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SEPTIC POLYARTHRITIS CAUSED BY *STAPHYLOCOCCUS AUREUS* POSSIBLY FOLLOWED BY REACTIVE ARTHRITIS

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SUMMARY – Three HLA-B27 positive patients with staphylococcal polyarthritis are reported. After six weeks of treatment with antibiotics, the bacterial infection was eradicated. However, clinical and laboratory signs suggestive of reactive arthritis developed during the convalescence period. The patient became subfebrile, with persistent arthralgias and elevated total level of circulating immune complexes and erythrocyte sedimentation rate. Further treatment consisted of non-steroidal anti-inflammatory drugs alone, with good response and complete recovery in several months. These observations require additional investigations, however, similar experience in the future may reduce too long and unnecessary antibiotic therapy.

Key words: *Arthritis, infectious – therapy; Arthritis, reactive – etiology; Staphylococcal infections – drug therapy*

Introduction

Infectious arthritis is relatively rare as compared with other types of arthritis[1]. On the basis of clinical manifestations alone, infectious arthritis may sometimes be misunderstood as a symptom accompanying sepsis, and can also be mistaken for reactive arthritis, acute gouty arthritis, or some other kind of arthropathy[2]. Infectious arthritis must be treated with targeted antibiotic therapy for at least 6 weeks, and in some cases even longer than conventionally recommended[1,3,4]. The reason for prolonged treatment may be persistent arthralgias and/or arthritis followed by some systemic symptoms and laboratory test findings indicating bacterial resistance.

This report refers to three patients treated at our hospital between 1995 and 1999 for staphylococcal arthritis. All of them had persistent arthralgias for several months upon discharge from the hospital. The possibility of postinfectious reactive arthritis was seriously considered. Literature data relate reactive arthritis to a wide spectrum of different agents including the recently reported Reiter's syndrome caused by *Streptococcus viridans*[5]. Bearing in mind the similarity of streptococcal and staphylococcal antigen structure[6,7], we concluded that staphylococcus should not have been excluded as a potential agent of reactive arthritis.

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Case Reports

Case 1

A 40-year-old, previously healthy man felt sudden pain in his left hip and knee on the same day after hard physical work. On the next day, he became febrile (up to 39 °C), with almost all joints severely painful. The treatment prescribed at his general practitioner's office consisted of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, because of suspected lumbar ischialgia and pneumonia. On the fifth day of illness, the patient was admitted to our hospital with clinical signs of sepsis, septic polyarthritis and pneumonia verified by chest x-ray.

Extreme tenderness and soreness of almost all joints were recorded on physical examination. The elbow, wrist, knee, ankle and toe joints were warm, erythematous and swollen. Laboratory tests showed an erythrocyte sedimentation rate (ESR) of 126 mm/h, white blood cell count

(WBC) of 23700/mm^3 with a 'shift to the left', and high antistaphylolysin antibody titer (ASA) of 6 IU/ml (normal value <2 IU/ml). HLA-B27 was positive. *Staphylococcus aureus* was isolated from three blood samples and throat swab. No signs of osteomyelitis or joint destruction were found on several periodical x-ray checks. A technetium radionuclide (^{99m}Tc) scan demonstrated pathologic radioactivity in most of the joints.

The patient was treated with cloxacillin infusion in a dose of 14 g/day for six weeks. On day 14 of the disease, a periarticular abscess of the right hip developed. Surgical drainage was performed and 300 ml of purulent matter were evacuated. *Staphylococcus aureus* was isolated from this sample as well. After 5 weeks of therapy, the patient became afebrile and all symptoms of affected joints subsided almost completely. At the beginning of the 6th week, he became subfebrile again, with an increase in ESR from 65 mm/h to 95 mm/h. A new series of blood cultures, throat swabs and sputum cultures were sterile. Echocardiography and chest x-ray were normal. The total level of circulating immune complexes (CIC) was slightly elevated, i.e. 334 mg/L (normal values: up to 220 mg/L). The patient was discharged after six weeks of antibiotic therapy. The pain in large joints (knees and ankles) persisted for an additional five months and was successfully treated with a NSAID. ESR did not exceed 44 mm/h and the level of CIC was up to 282 mg/L. Complete recovery ensued one month later.

Case 2

A 68-year-old woman was admitted to our hospital for painful and swollen large and small joints. At the time of presentation, she was febrile up to 39 °C, with typical signs of impetigo on both legs. No synovial fluid was obtained by needle aspiration of affected joints. Laboratory tests: ESR 114 mm/h; WBC 13400/mm^3, with a strong 'shift to the left'; blood glucose 19.0 mmol/L; antistreptolysin 0 titer 80 IU/ml (normal values <200 IU/ml); ASA titer at the time of admission was 3 IU/ml and two weeks later 6 IU/ml. The total level of CIC was 1774 mg/L. Three blood cultures were positive for *Staphylococcus aureus* and so were the swabs obtained from impetigo lesions. No signs of bone destruction were found on x-ray examination. Echocardiography and chest x-ray were within the normal range. HLA-B27 was positive. The ^{99m}Tc scan demonstrated pathologic radioactivity in most of the joints.

The patient was treated with cloxacillin infusion at a dose of 14 g/day because of the clinical and laboratory signs of sepsis and septic polyarthritis. Remarkable improvement occurred after six weeks of treatment. In the seventh week of the disease, some joints became much more painful, however, without any swelling. ESR increased to 145 mm/h. A new series of blood and urine cultures, and throat and skin swabs were negative. Repeated chest x-ray and echocardiography were normal.

The patient was discharged and successfully treated with a NSAID. Control values of antistaphylolysin antibody titer decreased from 6.0 to 2.0 IU/ml. Complete recovery was achieved five months later.

Case 3

A 22-year-old man was admitted to our hospital for mumps pancreatitis. Two weeks later, a pancreatic pseudocyst and abscess developed. Methycillin resistant *Staphylococcus aureus* (MRSA) was isolated from three blood cultures and needle aspirate of the abscess. Laboratory data: ESR 82 mm/h; WBC 23000/mm^3; ASA 16 IU/ml.

During abscess drainage, moderate pain was present in the left hip region and in the small of the back. X-ray examination revealed pathologic changes suggestive of an inflammatory process in the left hip and left sacroiliac articulation. The ^{99m}Tc demonstrated intensive collection of radioactivity in the affected joints. HLA-B27 was positive. The total level of CIC was 526 mg/L. Needle aspiration of the left sacroiliac articulation was also positive for MRSA. The patient was administered vanomycin, 2 g/day i.v., for six weeks. Three weeks after antibiotic withdrawal, arthralgias developed in both knees and ankles, without swelling. The patient became subfebrile again. The same diagnostic procedure was performed, and repeated blood and urine cultures as well as throat swab were negative. Control chest x-ray and echocardiography were normal. Abdominal ultrasonography revealed only minor residual changes following drainage of the pancreatic abscess. NSAIDs were introduced into therapy with a satisfactory result. A couple of weeks later, ESR, ASA and CIC were within the normal range, however, arthralgias of the large joints persisted for one more month. Complete recovery was reached about five months of the disease onset.

Discussion

We would like to emphasize some characteristics common to these three patients. Infectious polyarthritis was caused by the commonest agent, *Staphylococcus aureus*[1,3,4]. They all were HLA-B27 positive. It is well known that genetic marker systems such as HLA types and immunoglobulin heavy chain allotypic antigens may be associated with autoimmunity making the host susceptible in some

way to antiself immune cell activation. Most prominent is the increased frequency of HLA-B27 in certain rheumatic diseases, particularly ankylosing spondylitis, Reiter's syndrome, and reactive arthritis.

Although a reduced immune reactivity was probably present in all the three cases for different reasons[8], in our first patient hard physical work may have favored dissemination of the respiratory infection. The newly detected diabetes had probably precipitated the disease in the second patient with impetigo, and viral infection in the third patient[9]. However, in the latter, the subclavian catheter was the most suspect source of MRSA.

The hematogenous route of joint infection was the most plausible one in all three cases. The technetium radionuclide scan was found to be useful as an early indicator of the pathologic intra-articular process[10].

In the first two patients, six-week cloxacillin therapy proved to be a successful treatment, whereas the third patient required vancomycin for the same period of time. After antibiotic withdrawal, all bacteriologic samples were negative and clinical findings improved remarkably. However, 1-3 weeks later relapses of arthralgia and fever along with ESR increase were observed. Arthralgias were present even in the joints that had not been affected by the bacterial infection (case 3). There were no other local signs of inflammation.

In the absence of bacterial infection, arthralgias responded very well to NSAID therapy. All patients were HLA-B27 positive and had an increased total level of CIC. Numerous inflammatory diseases are accompanied by increased CIC levels. According to Waldvogel[7], an increased level of CIC was found in 50% of patients with staphylococcal endocarditis. In such circumstances, we seriously considered reactive arthritis as a possible immune disorder.

The pathophysiologic basis of reactive arthritis following infectious arthritis has been excellently explained by Rotrosen[4]. Synovial inflammation after bacterial eradication in predisposed persons is due to the effect of different bacterial products (endotoxins, exotoxins and peptidoglycans). These products stimulate the precipitation of immune complexes into the synovium and periarticular structures, and support sterile inflammation when the convalescent period is expected. The diagnosis of this immune reaction is not easy because reactive arthritis can involve the joints affected by the infection or any other joint. The same syndrome has been described after antibiotic treatment for Lyme disease, where arthralgias persisted for several months. The term Lyme-reactive arthritis is likely to be generally accepted[11].

Although joint stiffness or contractures may also cause arthralgias, reactive arthritis is usually accompanied by fever, elevated level of immune complexes, and increased ESR. However, there is general agreement that the diagnosis is neither certain nor easy[2]. Since the incidence of reactive arthritis after streptococcal infection seems to be higher lately[12], it would be logical to anticipate the possibility of the same pathogenic mechanism after staphylococcal infections. This thesis is supported by our own experience with patients suffering from reactive arthritis due to dental infective foci[13]. When these streptococcal or staphylococcal dental focuses were eliminated, reactive arthritis was solved as well. A point worth mentioning is that *Staphylococcus aureus* may provoke a postinfectious immune reaction in other, distant organs (pericarditis, myocarditis, pleuritis)[14,15].

In conclusion, after the treatment for staphylococcal arthritis, our patients exhibited clinical manifestations strongly suggestive of reactive arthritis. Reactive arthritis is a known complication of infection located elsewhere in the body. It is rarely a consequence of the joint infection itself.

The response to NSAIDs only was very good and all patients recovered completely in several months. Although these observations require further evaluation, similar experience in the future may reduce too long and unnecessary antibiotic therapy.

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Sažetak

REAKTIVNI ARTRITIS KAO MOGUĆA POSLJEDICA SEPTIČNOG POLIARTRITISA UZROKOVANOG BAKTERIJOM *STAPHYLOCOCCUS AUREUS*

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Opisano je troje bolesnika sa stafilokoknim poliartritisom pozitivnih na HLA-B27. Bakterijska je infekcija iskorijenjena šesttjednim liječenjem antibioticima. Međutim, tijekom razdoblja oporavka razvili su se klinički i laboratorijski znaci koji su upućivali na reaktivni artritis. Bolesnici su bili subfebrilni, uz ustrajne artralgije te povišenu ukupnu razinu cirkulirajućih imunokompleksa i sedimentaciju. Daljnje se liječenje sastojalo samo od nesteroidnih protuupalnih lijekova, uz vrlo dobar odgovor i potpun oporavak kroz nekoliko mjeseci. Ova zapažanja zahtijevaju daljnja ispitivanja, no slična bi iskustva ubuduće mogla skratiti predugo i nepotrebno liječenje antibioticima.

Ključne riječi: *Artritis, infektivni – terapija; Artritis, reaktivni – etiologija; Stafilokokne infekcije – medikamentna terapija*