Candida albicans arthritis in a nonimmunocompromised patient

Complication of placebo intraarticular injections

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A nonimmunocompromised 32-year-old man with arthrosis of the knee participated as a placebo control in a clinical trial of intraarticular injections of hyaluronan. After the fourth weekly injection of saline, he developed a warm and swollen knee, and synovial fluid cultures revealed growth of *Candida albicans*. Oral fluconazole treatment was instituted 2 weeks after onset of symptoms, but failed to eradicate the infection. The patient recovered after treatment with local and systemic amphotericin B, systemic 5-fluorocytosine and surgical synovectomy. Quantitation of joint cartilage proteoglycan fragments in synovial fluid indicated extensive breakdown of cartilage during the acute phase of arthritis but, parallel to clinical recovery, these levels returned to normal.

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Candida arthritis is rare and was first reported by Vialatte et al. (1960). It occurs mainly in the immunocompromised host, and in treatment with corticosteroids, cytotoxic drugs, and prolonged treatment with intravenous antibiotics (Cuéllar et al. 1992). Most commonly, septic *Candida* arthritis is a result of disseminated candidiasis while only 8 cases, usually associated with intraarticular injections of corticosteroids, due to direct inoculation, have been described (Katzenstein 1985, Cuellar et al. 1992). Only 1 case of iatrogenic *Candida* arthritis after an arthrotomy in a previously healthy person has been reported (Arnold et al. 1981). The overall infection risk of intraarticular injections has also been reported to be low. In a German study with voluntary reporting it was claimed that 960 surgeons performing 105,000 injections only had 3 infections (Bernau and Köpcke 1987).

We describe a case of *Candida* arthritis of the knee due to multiple intraarticular injections in a nonimmunocompromised patient with arthrosis.

Case report

A 32-year-old male former soccer-player had arthrosis of his right knee, but was otherwise healthy. He had undergone meniscectomy at age 14, and he had had repeated arthroscopies in recent years. The patient volunteered to participate in a placebo-controlled double-blind trial of 5 weekly intraarticular injections of hyaluronan or saline in patients with arthrosis (Dahlberg et al. 1994). The study was approved by the local ethics committee and was performed at the Department of Orthopedics.

The injections were done according to routine procedures. Thus profuse cleansing with chlorhexidine alcohol and sterile dressing was used, and the surgeon performing the injections wore sterile gloves. 3 days prior to the fourth injection he experienced mild pain when walking, and 3 days after his fourth (and final) injection the knee was warm and swollen. It was later revealed that the patient had received only placebo saline injections. Arthrocentesis yielded 125 mL of slightly cloudy, nonpurulent synovial fluid, which was analyzed by microscopy (negative) and culture. Next day another 100 mL of synovial fluid was obtained, revealing synovial fluid (SF) leukocytes 34×10^9/L, SF-glucose 5.6 mmol/L, B-glucose 6.3 mmol/L and again negative microscopy. The sedimentation rate was 24 mm/h and rectal temperature was 38 °C. Oral indomethacin was instituted, all symptoms subsided, and 6 days later only 50 mL synovial fluid could be obtained with similar results for SF-leukocyte and glucose levels. At this time, cultures of the first 2 synovial fluid samples grew *Candida albicans*, and the patient was transferred to the Department of Infectious Diseases.

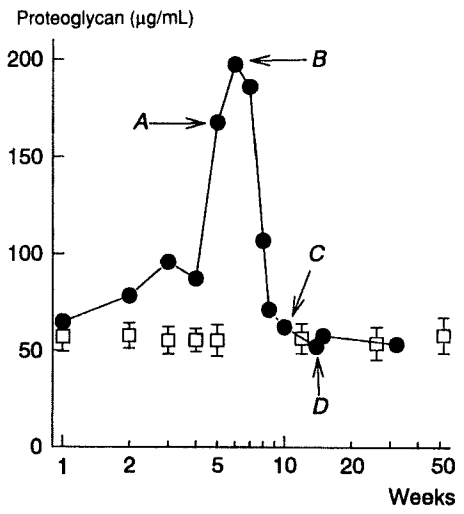

Figure 1. Concentration of proteoglycan fragments in joint fluid of a patient with *Candida albicans* arthritis. Note logarithmic time axis. A: start of symptoms. B: Start of fungicidal treatment. C: Surgical synovectomy. D: End of fungicidal treatment. Filled symbols (●) represent values for the arthritis patient. Open symbols (□) represent average values ± 95 percent confidence interval for the remaining group of 51 patients with arthrosis.

Oral fluconazole 200 mg daily was instituted and continued for 13 days. During this treatment there were no general symptoms and only mild joint effusion, but synovial fluid cultures still grew *Candida albicans* on Days 4, 8, and 13 of fluconazole treatment. Synovial fluid from these occasions was sent for culture in blood culture bottles and in sterile tubes. Only cultures from blood culture bottles were positive, probably due to the diluting effect on fluconazole by the liquid broth. Fluconazole concentration in synovial fluid was 3.3 mg/L. No fungicidal but only fungistatic activity of the fluid in 1/2 dilution was observed. Therefore, treatment was changed to daily intravenous amphotericin B with an initial test dose of 1 mg, subsequently increased to 40 mg/day. The day after amphotericin B was instituted, an arthroscopy revealed only a mild synovitis without cartilage involvement. A local irrigation drainage was kept for 2 days and thereafter the course was stationary for 3 days, with no further fluid exsudation. The knee then started to deteriorate and, on Day 12 of amphotericin B treatment, an arthrotomy was performed. A total synovectomy was done since aggressive synovitis was apparent. Histologic examination of the synovial membrane showed both acute and chronic inflammation, fibrosis, and a few multinucleated giant cells, but no definite blastospores. During amphotericin B treatment, multiple fungal cultures from synovia during surgery, as well as from synovial fluid 2 days before and 6 days after synovectomy, failed to grow *Candida albicans*.

A total dose of 925 mg amphotericin B was administered intravenously during 6 weeks, and on Days 2 and 6 after synovectomy 25 mg and 15 mg, respectively, was also administered intraarticularly. 5-fluorocytosine was also given orally during 3 weeks after surgery.

Transient elevations of serum creatinine levels from 73 µmol/L to a maximum of 166 µmol/L were found, and hemoglobin levels fell from 148 g/L to 95 g/L during treatment; B-leukocyte counts, platelet counts and liver enzyme levels remained normal. Synovial fluid leukocyte levels never exceeded 38×10^9/L during the course of infection, and synovial fluid glucose levels were consistently normal, always > 50 percent of corresponding blood glucose levels. Lymphocyte phenotyping was normal, as was in vitro lymphocyte activation with *Candida albicans* antigen. Serum immunoglobulin levels were normal, and no precipitating or hemagglutinating antibodies against *Candida* or free *Candida* antigen were detected in serum during the course of infection.

3 and 10 days after the amphotericin B treatment, synovial fluid fungal cultures were negative. 2 months later the patient had recovered clinically, and at 18 months he had suffered no relapse.

Cultures from the remaining batch of hyaluronan and saline were all negative for fungi. Pre-treatment cultures from the patient's urine, throat and multiple skin locations were negative. The patient's female cohabitant was suffering from a *Candida* vaginitis at the time of the fourth intraarticular injection.

Proteoglycan fragments in joint fluid were assayed (Björnsson 1993) in samples obtained during the clinical trial and during and after treatment for the *Candida* infection (Figure 1). Proteoglycan fragment levels were elevated even 2 weeks before onset of clinical symptoms, but showed a marked increase during the acute phase of infection. Parallel to clinical recovery, however, values returned to levels normal for arthrosis (Lohmander 1991).

Patients included in the clinical trial were covered by a specific insurance policy for clinical investigations according to Swedish routines. In the settlement, the specific policy proved to protect the general insurance policy for patients in Swedish hospitals, rather than the patient himself. Thus, the specific policy reimbursed our patient according to the rather moderate rules set by the general policy, and the outcome was a disappointment to all parties on the receiving end.

Discussion

Candida arthritis in nonimmunocompromised individuals is extremely rare; to our knowledge, this is the second case reported. Although there was no evidence of *Candida* colonization of the skin or mucous membranes in our patient, *Candida* was probably introduced from the skin of the patient during the repeated injections. There was a temporal relationship with a *Candida* vaginitis in the female cohabitant.

Systemic amphotericin B has generally been the most successful treatment of *Candida* arthritis (Bayer and Guze 1978, Fainstein et al. 1982), but intraarticular administration has been tried as an adjunct in selected cases (Bayer and Guze 1978, Downs et al. 1989). Oral 5-fluorocytosine has also been used as an adjunct to systemic amphotericin B because of its synergistic in vitro effect (Imbeau et al. 1977, Koch 1988). Ketoconazole remains a second-line drug (Fainstein et al. 1982, Katzenstein 1985, Koch 1988). Successful treatment of *Candida* arthritis with fluconazole has been reported, with high concentrations of the drug in synovial fluid (O'Meeghan et al. 1990). The role of fluconazole in the general treatment of invasive mycoses has, however, been questioned (Evans et al. 1991). Our case confirms the effectiveness of systemic amphotericin B treatment, but whether the addition of 5-fluorocytosine and intraarticular administration of amphotericin B contributed to the successful outcome is impossible to evaluate. However, the failure of fluconazole as monotherapy in this case was obvious. Although adequate fluconazole concentrations in synovial fluid were achieved, cultures remained positive. The repeated aspirations of synovial fluid and the surgical removal of synovial membrane probably contributed to the successful outcome, as did the relatively short delay between onset of infection and start of effective therapy. To avoid delay, growth of *Candida* in synovial fluid should never be regarded as a contaminant.

The very high levels of proteoglycan fragments in joint fluid at the time when treatment was initiated (Figure 1) are consistent with extensive breakdown of cartilage matrix in the acute phase of the arthritis (Lohmander 1991, Lohmander et al. 1992), which resolved during treatment over the next few weeks. Concentrations in samples obtained at the end of treatment and after treatment were within the normal range for this group of patients, which suggests that joint cartilage matrix metabolism had returned to normal at that time.

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