Clinical and histopathological presentation of pustular psoriasis in an HLA-B27-positive Caucasian with reactive arthritis

Toshiaki Nakano, Hikaru Eto

Department of Dermatology, St. Luke's International Hospital

A 35-year-old Caucasian male first presented with joint pain on his left knee. His symptoms then progressed to asymmetrical orthoarthralgias, lower back pain, morning stiffness, remittent fever, and psoriatic rashes. There were white plaques of circinate balanitis on the penis and macules and vesicles of keratoderma blennorrhagicum on both soles and multiple small erythemas with scales, crusts, and pustules over the whole body. Histopathological findings of the erythema were compatible with pustular psoriasis. We diagnosed him with reactive arthritis, classified as a type of seronegative spondyloarthritis, because clinical findings and examinations fulfilled the diagnostic criteria. His symptoms were resistant to both antibiotics and corticosteroid. However, an oral sulfasalazine enteric coating drug (1,000 mg daily) was effective for peripheral arthralgias and skin eruptions but did not alleviate the lower back pain. We report a rare case of an HLA-B27-positive Caucasian with reactive arthritis who presented with atypical pustular psoriasis over the whole body.

Key words: pustular psoriasis, reactive arthritis, spondyloarthritis, HLA-B27, sulfasalazine

Introduction

Reactive arthritis (ReA) was first described in 1916 by Hans Reiter, a German physician, and was known as Reiter's syndrome. The classic triad of Reiter's syndrome consists of post-infectious arthritis, nongonococcal urethritis and conjunctivitis. However, the term "Reiter's syndrome" was replaced with "reactive arthritis" in 2003 so as not to honor Hans Reiter, who was found guilty of committing war crimes in Germany during the Second World War. ReA is classified as one of the spondyloarthropathies (SpA), along with ankylosing spondylitis (AS), psoriatic arthritis (PsA) and inflammatory bowel disease (IBD)-associated spondyloarthritis. These are known as seronegative spondyloarthropathies (SNSA) because the rheumatoid factor (RF) is usually negative. The human leukocyte antigen, HLA-B27, is strongly associated with ReA (30%-70% HLA-B27 positive rate), including SpA groups. HLA-B27-associated arthritis is distinguished from HLA-B27 non-associated "infection-related arthritides," such as post-streptococcal, Lyme, and viral arthritis. Mucocutaneous lesions associated with sexually acquired reactive arthritis (SARA) are specific. White plaques of circinate balanitis on the penis and erythematous macules or vesicles of keratoderma blennorrhagicum on the palms and soles are characteristic symptoms. However, skin lesions are clinically and histopathologically similar to pustular psoriasis. Sulfasalazine (SSZ), used as second-line therapy for ReA, is a DMARD (disease-modifying antirheumatic drug) that is used effectively in the treatment of peripheral arthritis and skin manifestations in moderate to severe psoriatic arthritis (level A evidence) and is a promising treatment for persistent skin lesions in steroid-resistant ReA.

Case report

A 35-year-old Caucasian male first presented with monoarthralgia of the left knee joint that started in June 2007. The swelling and pain on his left ankle developed in September, and he was given oral diclofenac sodium (given dose unknown) and intramuscular injection of dexamethasone (given dose unknown). Nonetheless, the arthralgias progressed in the right side of the ankle, knee, and elbow, and he developed remittent fever (39-40°C). The symptoms temporarily relieved with oral prednisolone 45 mg daily and ciprofloxacin (given dose unknown). Nonetheless, the arthralgias progressed in the right side of the ankle, knee, and elbow, and he developed remittent fever (39-40°C). The symptoms temporarily relieved with oral prednisolone 45 mg daily and ciprofloxacin (given dose unknown). However, when the prednisolone dose was decreased to 30 mg daily, he suffered relapsing arthralgias,
including lower back pain and concurrent psoriatic skin lesions over the whole body. He came to St. Luke's International Hospital for consultation in December. He had no recent history of urogenital symptoms, such as dysuria, urinary frequency, or urethral discharge, or gastrointestinal symptoms, such as diarrhea or stomachache. There was no family history of psoriasis.

Clinical findings at the first visit
Slight fever (37°C), polyarthritis with tenderness, swelling, and joint pain upon motion (both elbows, knees, and ankles), lower back pain with restricted spinal mobility, buttock pain, morning stiffness (persisting 1.5-2 hours), no localized pain, no swelling or tenderness of Achilles tendon attachments were seen. There were no complaints or abnormal findings of the cardiovascular, respiratory, or gastrointestinal systems.

Laboratory data
WBC (white blood cell count) 9,170/μl, Neut 79.3%, Lym 11.9%, C-reactive protein (CRP) 25.2 mg/dl, erythrocyte sedimentation rate (ESR) 98 mm/1 hour, antinuclear antibody (ANA) negative, rheumatoid factor (RF) negative, CCP (anti-cyclic citrullinated peptide) antibody (Ab) negative, HCV (hepatitis C virus)-Ab negative, HBs (hepatitis B surface) antigen (Ag) negative, STS (serologic test for syphilis) negative, HIV (human immunodeficiency virus) Ab negative, HPV (human parvovirus) B19-Ab negative, ASO (antistreptolysin O) 206, serum Chlamydia trachomatis (enzyme

Figure 1. Erythematous papules and keratotic erythemas with annular, scaly crusts on the back, buttocks, and lower extremities. Geographic tongue was also observed concomitantly.

Figure 2. Small keratotic erythemas on the foreskin and circinate balanitis on the glans penis. Diffuse erythematous plaques with microabscess and microerosions on the scrotum.

Figure 3. Papuloerythematous lesions with microabscess on the right palm and keratoderma blennorrhagicum on both soles. There were no nail abnormalities.
immunoassay; normal cut-off index, <0.90; abnormal, 1.10; Mitsubishi Chemical Medicine®, Japan) IgA negative (A-index, 0.46), and IgG positive (G-index, 1.39). There were positive bacterial cultures of the mucocutaneous lesions on the penis: *Gardnerella vaginalis*, coagulase-negative staphylococci, *Gamma-hemolytic streptococci*, and Gram-positive rods. A *Chlamydia* DNA test was not performed because the patient did not give consent. X-ray and magnetic resonance imaging (MRI) revealed no abnormal ophthalmological findings and no abnormal radiographic findings, including bone erosion, syndesmophytes, or sacroiliitis in the lower extremities and the pelvis. HLA-B27, -A2, and -B40 were all positive.

**Skin lesions**

Clinical skin findings include annular, distributed, scaly crusted, itchy, indurated and keratotic erythemas over the whole body, and geographic tongue (Figure 1). Keratotic erythemas with yellowish crusts were seen on the false phimosis skin; and painless, irregular, moist, well-defined, keratotic erythemas with polycyclic, whitish horny crusts were seen on the glans penis. Additionally, concomitant reddish microerosions and micropustules with itching were seen on the scrotum (Figure 2). Micropustules and papuloeerythematous lesions were seen on the palms, and pustules and erythematos macules with thick horny crusts on the soles, but with no nail abnormalities (Figure 3).

*Histopathological findings from the erythemas of the chest and the scrotum*

Both biopsy specimens revealed similar histopathological changes that are compatible with pustular psoriasis, characterized by hyperkeratosis with parakeratosis, elongation hypertrophy of the rete ridges with epidermal hyperplasia, and extensive neutrophilic infiltrations with marked spongiform pustules, also known as Kogoj’s microabscesses, below the horny layer (Figure 4). CD4-positive T lymphocytes infiltrations were discovered in the upper dermis; in contrast, CD8-positive T lymphocytes showed remarkable penetration into the epidermis (Figure 4).

*Clinical course*

The patient was treated with oral epinastin (20 mg daily) and cutaneous pharmacokinetics of topically applied betamethasone butyrate propionate ointment,
maxacalcitol ointment, and tacalcitol hydrate lotion in parallel with a gradual dose reduction of prednisolone. However, we received no impression that the patient’s symptoms were alleviated or resolved by the topical treatments. However, when he was started on the SSZ enteric coating drug (Azulfidin® EN- Tabs [sulfasalazine delayed release tablets]) (and increased from 500 mg to 1,000 mg daily), the systemic symptoms, including fever, peripheral arthritis, and skin lesions, resolved gradually, in spite of the reduction in the oral prednisolone dosage. The lower back pain remained, however. Three months after starting the SSZ treatment, the erythematous macules over the entire body also resolved completely, except for some pigmentation that remained. Then, in January 2008, he developed avascular necrosis of the right femoral head due to chronic steroid therapy and received osteoporosis treatments with bisphosphonate. These symptoms did not recur despite the reduction in oral prednisolone dosage to 1 mg daily. ESR and CRP levels were normal in November 2008. However, he stopped coming to our hospital in November 2008. In April 2009, he visited our hospital again with urethritis symptoms. The attending physician observed some recurrence of psoriatic skin lesions on his back, similar to those in the patient’s previous infection. In August, low-grade fever and right hip pain persisted, Serum C. trachomatis IgA turned positive (A-index, 3.29), and IgG was weakly positive (G-index, 1.04) in serum blood tests. MRI revealed bone marrow edema caused by sacroiliitis in the right sacroiliac joint in September of 2009. Finally, we diagnosed him with reactive arthritis triggered by Chlamydia urethritis.

Due to his genetic background of HLA-B27 positivity, ANA negativity, RF negativity, mono- and oligoarthritis with axial arthritis, the infection triggered cascades of urethritis, high fever, and pustular psoriasis-like skin lesions.

**Discussion**

ReA is defined as a sterile synovitis developing after distant infections of genitourinary or gastrointestinal tracts. The former is referred to as SARA because it is usually triggered by a sexually transmitted infection. This condition is known as the classical Reiter’s syndrome.9 The incidence rate was calculated as 4.6 to 13 per 100,000 with a male-to-female ratio of 9:1 for SARA. On the other hand, the incidence rate has been 5 to 14 per 100,000 with a male-to-female ratio of 1:1 for enteric ReA. ReA usually occurs in adults between the ages of 20 to 40 years and develops within 1 to 4 weeks following infections.10-13

Clinical characteristics of ReA are: 1. peripheral arthritis syndrome: large, lower limb, nondestructive acute asymmetric oligoarthritis, chronic-recurrent arthritis (15%-30%), sausage digits (16%); 2. enthesopathic syndrome: heel pain, Achilles tendinitis, pain at the tibial tubercle (30%); 3. pelvic and axial syndrome: inflammatory lower back pain, sacroilitis (14%-49%), spondylitis (12%-26%), inflammation of ligamentous or tendinuous insertions in the ischial tuberosity (15%-30%); and 4. extramusculoskeletal syndrome: eye (conjunctivitis [35%], iritis [5%], keratitis, corneal ulceration, retrobulbar neuritis, and hyphema), genitourinary (urethritis, prostatitis [80%], hemorrhagic cystitis, cervicitis), gastrointestinal (diarrhea, endoscopic “bowel lesions” [25%-70%]), skin (keratoderma blennorrhagicum [5%-30%], circinate balanitis [20%-4%], oral ulcers [5%-10%], hyperkeratotic nails [6%-12%], erythema nodosum), cardiovascular system (aortic disease, ECG [electroencephalogram] conduction abnormalities [5%-14%]), central nervous system (peripheral/cranial nerve palsy, motor deficits), renal (proteinuria, microhematuria, aseptic pyuria, glomerulonephritis, and IgA nephropathy).

In our case, there were no extra musculoskeletal syndromes except for psoriatic skin lesions and fever. ReA, as well as AS, PsA, and IBD-associated SpA, is one of the spondyloarthropathy groups characterized by RF seronegative inflammatory arthritis and is referred to as seronegative spondyloarthropathy (SNSA). SNSA represents variable expression of the major characteristic features: axial disease, peripheral arthritis, enthesitis and dactylitis, uveitis, gastrointestinal, cardiovascular, renal, and skin involvements.4 There are two classification criteria for SpA: criteria defined by Amor et al. (sensitivity, 90%; specificity, 86.6%)14 and criteria defined by the ESSG (European Spondyloarthropathy Study Group) (sensitivity, 87%; specificity, 87%).15 The present case fulfilled both of these criteria.

HLA-B27 is strongly associated with the development of SpA. HLA-B27 positivity is more common in patients with chronic or relapsing arthritis, uveitis, aortitis, saccroilitis, and spondylitis.16 HLA-B27 positive rates have been calculated as AS (96%), ReA (30%-70%), PsA (40%-50%), and IBD-associated SpA (33%-75%).4 HLA-B27 could predict the diagnosis of ReA with a sensitivity of 69.2% and a specificity of 93.5%.17 However, physicians should be especially cautious as there are ReA cases that are HLA-B27 negative. HLA-B27 is present in 8% of healthy Caucasians, of whom about 90% will never develop SpA.6

*C. trachomatis* is the microorganism that has been the most common identifiable cause of SARA. Urogenital
"C. trachomatis" infection was identified in 36% to 50% of SARA cases and in 69% of patients who presented with urogenital symptoms at the time of examination. In patients with persistent infections, as in the present case, detecting the microorganism responsible for the initial infection can be difficult. In this patient, various resident flora were found on the penis, but they were Gardnerella vaginalis, one of the vaginal bacterial flora; and we did not consider them to be the pathogen responsible for the urogenital infection. In enteric ReA, various bacterial microorganisms can induce arthritis (Salmonella, Shigella, Yersinia, Campylobacter, Clostridium, etc.). In this serum "C. trachomatis" IgG positive case, we diagnosed the patient with SARA clinically because the symptoms were recurrent after a urogenital infection, and gastrointestinal symptoms had not developed during the course.

Mucocutaneous lesions are specific and occur in up to one-third of SARA patients. The initial lesions of keratoderma blennorrhagicum are small vesicles or erythematous macules. These lesions progress to thickened, small plaques or nodules. The appearance of the lesions varies from a scaling plaque-like process that resembles pustular psoriasis to combinations of crusting, exudation, and erosion associated with erythema. The circinate balanitis lesions are initially vesicular with little or no surrounding erythemas. Irregular, moist, superficial ulcers form on the penis of the uncircumcised male, as in the present case. In the circumcised male, the lesions develop to form hard crusts and plaques. Oral mucosal lesions may show painless ulcers on the tongue, palate, buccal mucosa, and lips. Oral psoriasiform lesions, like geographic tongue, sometimes occur concomitantly. The present patient showed dense indurated keratotic erythemas over his entire body with annular crusted scales, in addition to pustules on the palms and soles, typical keratoderma blennorrhagicum, and circinate balanitis. The presence of these skin lesions was compatible with atypical pustular psoriasis. Despite multiple joint symptoms, the present case did not fulfill the CASPER criteria (CIASification criteria for Psoriatic ARthritis). In the present case, histopathological findings of skin biopsies from both chest and scrotum showed changes similar to pustular psoriasis. In particular, lymphocyte infiltrations into both the epidermis and the upper dermis are characteristic in both specimens. Antigen specific CD4 and CD8 T lymphocytes play important roles in the pathogenesis of ReA. Both CD4 and CD8 T lymphocytes have been detected in synovial tissues (fluid and membranes). In the early phase of the disease, a CD4 T lymphocyte response at the site of inflammation is triggered and maintained by the microbial components. Later, the CD8 T lymphocytes also become involved. The responses of CD4 T lymphocytes in the upper dermis and CD8 T lymphocytes in the epidermis in this patient support this theory. The responses of CD8 T lymphocytes may play critical roles in the pathogenetic mechanism in the processing and presentation of bacterial antigens.

The diagnosis of ReA is approached through and most often made using the diagnostic algorithm proposed by Sieper et al. The first criterion is having mono- or oligoarthritis of the lower extremities. The second criterion is the exclusion of other diagnoses including septic or traumatic arthritis and other rare conditions. If both criteria are present, the probability of ReA is 40%. Evidence of a previous infection increases the probability to 60%, a history of symptomatic proceeding infection with "C. trachomatis" increases the probability to as much as 90%. If bacteria are cultured from the stool, the probability of ReA increases to 70%. However, proceeding infections, particularly Chlamydia, may be asymptomatic. Chlamydia examinations (Chlamydia-specific antibodies by serologic test, the detection of Chlamydia in urine, urethra, or cervix, Chlamydial culture) are recommended if SARA is suspected. Zhang et al. amplified DNA assays (PCR) polymerase chain reaction, [LCR] ligase chain reaction, etc.) in the first portion of the morning urine seem to be an acceptable and relatively easy diagnostic approach. Meanwhile, a stool culture is recommended if enteric ReA is suspected. MRI is also helpful for diagnosing sacroiliac and spinal involvements.

The treatments of SARA and enteric ReA are described. First-line therapies of arthritis recommend rest, physiotherapy, physical therapy, NSAIDs (non-steroidal anti-inflammatory drugs), and intra-articular corticosteroid injections. The patient in the present case was resistant to all first-line therapies. Second-line therapies for moderate to severe arthritis, or failure of first-line therapies, include systemic corticosteroids (beginning with oral doses of 10-25 mg daily), and sulphasalazine (SSZ), which is indicated when disabling...
symptoms persist for 3 months or more, or when evidence of erosive joint damage is present. High doses of SSZ (3 g daily) are associated with significant toxicity, particularly to the gastrointestinal system. While, SSZ at 2 g daily appears equally effective and better tolerated. Methotrexate (MTX), azathioprine, gold salts, and antibiotics (short- or long-course antibiotic therapy for SARA, ciprofloxacin against C. trachomatis at recommended dosages) are also used. Moreover, SSZ, one of the treatments for psoriatic arthritis of the SpA group, is the most recommended treatment for moderate to severe peripheral arthritis and skin involvements of psoriatic arthritis (level A evidence, the EULAR [European League Against Rheumatism]). The goals of ReA treatment are to decrease pain and inflammation, minimize disability, and prevent relapse or progression to chronic disease. We reported a successful case of SSZ enteric coating drug treatment for a rare case of pustular psoriasis in an HLA-B27-positive Caucasian patient who suffered severe, persistent reactive arthritis.

References