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CASE REPORT

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A boy with erosive arthritis during treatment of severe group-A streptococcal infection

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Abstract The patient was admitted to our department with major complaints of fever, swelling of the left thigh, and a cognition disorder. A blood culture yielded type T1, toxin-B-positive group-A streptococcus. Magnetic resonance imaging of the left foot showed fasciitis. Severe group-A streptococcal infection was diagnosed, and the administration of antibiotics, a massive dosage of gamma-globulin, and a steroid preparation were prescribed, which resulted in a general improvement in the symptoms and reductions in the swelling of the left foot and the second finger of the left hand without any sequelae. Following discharge from the hospital, however, destruction of the joint of the first toe of the right foot was recognized. A number of cases of post-streptococcal reactive arthritis (PSRA) have recently been reported, and the pathogenicity of this arthritis, which is different from that of rheumatic fever, has been noted. Severe group-A streptococcal infections, such as the one described here, may develop into erosive arthritis after the symptoms, that affect several organs, have disappeared. We believe that because it is possible for post-streptococcal reactive arthritis to develop, one should be aware of this when dealing with all clinical patients who have streptococcal infections.

Key words Toxic shock-like syndrome · Group-A streptococcal infection · Erosive arthritis · Reactive arthritis

Introduction

Group-A streptococci have been known for many years as a group of bacteria responsible for bacterial inflammation of the upper airway in children. They have been considered to be responsible for the development of acute glomerulonephritis and rheumatic fever as secondary afflictions. With the administration of antibiotics at the onset of the infection, however, the incidence of these diseases has been rapidly reduced. Instead, a toxic-shock-like syndrome (TSLS) that mostly affects adults, and is associated with necrosis of the soft tissue (such as necrotic fasciitis and myositis) and progressive circulatory failure, began to emerge as a new type of infection by group-A streptococci. Recently we had an opportunity to observe a boy with a severe group-A streptococcal infection. A correct diagnosis was given early, and the patient recovered from a life-threatening state. Unfortunately, however, he later developed erosive arthritis. We believe that our experience may have clinical relevance to the study of reactive arthritis caused by streptococci.

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Case report

The patient was a 9-year-old boy who had been referred to our department with major complaints of fever, swelling of the left thigh, and consciousness disturbance. On July 4, 1996, preceding hospital admission, he sprained his left ankle during athletic activities. On the following day, he developed a fever of 38.5°C with swelling at the site of the sprain. Because a cognition disorder was also apparent, the patient was admitted to our department. Symptoms at admission were mild deviations of consciousness level, slight hypotension (systolic pressure, 74 mmHg), and nonspecific pharyngeal redness. An area from the center of the left thigh toward the ankle joint was extremely swollen, with a wooden board-like stiffness. The area from the mid-phalangeal to the proximal interphalangeal joints of the second finger of the left hand was also swollen in a similar manner.

Hematological examinations showed an increase in the number of leukocytes, with a marked nuclear shift to the left (WBC 14500/μl; neutrophils 90%, lymphocytes 6%,

monocytes 3%, eosinophils 0%, basophils 0%) and a slight reduction in the platelet count (13.2 × 10^4/μl). Blood chemical analysis indicated a slight increase in aspartate aminotransferase (43 IU/l) and a rise in the lactic dehydrogenase (473 IU/l) level, with associated rises in isozyme fractions IV and V. Among the protein fractions, the alpha 2-globulin fraction increased (TP, 6.9 g/dl; Alb, 56.3%; alpha 1-globulin, 5.4%; alpha 2-globulin, 16.9%; beta-globulin, 8.4%; gamma-globulin, 13.0%). The inflammatory reactions were represented by a C-reactive protein content of 12.6 mg/dl and an erythrocyte sedimentation rate of 24 mm/h. Except for anti-strepto-polysaccharide, the antibody titers against streptococci at admission showed increases (anti-streptolysin O, 1280 U/ml; anti-streptokinase, 1280×; anti-deoxyribonuclease-B, 1280×; anti-streptopolysaccharide, 8 U). The rheumatoid factor was positive (26 U/ml), but the antinuclear antibody was negative. The urinalysis showed mild hematuria and proteinuria. Bacteriological examinations detected type T1, toxin B-positive group-A streptococcus from a blood culture, but no group-A streptococci were isolated from other sources, including biopsied tissue from the left thigh. Magnetic resonance imaging of the left thigh depicted the muscle fibers as appearing generally whitish, and the fascia was enhanced in gadolinium DTPA imaging. A biopsy of the same area produced a copious amount of pus. The fascia was marked by neutrophil infiltration but was not necrotic, exhibiting the early stages of fasciitis.

From the findings given above and the clinical course, severe group-A streptococcal infection was suspected and treatment consisting of antibiotics, a massive dosage of gamma-globulin, and steroid preparations was initiated (Fig. 1). Consequently, the patient became normothermic and his consciousness level was restored to a normal state. The swellings of the left leg and the second finger of the left hand were reduced without any sequelae. The patient was placed on benzylpenicillin benzathine and observed for approximately 8 months following discharge. The anti-streptolysin O and immunoglobulin levels were gradually reduced, but the soluble interleukin-2 receptor content, which was abnormally high (2780 pg/ml) before treatment and was reduced after various therapeutic modalities, rose again after 6 months of treatment and remained high (300–400 pg/ml). The rheumatoid factor and immune complex levels were temporarily reduced but rose again after 6 months treatment, suggesting the development of a certain immune reaction (Fig. 1). Following discharge, the patient complained of restricted movement of the joints of the right toe. The right foot was examined with plain radiography and magnetic resonance imaging. The former showed joint destruction which was not found at that site at the previous observation. The magnetic resonance images depicted the joint as a low-intensity area, and delineated the details of the destructive process (Fig. 2).

Discussion

An increasing incidence of poststreptococcal reactive arthritis (PSRA) has been reported.[1,2] In reality, however, the concept of PSRA is not at all new: it has previously been reported as benign rheumatoid arthritis that presents as a transient form of arthritis,[3,4] which was later understood to be rheumatoid arthritis that improves after tonsillectomy. In 1982, for the first time, Goldsmith and Long[5] proposed

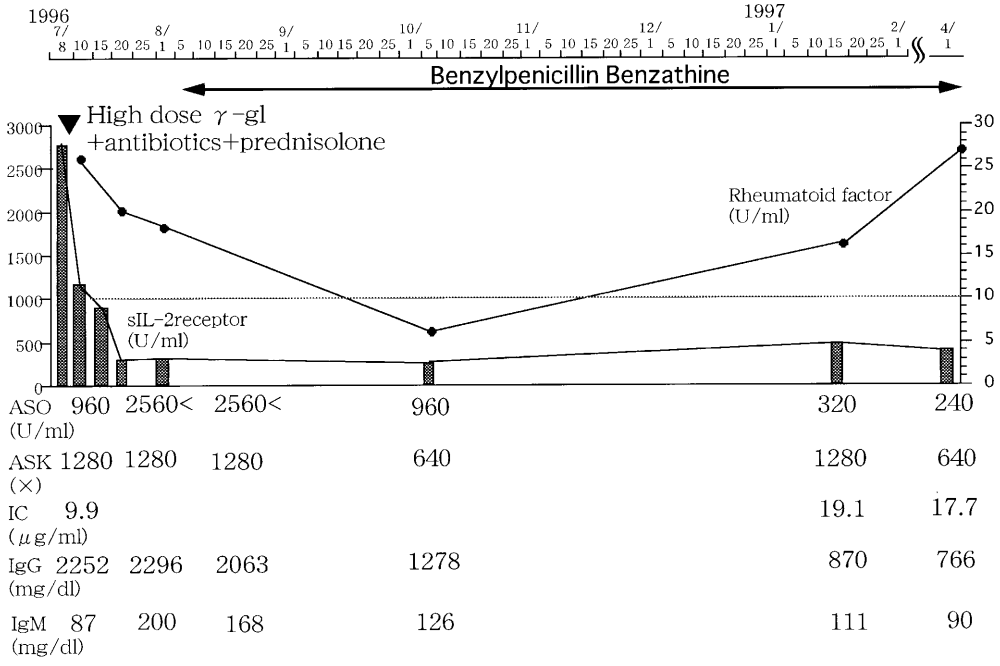

Fig. 1. Laboratory data gathered during the clinical course of this case

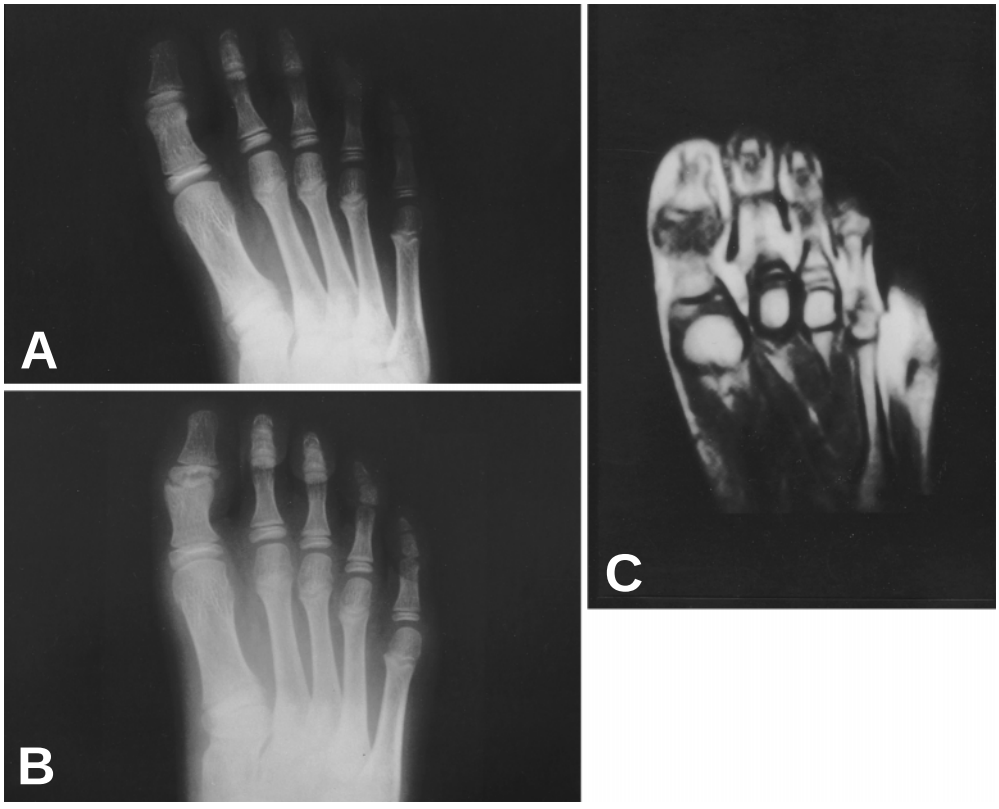

Fig. 2. Radiological images of the joint of the first toe of the right foot. **A** Plain radiography (at admission); **B** plain radiography (with erosive arthritis); **C** magnetic resonance imaging (with erosive arthritis)

the concept of PSRA for transient arthritis in young children which follows streptococcal infection of the upper airway. It was reported that PSRA was characterized by onset at an early stage of streptococcal infection, resistance to salicylic acid preparations, persistence of its symptoms, and reactive arthritis-like disease patterns. It was also reported that bacterial cultures of the PSRA-affected synovial fluid produced negative results in most instances. However, when polymorphonuclear leukocytes collected from the synovial fluid were fixed and allowed to react with rabbit anti-streptococcus and anti-*Escherichia coli* sera to locate bacterial components in the PSRA-affected joints, the anti-streptococcus serum detected coccoid substances in the cytoplasm, but the anti-*Escherichia coli* serum detected none.[6–8] In evaluations of the homology between PSRA and rheumatic fever as two disease entities, many samples from PSRA showed a negative reaction to monoclonal antibody D 8/17 as a non-HLA B-cell alloantigen which is detected in over 90% of B lymphocytes derived from patients with rheumatic fever.[9,10] As for the clinical course of patients who were under treatment, PSRA shows marked improvement in the arthritic symptoms within 3 weeks after tonsillectomy.[11] There are many unanswered questions about the currently proposed etiological mechanism related to PSRA: it is generally believed that M protein and other streptococcal cell components cross-react with a number of substances in the body (with tissue such as myocardium), contributing to a mechanism of development similar to that of rheumatic fever.[5] However, with respect to the mechanism of development of erosive arthritis in this case, which developed after infection with streptococcosis as do PSRA and rheumatic fever, it is surmized that T-cells strongly activated by superantigen are also involved in making the pathogenesis of this case particularly complex.

It is generally believed that the presence of pyrogenic toxins of group-A streptococci is a prerequisite for the development of TSLS. Pyrogenic toxins are associated with the activities of a superantigen. Within the organs that are exposed to this superantigen, a tremendous number of T-cells are activated in a short time, releasing a variety of cytokines and triggering acute abnormal reactions in the body, which culminate in systemic multiple organ failures.[12] In addition to multiple organ failures caused by the pyrogenic toxin, TSLS is characteristically associated with conditions such as necrotic inflammation of the soft tissue, which cannot be explained by the mechanism attributed to the pyrogenic toxin alone. Akaike[13] suspects that the pyrogenic toxin also activates matrix metalloproteinase (MMP), an endogenous proteinase which has a role in the development of TSLS. It is known that MMP is a protein-decomposing enzyme that uses extracellular matrix-composing proteins such as collagen and gelatin as its substrate, and in inflammatory condition such as rheumatoid arthritis and degenerative arthritis, it is activated excessively, resulting in tissue dysfunctions such as cartilaginous destruction.[14] In addition, it has been believed that group-A streptococci possess a cell surface serine proteinase called C5a endopeptidase on their surface layer, and the coordinated action of these two types of proteinases causes decomposition of the extracellular matrix, presenting a variety of disease conditions in TSLS.

The diagnosis of TSLS was not definitive in our case, and we hesitate to declare that the etiological mechanism of arthritis caused by proteinases such as MMP associated with TSLS applies to our patient. However, the fact that erosive arthritis developed at the joint of the right toe, opposite to the site that was initially traumatized, suggests the strong possibility that group-A streptococcal septicemia did occur in this patient, where proteinases such as MMP were activated, followed by the development of arthritis. It is also possible that these superantigens are involved to cause the activation of T-cells, as represented by a re-increase of soluble IL-2 receptor even after the disappearance of symptoms, and furthermore that a rheumatoid factor and a circulating immune complex are involved to exert some effects on the formation of erosive arthritis. We were convinced that in severe group-A streptococcal infections such as TSLS, it is necessary to observe the clinical course very carefully even after symptoms such as systemic multiple organ failures have been eliminated, and to guard against the possible development of other articular symptoms.

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