Letters to the Editor

Antibiogram-driven antimicrobial treatment for *Ureaplasma urealyticum* genitourinary infection can be effective against chronic monoarthritis

Sirs,

The role of *Ureaplasma urealyticum* (UrU) in inducing reactive arthritis (ReA) is still uncertain. While its involvement in septic arthritis of immunodeficient patients seems confirmed (1), there is contrasting data on the role of UrU in the immune process of ReA (2). On the other hand, the recent detection of UrU DNA (3) or viable UrU (4) in the joints of ReA patients [as previously demonstrated for other organisms (5)] makes the limits between UrU-induced ReA itself and septic arthritis less definite.

Between November 1997 and July 1999 we observed 10 female patients who had previously developed chronic monoarthritis 2-4 weeks after an acute genitourinary inflammation (cystitis in 7, urethritis in 2 and cervico-vaginitis in 1) and were admitted with a positive culture for UrU in urine and urogenital swabs. Six presented with arthritis of the ankle, 2 with sacroiliitis, and one each with knee and hip involvement. The duration of the joint disease ranged from 3 months to 2 years (Table I).

The initial acute genitourinary inflammation had been treated by family doctors in 4 patients with cotrimoxazole or ampicillin/clavulanic acid after the detection of leucocyturia, plus bacteriuria (with positive colture for *Escherichia coli*) in 2 of them. *Chlamydia trachomatis* (CT) and UrU were not searched for at that moment. Each patient's history was negative for other episodes of arthritis,enthesitis, skin and mucosal diseases, and bowel or ocular involvement. Their family histories were negative for the above-mentioned disorders. In all cases previous administration of an NSAID produced partial and transient relief of the symptoms. Additional low dose steroids (8 mg/day methylprednisolone) had similar effects in patients no. 2 and no. 3 (Table I).

In the subjects with ankle and knee involvement, roentgenograms showed soft tissue swelling; diffuse regional osteopenia was also present in 4 patients with ankle arthritis. The subjects with sacroiliitis underwent computerized tomography that disclosed marginal sclerosis and mild erosions. In the patient with hip arthritis MRI examination revealed joint effusion and osteopenia.

An extensive battery of laboratory tests showed high ESR and C-reactive protein values. Routine synovial fluid culture (in the subject with knee arthritis), stool culture, routine urine culture and CT exams of urine and urogenital swabs by enzyme-linked immunosorbent assay (ELISA) and immunofluorescence (IF) were also negative. Urine and urogenital swab cultures were positive for UrU in all patients. The antibiogram led us to treat the infection with ciprofloxacin (500mg daily) in 5 cases, ofloxacin (600mg daily) in 2 cases, minocycline (200mg daily) in 2 cases, and aztreonam (2g daily) in the last subject. The treatments induced the remission of all signs of arthritis in 6 patients. Patient no. 8 (Table I) became asymptomatic, although ESR and PCR values remained raised, even if less markedly than before. Three subjects failed to respond to treatment with quinolones. Aztreonam was effective within 4 days, ciprofloxacin and ofloxacin in a week (in 4 patients), and minocycline in 10-14 days. When effective, the antimicrobial therapy was continued for a period after remission of the clinical manifestations (Table I). The sexual partners of the patients also underwent an UrU search and, when positive, received antibiogram-driven antimicrobial treatment.

In all patients (including the non-responsive ones) urine and urogenital swab cultures were negative 20 days after the end of the therapy. Tests for CT in urine and swabs by ELISA and IF also remained negative. No relapses of arthritis have been documented so far (follow-up 12 to 29 months).

There are no univocal diagnostic criteria for ReA (6), although some authors have attempted to fill this lacuna (7, 8). At the moment, although it is generally agreed that ReA involves one or more joints of the lower limbs in an asymmetric manner (7), suitable methods for identifying the triggering infectious agents of ReA are lacking.

In 1997 we described the effectiveness of quinolones in 5 patients with chronic monoarthritis or dactylitis following acute genitourinary inflammation (9). In these patients we were unable to identify a possible triggering agent. Recently Sieper *et al.* failed to demonstrate any benefit with long-term ciprofloxacin in patients with enterogenic ReA, but indicated a possible role for this antimicrobial agent in subjects suffering from CT-induced arthritis (10).

Based on the classification criteria proposed by Pacheco-Tena *et al.* (8),the cases described in the present paper could be classed as "probable ReA", although in our patients genitourinary mucositis generally took the form of cystitis rather than urethritis or cervicitis. Furthermore, a possible causative microorganism was found in UrU.

We believe that our findings are of interest for the following reasons: (1) they support the potential role of antimicrobial drugs in the treatment of urogenicReA; (2) they suggest that antimicrobial drugs work quickly, when effective; (3) they indicate that antimicrobial treatment may be a possible first therapeutic approach, because it is short and safe. The effectiveness of the antibiogram-driven treatment in 7 subjects out of 10 could also lead to a re-evaluation of the role of UrU in inducing ReA.

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Table I. Main characteristics of the reported cases of chronic monoarthritis treated with antimicrobial drugs.

Patient	1	2	3	4	5	6	7	8	9	10
Sex/age	F/60	F/56	F/28	F/23	F/25	F/33	F/54	F/68	F/47	F/61
ESR (mm/hr)	34	38	43	29	37	34	41	47	50	35
Joint involved	ankle	ankle	knee	ankle	ankle	hip	ankle	sacroiliac	sacroiliac	ankle
Arthritis duration	3 mos.	5 mos.	3 mos.	4 mos.	18 mos.	8 mos.	4 mos.	4 mos.	6 mos.	24 mos.
Treatment	Aztr.	Cipr.	Min.	Cipr.	Cipr.	Ofl.	Ofl.	Cipr.	Cipr.	Min.
Remission	4 days	6 days	10 days	7 days	no	5 days	no	7 days	no	14 days
Treatment duration	10 days	20 days	1 month	20 days	20 days	20 days	20 days	20 days	20 days	1 month

Aztr.. = Aztreonam; Cipr. = Ciprofloxacin; Min. = Minocycline; Ofl. = Ofloxacin.

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Streptococcal toxic shock syndrome in a patient with rheumatoid arthritis

Sirs,

Streptococcal toxic shock syndrome (STSS) attributed to group A Streptococcus (GAS) is a disease that presents suddenly with circulatory failure followed with rapid failure of multiple organs. Cases of STSS were reported by Adams *et al*. (1) in 1985 and by Cone *et al.* (2) in 1987. In Japan 198 cases of STSS have been reported between 1993 and 1999, after the first report by Shimizu *et al*. (3) in 1993. Recently, many cases (4) involving perinatal women who developed STSS triggered by uterine contraction caused by purulent myometritis have been reported. In this paper, we report our encounter with fulminant STSS caused by GAS in a patient with rheumatoid arthritis (RA).

A 67-year-old male was admitted to the hospital with edema and pain in the left lower extremity that had developed 2 days before and quickly worsened. He had no obvious injury or preceding infection. The patient was diagnosed as having stage IV RA based on the criteria proposed by the American College of Rheumatology in 1987. The patient's condition was controlled with prednisolone at 10 mg/day.

At admission, the patient's blood pressure was 100/62 mmHg, pulse rate 90/min and body temperature 36.2°C. Edema with severe pain was evident in the entire left lower extremity; changes in skin color suggestive of necrotizing fasciitis were not observed. Blood test results are shown in Table I.

The results of the physical examination and laboratory tests were indicative of septicemia. Blood samples were cultured to isolate the pathogenic organism and the patient was treated with piperacillin sodium at 4 g/day, imipenem 1 g/day and -globulin 2500 mg/day. Although the serum concentration of CPK was abnormally high, the serum CPKMB level of 3% was normal. There was no abnormal ST segment changes observed in the electrocardiogram. The CPK isozyme patterns showed 0% BB and 97% MM.

On physical examination, a 10 cm epidermolytic lesion was present on the lateral side of the left lower extremity, with a large amount of serosanguineous, low viscous effusion. Afterward, the patient's confusional state worsened. He suddenly lost consciousness and was in cardiopulmonary arrest. Cardiopulmonary resuscitation was immediately performed, but the patient died approximately 12 hr after admission. GAS was isolated from the blood specimens. The bacteria was later typed as T22/M22 and was found to be producing streptococcal pyogenic exotoxin (SPE) B and C *in vitro*.

Diagnostic criteria (5) for STSS have been proposed by the Centers for Disease Control and Prevention (Atlanta, USA). In the present case, AI section: GAS was isolated from peripheral blood; B1 section: Renal impairment; creatinine ≥ 2 mg/dl for adults or ≥ twice the upper limit of normal for age. In patients with preexisting renal disease, a ≥ 2-fold elevation over the baseline level; B3 section: Liver involvement; SGOT, SGPT, or total bilirubin levels ≥ twice the upper limit of normal for age. In patients with pre-existing liver disease, a ≥ 2-fold elevation over the baseline level. Unfortunately, an autopsy could not be performed for ethical reasons.

STSS is a disease that presents suddenly with circulatory failure followed by rapid failure of multiple organs. In Japan, approximately 70% of the reported STSS cases are preceded by some form of infection such as respiratory (e.g. upper and lower airways) or urinary tract infection. However, only an accurate diagnosis and prompt treatment at an early stage may save patients with septicemia caused by GAS (6). The recommended therapy includes administration of a large dose of penicillin, -globulin preparation, supportive treatment for shock which often occurs with septicemia, and aggressive debridement of necrotic tissues (7). Despite these aggressive treatments,the mortality rate in cases of STSS with septicemia remains high at 30% to 40% (8).

Most SPEs belong to the large family of superantigens that are potent stimulators of lymphocytes from mice, rabbits and humans (9). SPE-stimulated lymphocytes may contribute significantly to the development of STSS through the massive release of cytokines (9). On the other hand, GAS also produces many extracellular products such as streptolysine-O, streptolysine-S, streptokinase and hyaluronidase, and these may also play a role in the development of STSS.

Our patient suffered from edema and pain of the left lower extremity associated with epidermolysis and leakage of effusion. We did not perform aggressive debridement because of the lack of skin color changes suggestive of necrotizing fasciitis. However, given the increased levels of serum CPK and Mb, it is legitimate to assume the presence of necrotizing fasciitis and myolysis involving the left lower extremity.

In only 30% to 35% of reported STSS cases was there a clear underlying disease, such as tumor, diabetes mellitus and liver disorder and drug abuse (6). Only one case of STSS as a complication of RA has been confirmed by the research group in the Ministry of Health and Welfare of Japan. The patient in our case had a history of RA complicated by the long term administration of steroids and NSAIDs. It is most likely that the patient's immune function was

Table I. Laboratory findings after admission.

	Values		Normal ranges
WBC	1700		4000 - 8000/ l
RBC	322 x 10^4		450 - 550 x 10^4/ l
Hb	10.7		14 - 18 g/dl
PLT	8.2		20 - 40 x 10^4/ l
GOT	257	≠	10 - 28 IU/l
GPT	98	≠	5 - 33 IU/l
CPK	9,189	≠	35 - 200 IU/l
Mb	29,953	≠	0 - 65 ng/ml
Na	139		135 - 150 mEq/l
K	4.8		3.5 - 5.3 mEq/l
Cl	96		96 - 107 mEq/l
BUN	69.4	≠	7 - 22 mg/dl
Cre	4.73	≠	0.6 - 1.2 mg/dl
TP	5.4		6.7 - 8.5 g/dl
Alb	2.8		3.8 - 5.5 g/dl
CRP	35.4	≠	0.4 mg/dl >
IgG	1,171		680 - 1620 mg/dl
IgA	303		84 - 438 mg/dl
IgM	66		57 - 288 mg/dl