Case report

Efficacy of methotrexate in the treatment of a HLA–B27–positive Japanese patient with reactive arthritis

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summary

We report a case of reactive arthritis in a 21–year-old man who was successfully treated with methotrexate. In July 2008, the patient experienced arthritis in the left knee 3 days after being diagnosed as having urethritis by the urology clinic. The patient was treated with loxoprofen sodium and fosfomycin calcium at an orthopedic clinic. Antibiotics induced clinical improvement of urethritis, although arthritis became worse. Even after sulphasalazine and corticosteroid were started, polyarthritis remained persistent. Finally, methotrexate was added; thereafter, polyarthritis and elevated CRP were resolved. HLA–B270502 was positive. Methotrexate could be one of the choices for sulphasalazine–resistant reactive arthritis.

Key words — reactive arthritis; seronegative; Chlamydia; chlamydial; spondyloarthropathy; methotrexate

Introduction

Reactive arthritis (ReA) is an inflammatory joint disorder that may occur following genito–urinary infection with Chlamydia trachomatis or enteral infection with Yersinia, Salmonella, Shigella or Campylobacter\(^{1}\). Reactive arthritis is usually self-limited and can be either monoarticular or oligoarticular, although some cases progress to chronic arthritis. The disease is strongly associated with HLA–B27 in Caucasians, but not in Japanese people. Although the pathogenesis of arthritis remains unknown, the treatment rests mainly on anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

Here, we describe a case of reactive arthritis that was resistant to sulphasalazine and corticosteroid but successfully treated with methotrexate (MTX).

Case

A 21–year-old Japanese male was diagnosed as having urethritis at the urology clinic in July 2008 and treated with levofloxacin 300 mg/day. Gonorrhea and syphilis were ruled out at that time. After 3 days, low grade fever and left knee pain developed. The patient was treated with loxoprofen and fosfomycin calcium sodium at an orthopedic clinic. Antibiotics induced clinical improvement of urethritis but arthritis worsened; then, he consulted a local rheumatology clinic. The left knee was swollen and painful. X–P of the knee showed normal findings. On examination, blood pressure was 120/80 mmHg. Laboratory data were as follows : ESR 115 mm/h, WBC 15000/micro L, Hb 13.5 g/dl, C–reactive protein (CRP) 8.67 mg/dl. Renal and liver functions were normal. Antinuclear antibody and RAPA were negative and anti CCP antibody < 0.6 U/ml. Levels of serum IgA and IgG antibodies for Chlamydia trachomatis were both negative on enzyme linked immunosorbent assay (ELISA). TPHA was also negative. The patient was treated with sulphasalazine (1000 mg/day) and corticosteroid (10 mg/day) for reactive arthritis; however, polyarthritis was persistent. Finally, he consulted our out–patient clinic in September 2008.

At consultation, painful swelling of the left knee and right foot were noted. Radiography showed that these joints were intact. Laboratory data were as follows : ESR 83 mm/h, WBC 8100/µL, Hb 10.9 g/dl, CRP 8.27 mg/dl. Renal and liver functions were normal. Antinuclear antibody and RAPA were negative and anti–CCP antibody < 0.6 U/ml. MMP–3, 238.5 ng/ml. HLA–B 270502 was positive. Levels of serum IgA and IgG antibodies for Chlamydia trachomatis were both negative in ELISA. There was no protein in urine. TPHA was also negative. Both ophthalmology exam and cardiac echocardiogram were intact. Two months after MTX (8 mg/week) was added, CRP was decreased. After six months, polyarthritis was finally resolved and the elevated level of serum CRP was normalized (Figure 1).
Here, we present a case of reactive arthritis. The patient developed left knee swelling a few days after urethritis was noted. Antibiotics induced clinical improvement of urethritis, but polyarthritis persisted. Neither sulphasalazine nor corticosteroid were effective for polyarthritis. HLA–B270502 was positive. Finally, after MTX (8 mg/week) was added; then, polyarthritis and elevated CRP resolved.

Our case is a Japanese male with HLA–B27. However, both of his parents are Koreans living in Japan. Positivity for HLA–B27 antigen is much higher among Korean people than in Japanese people; ReA is rare in Japan, but not in Korea. Thus, checking for HLA–B27 positivity and nationality would be very important to diagnose ReA in Japan.

There are possible interactions between HLA–B27 and reactive arthritis. Reactive arthritis is typically triggered by Gram-negative bacteria, which have lipopolysaccharide as an integral component of their outer membrane. Experimental evidence from humans and transgenic rodents has suggested that HLA–B27 is itself involved in the pathogenesis of spondyloarthropathies (SpA). Population and peptide–specificity analysis of HLA–B27 suggest that it has a pathogenic function related to antigen presentation. Inman et al. reported that HLA–B27 and proteins from enteric bacteria are structurally related, in a manner that may affect T cell response to enteric pathogens. HLA–B27 may also directly affect host–microbe interactions by modulating the potential of these bacteria to invade target cells. Latio et al. reported that HLA–B27 modulates intracellular survival of *Salmonella enteritidis* in human monocyte cells. Moreover, interestingly, Lorrea et al. reported that molecular mimicry between bacterial epitopes that cross–react and self–B27 peptides is a possible pathogenesis.

Recent studies in vivo and in vitro obtained from patients with ReA and from different model systems suggest that in addition to its function as an antigen–presenting molecule, HLA–B27 might also have other functions that could modulate the inflammatory response and thus might promote susceptibility to SpA. HLA–B27 would modulate LPS–induced TNF–α production by monocytes/macrophages in the joints of HLA–B27–positive patients. LPS–induced TNF–α production is controlled by the transcription factor nuclear factor κB and mitogen–activated protein kinases in monocytes/macrophages. Penttinen et al. reported that HLA–B27 modulates the regulation or activation of these signalling molecules after stimulation with LPS and that the secretion of TNF–α was accelerated in HLA–B27–expressing cells after stimulation with LPS.

Transgenic mice expressing HLA–B2705 were reported to develop inflammatory arthritis. Kollnberger et al. show that HLA–B27 tetramers can induce TNF–α production by binding to paired Ig–like receptors. Taken together with in vivo findings from patients with ReA, in vitro results as well as from animal model systems suggest that HLA–B27 expression can modulate the host–microbe interaction.

In the present case, MTX was effective. Most cases of ReA are self–limited, and respond well to NSAIDs. Although some cases run a chronic disabling course, requiring immunosuppressants. Sulfasalazine and corticosteroid are commonly administered for chronic arthritis. The effectiveness of other Disease Modifying Anti Rheumatic Drugs (DMARDs) such as azathioprine and cyclosporine has been reported sporadically. TNF–α blockers could also represent an effective choice.

Although studied in a mainly uncontrolled trial, MTX has been shown to be effective in SpA. Koga et al. reported a patient with ReA occurring one year after acute chlamydial urethritis, MTX was effective for dactylitis and sacroiliitis. In that case, CRP was normalized 1.5 months after MTX (6 mg/week) was added. Marquardt et al. reported a patient with suppurative hidradenitis who developed ReA and administration of MTX improve his symptoms. Lally et al. reviewed 21 case reports of Reiter syn-
drome treated with MTX in the English literature. The majority patients were refractory to conventional NSAIDs and/or corticosteroid. Seventy five % of articular manifestations were improved by MTX (up to 25 mg/week). Azuma et al\textsuperscript{5} reported a case of Achilles tendon rupture in patient of refractory Reiter’s syndrome. In that case, predonisolone (30 mg/day) and MTX (8 mg/week) were effective and clinical symptoms and CRP were normalized in 3 weeks. We believe that MTX is beneficial in the management of certain patients with ReA refractory to conventional therapy.

In summary, we described herein a case of ReA that was resistant to sulphasalazine and corticosteroid but successfully treated with MTX. HLA–B270502 was positive, which may have contributed to persistent infection and development of chronic arthritis in this patient. The positivity of HLA–B27 is low in Japan; thus, checking the patient’s nationality and HLA status would be very important to diagnose ReA in Japan. For the management of chronic and refractory arthropathy due to ReA, MTX is beneficial.

References


