/day) after receiving intravenous steroids for one week. After six weeks of steroid therapy, additional methotrexate 15 mg weekly was initiated. Over the next 4 months, the dose of methylprednisolone was tapered to 4 mg/day with satisfactory control.

Discussion

AOSD is a rare systemic inflammatory disease of unknown etiology. Since it was first described by Bywaters in 1971, it has been widely reported across the world. However, the diagnosis of AOSD is difficult because of its diverse clinical symptoms and low prevalence. Although several classification criteria have been suggested (1,3,4), Yamaguchi's criteria are currently the most sensitive and specific (1). The detection of an increased ferritin level can also be helpful for the diagnosis of AOSD. Fautrel et al. (5) indicated that AOSD can be diagnosed with a 93% specificity when the serum ferritin is 5 times higher than normal and glycosylated ferritin is less than 20% of normal levels.

Although the pathogenesis of AOSD is unclear, it is thought to occur in individuals with a genetic susceptibility to immune system activation, including cytokine activation caused by viral or bacterial infection. The current clinical treatment for patients with AOSD includes the administration of steroids and immunosuppressants because these cases typically demonstrate higher levels of Th1-related cytokines (e.g., IL-2, IFN-γ, TNF-α, and IL-18) than those without AOSD (6). In the skin, IL-18 is produced by keratinocytes, Langerhans cells, and dermal dendritic cells. Studies have suggested that IL-18 may stimulate ferritin synthesis or inhibit its clearance (2).

The clinical symptoms of AOSD include high-spiking fever, arthritis, skin rash, and sore throat. Of these symptoms, the typical skin rash is an evanescent, salmon-pink, maculopapular eruption, which usually appears along with the spike in fever. The rash is observed in more than 87% of AOSD patients and is predominantly found on the proximal limbs and trunk (7). The presence of the typical skin rash is highly sensitive and specific to the diagnosis of AOSD among patients who present with a fever of unknown origin that is not accompanied by a specific arthritis (1). Whilst a skin biopsy is not essential for the diagnosis of the typical skin rash, most patients with AOSD show mild perivascular infiltration of the superficial dermis with lymphocytes and histiocytes (8,9). On the other hand, AOSD can also be accompanied by a variety of atypical skin rashes, including persistent plaques, urticaria, acne-like lesions, alopecia, and bullous lesions (10). Recently, a case study reported an erythematous eruption similar to cellulitis that presented on the left thigh of a patient with AOSD that was successfully treated using steroids and methotrexate (11). The histology of the cellulitis-like erythema was non-specific but was consistent with a typical Still's rash.

For patients who present with fever accompanied by skin rash, the differential diagnosis should include a range of infectious and non-infectious diseases. Particularly in the case of lesions that mimic periorbital cellulitis, diseases that should be considered in the differential diagnosis include angioedema, lymphoma and connective tissue disease such as dermatomyositis. There was a case report of AOSD presenting with angioedema of the lips, palms and soles (12). In the present case, her initial symptom was similar with angioedema. However, she had neither family history nor past history of angioedema. In addition, her symptoms lasted for more than 2 weeks and there was no other mucosal involvement such as lips, larynx, and extremities. It is not a typical finding of angioedema. Other connective tissue diseases such as systemic lupus erythematous (SLE) and dermatomyositis can also cause periorbital swelling. However, in the present case, her anti-nuclear and anti-ds DNA antibodies were negative and other systemic symptoms of myositis were not present. Therefore SLE and myositis could be ruled out.

Skin rash and lymphadenopathy commonly occur in patients with AOSD, and the histological pattern may occasionally be

confused with that of lymphoma (13). Furthermore, malignant lymphoma should not be excluded from the diagnosis because it may develop in patients with AOSD (14). In the present case, the periorbital skin lesion may not have been associated with cellulitis because it did not respond to antibiotics and was resolved with steroid treatment. Furthermore, the possibility of lymphoma was low because of the patient's history of AOSD and her rapid response to steroids. Even during the hospitalization period, her systemic symptoms were similar to those observed at the time of her diagnosis of AOSD. In addition, her serum ferritin, which aided in the diagnosis of AOSD, was 40-times higher than normal. Macrophage activation syndrome can also occur during the course of AOSD (15). It is a severe, life-threatening complication of several rheumatic diseases. If a patient were worsening after treatment, further evaluation of lymphoma and macrophage activation syndrome including natural killer cell activity, soluble CD 25 level, parotid gland biopsy, and bone marrow examination would be considered.

This is a rare reported case of AOSD that presented in the skin around the eyes and parotid gland. When steroids and immunosuppressnts are used to treat AOSD, the risk of infection increases. Furthermore, because fever and increased inflammatory makers are also observed in acute flare-ups of AOSD, it is difficult to distinguish an acute flare-up of AOSD from infections such as preseptal cellulitis and parotitis, such as those that were observed in this patient. Hence, early and correct diagnosis may be delayed. If a patient who presents with periorbital swelling and erythema has systemic symptoms, including fever, arthralgia, and skin rash, the possibility of an atypical dermal presentation of AOSD should be considered. Early examination and proper treatment of such symptoms will reduce the clinical complications associated with this disease.

Summary

Recently, an atypical manifestations of AOSD and their diagnostic importance have been reported. Here, we report an unusual case of AOSD that presented with periorbital swelling and erythema.

Acknowledgements

The author reported no conflict of interest and no funding was received on this work.

References

1. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424-30.
2. Yamamoto T. Cutaneous manifestations associated with adult-onset Still's disease: important diagnostic values. Rheumatol Int 2012;32:2233-7.
3. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum 1987;30:186-94.
4. Reginato AJ, Schumacher HR Jr, Baker DG, O'Connor CR, Ferreiros J. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. Semin Arthritis Rheum 1987;17:39-57.
5. Fautrel B, Le Moël G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 2001;28:322-9.
6. Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F. Adult-onset Still's disease. Rheumatol Int 2010;30:855-62.
7. Ohta A, Yamaguchi M, Kaneoka H, Nagayoshi T, Hiida M. Adult Still's disease: review of 228 cases from the literature. J Rheumatol 1987;14:1139-46.
8. Wolgamot G, Yoo J, Hurst S, Gardner G, Olerud J, Argenyi Z. Unique histopathologic findings in a patient with adult-onset Still disease. Am J Dermatopathol 2007;29:194-6.
9. Han SH, Choi GS, Shin J. A clinicopathological study on skin manifestations of adult-onset still's disease (AOSD). Korean J Dermatol 2010;48:283-9.
10. Affleck AG, Littlewood SM. Adult-onset Still's disease with atypical cutaneous features. J Eur Acad Dermatol Venereol 2005;19:360-3.
11. Inaoki M, Nishijima C, Kumada S, Kawabata C, Yachie A. Adult-onset Stills disease with a cellulitis-like eruption. Eur J Dermatol 2009;19:80-1.
12. Soy M. A case of adult-onset Still's disease presenting with angioedema. Clin Rheumatol 2004;23:92.
13. Jeon YK, Paik JH, Park SS, Park SO, Kim YA, Kim JE, et al. Spectrum of lymph node pathology in adult onset Still's disease; analysis of 12 patients with one follow up biopsy. J Clin Pathol 2004;57:1052-6.
14. Trotta F, Dovigo L, Scapoli G, Cavazzini L, Castoldi G. Immunoblastic malignant lymphoma in adult onset Still's disease. J Rheumatol 1993;20:1788-92.
15. Hot A, Toh ML, Coppéré B, Perard L, Madoux MH, Mausservey C, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore) 2010;89:37-46.