

## Case report

# Cryptococcal arthritis and cellulitis

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**SUMMARY** A middle-aged man with diabetes mellitus and cardiomyopathy developed both cryptococcal arthritis and cellulitis. Unusual aspects included the benign nature of the joint effusion and lack of contiguous osteomyelitis.

Cryptococcal arthritis is rare, with only 7 well described cases reported in the English-language literature. It is usually associated with an underlying osteomyelitis.<sup>1</sup> Cryptococcal cellulitis is equally rare and almost invariably occurs in an immunosuppressed host.<sup>2</sup> The patient in this report had both cryptococcal arthritis and cellulitis associated with diabetes mellitus and an idiopathic cardiomyopathy. Unusual features included a noninflammatory synovial fluid and an absence of any osteomyelitis.

### Case report

A 54-year-old black man was admitted to Washington Hospital Center for treatment of congestive heart failure in July 1981. Five days earlier he had first noted pain and swelling in his left knee. The patient reported having 'pneumonia' at age 8 with resultant 'heart disease,' and was told he had an irregular heart rate and murmur at age 16. The patient had diabetes mellitus for 4 years, refused insulin therapy, and received an oral hypoglycaemic agent with only fair control. Serum glucose was typically in the 150–250 mg/dl (8.3–13.9 mmol/l) range. He had been treated for hypertension for 3 years. He developed congestive heart failure secondary to an idiopathic cardiomyopathy in January 1981. A cardiac catheterisation in June 1981 revealed an ejection fraction of 15% and normal coronary arteries. Medication included digoxin, isorbide dinitrate, 2% nitroglycerin ointment, furosemide, hydralazine hydrochloride, and potassium chloride. On admission the knee was described as warm and erythematous, and the patella

was ballotable. Full range of motion was present. Knee roentgenograms showed no abnormality. Blood uric acid was 5.9 mg/dl (0.35 mmol/l). Knee symptoms were treated empirically with ibuprofen, 400 mg by mouth every 6 hours and improved. Congestive heart failure responded to diuresis, and he was discharged 3 days later.

Six days later he was readmitted because of increasing pain in the left knee, aggravated on flexion and now present at night. The patient was afebrile. Cardiac examination revealed a diffuse point of maximal impulse (PMI), a II/VI apical systolic murmur, and a summation gallop. The knee was hot, red, and swollen, with flexion limited to 60°. Left pedal oedema was noted, but examination of the skin was otherwise normal. Laboratory studies at this time included a white cell count of  $7.6 \times 10^9/l$  with a normal differential count, a serum glucose of 423 mg/dl (23.5 mmol/l) and uric acid of 5.9 mg/dl (0.35 mmol/l). Chest roentgenograms showed evidence of congestive heart failure. Knee roentgenograms were again normal. The knee was aspirated and cultures obtained (Table 1, column 1). Indomethacin, 50 mg 3 times a day was substituted for ibuprofen. Because of subsequent hyperkalaemia, sulindac was substituted for indomethacin.

Examination of the left leg at this time revealed 3+ pitting of the left ankle with 1+ pitting of the left thigh. A trace of pedal oedema was present on the right. A venogram of the left leg was normal. A second knee aspiration was done (Table 1, column 2). Three days later the skin overlying the left tibia became diffusely warm. On the following day induration of the skin anteriorly from the left mid calf to mid thigh was noted. Nafcillin was started for a presumptive cellulitis, with no improvement over 2 days. The patient remained afebrile, and the white blood count

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Table 1 Results of joint fluid aspirations

	Column 1	Column 2	Column 3
	31 July 1981	3 August 1981	14 August 1981
Cell count	412	200	689
% Lymphocytes	60	87	83
% POLY. leucocytes	40	13	17
Erythrocytes	5344	90	689
Protein (g/dl)	1.0	0.4	1.4
Joint fluid glucose (mg/dl)	372	483	411
Serum glucose (mg/dl)	423	355	263
Appearance	Hazy yellow-red	Yellow, hazy	Hazy yellow, viscous
Crystals	None	None	None
Specific gravity	1.015	1.010	1.015
Culture for cryptococcus	Positive	Not done	Positive

SI conversion: protein g/dl  $\times$  10 = g/l, glucose mg/dl  $\times$  0.0555 = mmol/l.

was normal. He was discharged on sulindac and cephalexin.

On the following day the joint fluid culture obtained 16 days earlier became positive. The organism was identified as *Cryptococcus neoformans* by the Washington Hospital Center Microbiology Laboratory by standard techniques. The patient was readmitted, and underwent lumbar puncture, skin biopsy, knee aspiration (Table 1, column 3), and blood and urine cultures. The skin biopsy and knee aspirate were positive for *Cryptococcus neoformans*. Cerebral spinal fluid (CSF), blood, and urine cultures were negative. CSF cryptococcal antigen was negative. A bone scan of the left leg showed no evidence of osteomyelitis. Serum cryptococcal antigen was positive at a titre of 1:4096. Serum creatinine was 1.6 mg/dl (141  $\mu$ mol/l).

Treatment with 75 mg/kg/d of 5-fluorocytosine (5-FC) by mouth in 4 divided doses and 0.6 mg/kg of intravenous (IV) amphotericin B was given every other day for 40 days. The dosage schedule for 5-FC reflected a 50% reduction for mild renal insufficiency. Serum creatinine varied during therapy between 1.6 and 2.1 mg/dl (141 and 186  $\mu$ mol/l). After 10 days of treatment the patient developed a soft tissue abscess at both sites of skin biopsy, one anterior to the distal femur and one anterior to the proximal tibia. These drained spontaneously. Bacterial cultures of the wounds revealed no growth. India ink stains showed yeast forms. As an outpatient he continued receiving intravenous amphotericin B 3 times a week and 5-FC by mouth for 20 days. The total dose of amphotericin B was 750 mg, given over 9 weeks. He stopped treatment against medical advice. His cryptococcal antigen titre at that time was 1:1024.

Over the next 22 months he was admitted to another hospital several times for progressive con-

gestive heart failure. He refused any further treatment for his cryptococcal infection. Except for one brief episode of left knee pain in April 1982 his joints have been asymptomatic. His most recent test for cryptococcal antigen was negative.

## Discussion

In most cases inhalation of the fungus *Cryptococcus neoformans* results in an asymptomatic self-limited pulmonary infection. Occasionally progressive pulmonary infection or central nervous system involvement occurs. Cutaneous involvement manifest by papules, nodules, acneiform lesions, ulcers, plaques, or superficial granulomas occur in 10–15% of patients.<sup>2</sup> Cryptococcal cellulitis is rare, previously recorded in only 9 patients. All 9 were on prednisone and 8 were on additional cytotoxic drugs for conditions such as renal transplants, systemic lupus, leukaemia, and myeloma. Even in this group of severely immunosuppressed patients cellulitis is an acute event, becoming apparent over one to 2 weeks.<sup>2</sup>

The patient described here presented with knee symptoms almost 4 weeks before the cellulitis became apparent in his calf and thigh. *Cryptococcus* was grown from a knee effusion cultured one week before any apparent involvement of the surrounding skin. The skin directly overlying the site of aspiration was never clinically abnormal. It is possible that the cellulitis developed secondarily to aspiration of the infected joint. It is also possible that the initial joint aspiration was done during a transient fungaemia, and that the organism was introduced during this procedure. However, the 4 weeks of antecedent knee signs and symptoms make this possibility less likely.

Only 7 cases of cryptococcal arthritis have been well documented in the English-language literature.

All patients were under age 40 and usually lacked any other associated systemic disease. All presented as a monoarthritis, and in 5 of 7 the knee joint was involved. Presentation was subacute, and in 4 cases symptoms had been present for 6–8 months. All were febrile on admission. The only recorded synovial fluid white cell count previously reported was  $19.7 \times 10^9/l$  with 60% lymphocytes.<sup>1</sup> The patient of this report was 54 years old. He remained afebrile throughout the course of his disease. His average synovial fluid white cell count was only  $0.4 \times 10^9/l$ , with a range of 0.2 to 0.689.

Osteomyelitis is a common feature of systemic cryptococcal infection and is present in up to 10% of patients.<sup>1</sup> Among these 7 patients with cryptococcal arthritis evidence of contiguous osteomyelitis was present on roentgenograms in 3 and documented in a fourth at necropsy. The patient in this report did not have evidence of osteomyelitis on bone scan or on multiple roentgenograms.

There is an intriguing association of cryptococcal infection and cardiomyopathy.<sup>3,4</sup> This patient had a cardiac catheterisation 2 months prior to his diagnosis of cryptococcal arthritis. It is remotely possible that cryptococcal infection contributed to this patient's heart disease, or was introduced during cardiac catheterisation.

A recent report describes 15 patients with cryptococcaemia who were treated with a median dose of 710 mg amphotericin B and with 5-FC for a median

duration of 22 days.<sup>5</sup> Only 4 of 15 survived for one year. One of the first reports of combined therapy described improvement in 16 of 24 patients with cryptococcal meningitis. These patients received approximately 42 days of 0.3 mg/kg amphotericin B daily and 150 mg/kg of flucytosine.<sup>6</sup> The patient in this report received 60 days of amphotericin B at 0.6 mg/kg every other day (total dose 750 mg) and 5-FC at a renal-adjusted dose of 75 mg/kg. With 20 months of follow up this treatment schedule appears adequate.

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