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CASE REPORT

Junichi Asakawa · Yoshihiro Torikoe · Itsuko Kondo
Masahiko Yasuda · Shigeto Kobayashi
Hiroshi Hashimoto

Reactive arthritis after pharyngeal infection: report of two siblings

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Abstract In this report we describe the cases of two siblings with reactive arthritis (ReA) induced by pharyngeal infections. The patients were a man and his sister living with their parents. He developed arthritis in August 1997, and his younger sister developed similar symptoms in September 1998. Their disease conditions were both severe and required hospitalization. Their conditions improved with the administration of nonsteroidal anti-inflammatory drugs together with antibiotics, and both fully recovered within 1–2 weeks. Rheumatic fever was ruled out since streptococcal infections were not demonstrated with antistreptolysin O (ASO) or antistreptokinase (ASK) titers, or with pharyngeal culture. The sister suffered from a rash which was similar to erythema nodosum on her lower extremities, but neither chorea nor carditis was observed. Both human leukocyte antigen (HLA) typing analyses revealed positive results for HLA-B40 and -B39 for the brother and sister, respectively. Both HLA-B40 and -B39 are considered to be related to HLA-B27-negative ReA, most likely poststreptococcal reactive arthritis (PSRA). Therefore, the two patients were tentatively diagnosed as suffering from PSRA.

Key words Group-A streptococcal infection · Human leukocyte antigen (HLA)-B27, 39, 40 · Human leukocyte antigen (HLA) typing · Reactive arthritis (ReA)

J. Asakawa (✉) · Y. Torikoe · I. Kondo
Department of Medicine, Yanagibashi Hospital, 2-20-4 Yanagibashi, Taito-ku, Tokyo 111-0052, Japan
Tel. +81-3-3851-9375; Fax +81-3-3866-3745
e-mail: jm5j-askw@asahi-net.or.jp

M. Yasuda
Department of Medicine, Nakaizu spa Hospital, Tagata-gun, Shizuoka, Japan

Y. Torikoe · S. Kobayashi · H. Hashimoto
Department of Rheumatology, Juntendo University, School of Medicine, Tokyo, Japan

Introduction

Reactive arthritis (ReA) is a clinical entity which is referred to as a sterile inflammatory arthritis occurring secondary to a microbial infection at a distant site in the body.[1,2] It has been ascribed to human leukocyte antigen (HLA)-B27-related arthritides, which are collectively classified into the seronegative spondyloarthropathy (SpA) group, together with Reiter's syndrome and ankylosing spondylitis. In Japan, the occurrence rate of HLA-B27 is less than 1% among the healthy population, in contrast to 7% to 14% in the United States and Europe. Thus, HLA-B27-related arthritides, including ReA, are considered to be rare in Japan.[3] Recently, HLA-B27-unrelated ReA, i.e., poststreptococcal reactive arthritis (PSRA) after pharyngeal infection, has been reported. The pathogenecity of this arthritis, which is different from that of rheumatic fever, has been noted. In this report, we described the case of two siblings with ReA after pharyngeal infection. They had suffered from ReA consecutively, and the similarity of their manifestations had attracted our attention. Intrafamilial occurrence of HLA-B27-unrelated ReA is a rare event and worthy of mention.

Case report

The first case was a 32-year-old man who sought medical attention at the Department of Medicine, Yanagibashi Hospital, on August 3, 1997. His chief complaints were sore throat and high-grade fever. He was treated with oral administration of amoxicillin and loxoprofen sodium. Remission of the sore throat was attained shortly after the administration of medication, but the high-grade fever persisted and he subsequently suffered from systemic polyarthritis, bilateral severe pains in the elbows and wrist joints, and bilateral marked swellings of the knees and ankle joints. He was admitted to Yanagibashi Hospital on August 26 owing to persistent fever and arthritis. Laboratory examinations revealed a slight increase in leukocyte

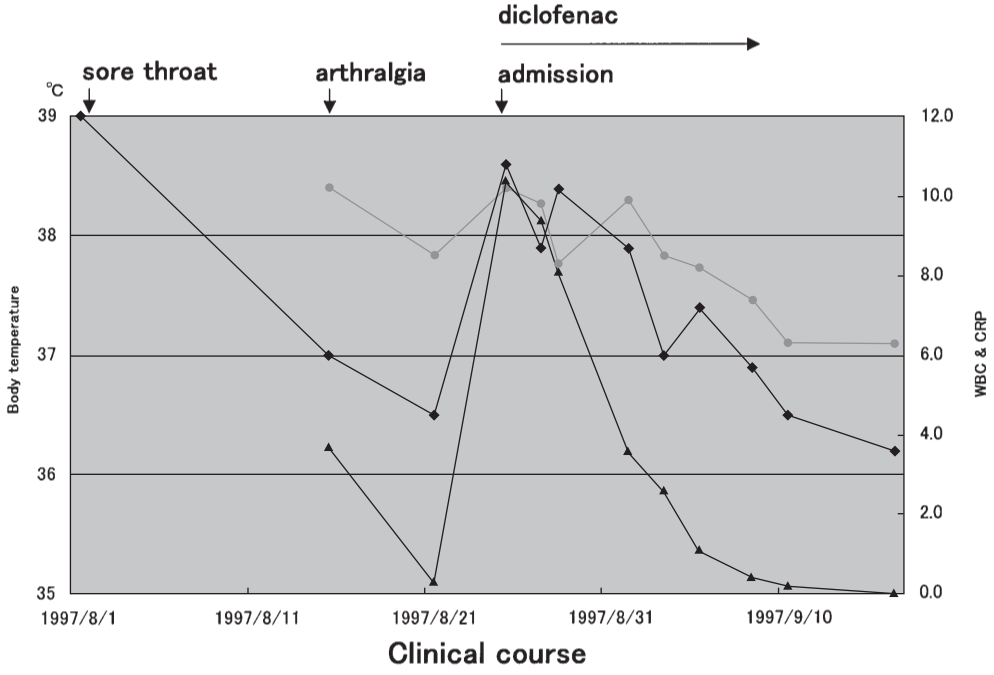

Fig. 1. Clinical course of the brother. *CRP*, C-reactive protein. *Diamonds*, body temperature; *circles*, WBC (×1000); *triangles*, CRP (mg/dl)

count (WBC 10200/mm^3: neutrophils 64%, lymphocytes 29%, eosinophils 3%, monocytes 2%, basophils 2%) and aspartate and alanine aminotransferase levels (GOT 40 IU/l, GPT 105 IU/l). A C-reactive protein (CRP) content of 10.6 mg/dl and an erythrocyte sedimentation rate (ESR) of 65 mm/h indicated inflammation. ASO and ASK titers were within normal limits, and a throat culture revealed normal flora. Other findings were normal, including serum IgG 970 mg/dl, IgA 264 mg/dl, IgM 208 mg/dl, and CH50 43.2 U/ml. Antinuclear antibodies (ANA), anti-DNA antibodies, and rheumatoid factors (evaluated with both rheumatoid arthritis (RA) and rheumatoid arthritis particle agglutination (RAPA) tests) were also negative. Although the patients symptoms were relatively serious, with the administration of diclofenac sodium he recovered satisfactorily within 2 weeks after admission (Fig. 1).

The second case was his 31-year-old younger sister. She first sought medical attention at the otorhinolaryngology department of our hospital on September 11, 1998, because of pharyngeal pain and high-grade fever. She was diagnosed on admission as suffering from pharyngitis, and recovered almost completely after intravenous injections of minocycline for 1 week. Two weeks after discharge she sought medical attention in our department on October 8 complaining of moderate fever (38.5°C) and polyarthritis, which bilaterally involved the elbows, knees, and ankle joints. The deterioration of her arthritic condition had prevented her from carrying out the normal activities of daily life. Cefaclor and loxoprofen were administered without favorable results, and she was hospitalized on October 12. On admission, a rash which was similar to erythema nodosum was observed on her lower extremities, but oral ulcers, genital ulcers, and uveitis were absent. A laboratory examination showed a normal leukocyte count (7900/mm^3) with slightly increased inflammatory reaction parameters, a CPR content of 3.9 mg/dl, and an ESR of 61 mm/h. ANA and rheumatoid factors (RA and RAPA tests) were also negative. Although antistreptolysin O was slightly elevated (320 U/ml; normal $<$ 240 U/ml), antistreptokinase was within normal limits (1280; normal $<$ 2560), and a throat culture revealed normal flora. The administration of indometacin farnesil and intravenous injections of minocycline were started.

The patient recovered without any sequelae within 1 week (Fig. 2). The similarity of these clinical courses led us to speculate about intrafamilial onset of ReA, and we conducted HLA typing analysis of both patients. Case 1 was positive for HLA-A24, -33, -B40, -44, and -Cw4, whereas case 2 was positive for HLA-A2, -33, -B39, -52, and -Cw7. Neither of the patients had HLA-B27 or -B51 haplotypes. As of May 2001, neither of the patients showed evidence of carditis or a recurrence of ReA.

Discussion

The concept of ReA was first proposed by Ahvonen et al.[4] in 1969 as an acute nonsuppurative, sterile, inflammatory arthropathy arising after an infectious process, but at a site remote from the primary infection. In the United States and Europe it was known that ReA is strongly associated with the HLA-B27 haplotype. The presence of this class I major histocompatibility complex (MHC) molecule is observed in 60% to 80% of patients with ReA, and varies according to the frequency of the gene in the population at risk.[5,6] This gene product confers increased disease susceptibility and

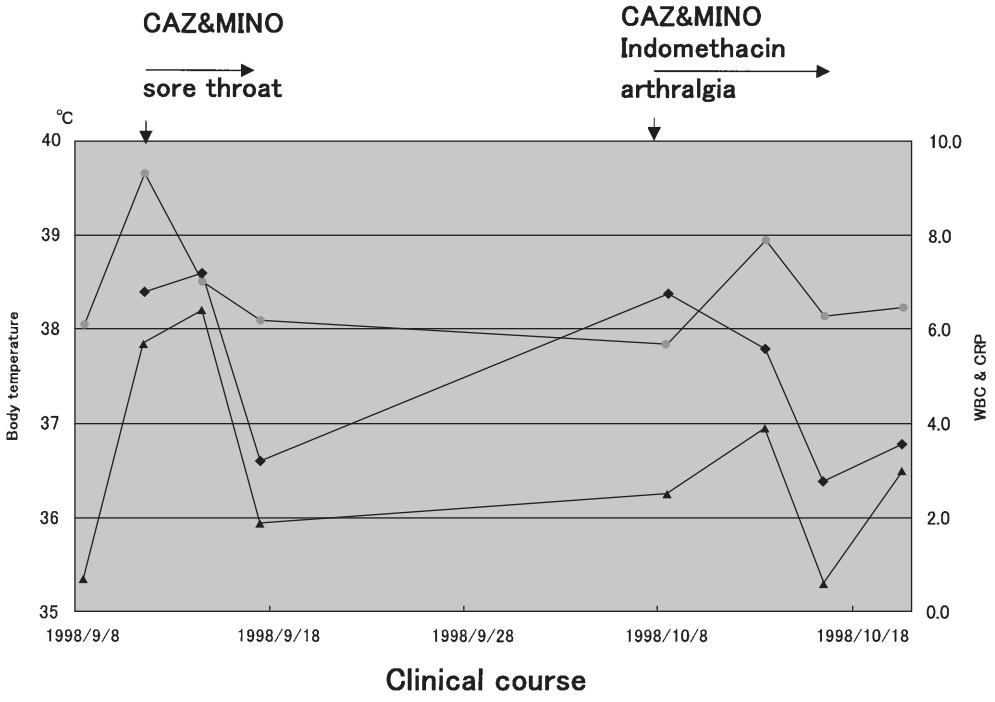

Fig. 2. Clinical course of the sister. *Diamonds*, body temperature; *circles*, WBC (×1000); *triangles*, CRP (mg/dl). *CRP*, C-reactive protein; *CAZ*, ceftazidime; *MINO*, minocycline

also influences disease severity and expression. Therefore, HLA-B27-positive patients with ReA are more likely to have a prolonged disease course, with a greater potential for chronicity.[7] Leirisalo et al.[8] reported that patients with ReA who were HLA-B27-positive had a more severe and chronic disease course (more frequent back pain, sacroilitis, and a longer duration of the disease). Microbial organisms such as *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Vibrio* are known to be causative microbes for HLA-B27-related ReA. In epidemics associated with known arthritogenic bacteria, no more than 20% of the HLA-B27-positive individuals develop the incomplete form of Reiter's syndrome, and even fewer cases develop the classic Reiter's syndrome.

On the other hand, PSRA, lyme disease, postviral arthritis, and acne arthritis are all known to be HLA-B27-unrelated ReA. Goldsmith and Long et al.[9] first reported PSRA in 1982 as a temporary arthritis in children after pharyngeal infection with *Streptococcus*. They described such characteristics as prolonged joint manifestations with a symmetrical distribution and poor response to aspirin as indicators of acute rheumatic fever (ARF) without carditis. They had also pointed out the resemblance of the disease course to ReA associated with enteric pathogens. Jansen et al.[10] reported that the way to differentiate between PSRA and ARF is based on the absence of sufficient features to establish a diagnosis of ARF based on the Jones criteria. These are usually the absence of the classic cutaneous, cardiac, and neurologic findings of ARF. Moreover, in the majority of the cases, arthritis is a nonmigratory oligo- or polyarthritis. Characteristically, the response to therapy with salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs) is slow or incomplete, but the disease course is often benign with favorable results. In Japan, HLA-B27 expression itself is extremely rare (1% in the healthy population), and thus ReA has been considered to be a rare entity. We have previously reported 13 adult cases after pharyngeal infections, and we conducted HLA typing analysis in 10 of these 13 cases.[11] The results revealed that four cases were positive for HLA-B39, whereas five cases were positive for HLA-B40. The frequency of HLA-B39 in these patients was statistically high, since HLA-B39 was positive in only 4.3% of healthy Japanese controls. Moreover, Yamaguchi et al.[12] had reported the association of HLA-B39 with HLA-B27-negative ankylosing spondylitis and pauciarticular juvenile rheumatoid arthritis in Japan. They had also reported on the molecular homology of these two haplotypes (which share Glu at position 45 and Cys at position 67, both of which are components of the peptide-anchoring B pocket). On the other hand, the serological cross-reactivities between HLA-B27 and -B40 are known.[13] Other HLA-B27 cross-reactive haplotypes are -B7, -B42, and -B60, which are all known frequently to be positive in patients with -B27-negative ReA in the United States and in Europe. Robinson et al.[14] reported a high incidence of -B40 in HLA-B27-positive ankylosing spondylitis patients in the United States. These data strongly suggest the relevance of these haplotypes, especially in Japanese patients with ReA, whose HLA-B27 expression is rarely demonstrated. Although reports of intrafamilial onset of -B27-positive ReA, including cases of twins, can be found in European populations,[15] this is the first report of -B27-negative ReA in Japan. Special attention should be paid to these HLA haplotypes in order to elucidate the pathogenicity of this rare entity. In addition, ReA should be considered as one possible diagnosis when patients with seronegative arthropathies and/or rheumatoid arthritis are examined, especially when this is in its early stage.

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