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Hematogenous Candida Vertebral Osteomyelitis Treated with Ketoconazole

Summary: Candida vertebral osteomyelitis was diagnosed in a patient with systemic lupus erythematodes following X-ray evidence of osteomyelitis and the repeated culturing of *Candida albicans* from material obtained by needle biopsies from the third lumbar vertebra. The patient had been on glucocorticosteroids and parenteral nutrition six months previously. At that time, a yeast was cultured from the blood and the tip of the subclavian catheter which had been removed. After candida vertebral osteomyelitis was diagnosed, she was treated with ketoconazole for seven months. Recovery was impressive, as judged by the clinical and radiographic findings. At the time of writing this paper – 12 months after the withdrawal of ketoconazole – the patient showed no signs of recurrence.

Zusammenfassung: *Behandlung einer hämatogenen Candida-Wirbelosteomyelitis mit Ketoconazol.* Bei einer Patientin mit systemischem Lupus erythematodes wurde röntgenologisch eine Wirbelosteomyelitis diagnostiziert. In Material, das durch Punktur des dritten Lendenwirbelkörpers gewonnen wurde, ließ sich kulturell wiederholt *Candida albicans* nachweisen. Sechs Monate vorher war die Patientin mit Kortikosteroiden behandelt und parenteral ernährt worden. Zu dieser Zeit wurden aus dem Blut und von der Spitze des entfernten Subclavia-Katheters Hefen kultiviert. Nachdem eine Wirbelosteomyelitis durch *Candida* diagnostiziert worden war, wurde die Patientin sieben Monate lang mit Ketoconazol behandelt. Entsprechend den klinischen und röntgenologischen Befunden kam es zu einem eindrucksvollen Heilungsverlauf. Zwölf Monate nach Beendigung der Ketoconazolbehandlung – zum Zeitpunkt der Manuskripterstellung – waren bei der Patientin keine Zeichen für einen Rückfall festzustellen.

Introduction

Ketoconazole is a new antifungal drug which is absorbed from the gut after oral administration (1). The results obtained *in vitro* and in experimental animals with coccidiomycosis and histoplasmosis suggest that this is a potent drug (2–5). Experience in patients with serious fungal infections is limited, and the results are difficult to assess (6). Recently, we successfully used ketoconazole to treat a patient with a deep-seated candida infection.

Case Report

A 30-year-old Chinese woman was admitted to our hospital in March 1980 with a history of backache and vomiting. Systemic lupus erythematodes had been tentatively diagnosed elsewhere in June 1979; the following September, she had been treated with 40 mg prednisone daily for a nephrotic syndrome in another hospital. During that period, the patient received parenteral nutrition. On September 30th, she developed fever and chills; a yeast was cultured from the blood and from the tip of the subclavian catheter which had been removed. No antifungal treatment was given. The pain in the lumbar region had started in January 1980 and had increased steadily, irradiating to the right gluteal area. During the last few days prior to admission, she had been vomiting. She had lost 5 kg bodyweight in the previous two weeks.

Physical examination revealed a thin, severely ill woman. She weighed 44 kg and was 160 cm tall. Her temperature was 37° C, pulse rate 64/min and blood pressure 130/70 mmHg. There was slight facial and pretibial edema. The abdomen was swollen and the peristalsis weak. On palpation, the abdomen was diffusely tender. Rectal examination disclosed no abnormalities. A slight swelling was observed on the back to the right of L2. There was percussion pain over L3–L4 and pain at axial pressure. On admisson, the erythrocyte sedimentation rate was 68 mm in the first hour (Westergren). The patient had mild anemia: hemoglobin was 7.3 mmol/l and hematocrit 39%. The white cell count was 6.7 × 10^9/l with normal differentiation; the thrombocyte count was 80 × 10^9/l. Renal function was severely impaired (serum creatinine:85 µmol/l; creatinine clearance: 30 ml/min) and a nephrotic syndrome was present (serum protein concentration: 52 g/l; serum albumin: 19 g/l; urinary protein excretion: 8–22 g/day).

Systemic lupus erythematodes was diagnosed on the basis of proteinuria, thrombocytopenia, strongly positive antinuclear antibodies, a positive LE cell phenomenon (class Ⅴ A) and a history of pleurisy of unknown cause.

The complement profile was in accordance with this diagnosis: C3: 0.20 g/l (normal: 0.55–0.73); C4: 0.05 g/l (0.16–0.27); Clq: 0.53 g/l (0.94–1.22); and CH50: 54 U/ml (185–261).

A lateral tomogram of the lumbar vertebral column showed the typical changes found in spondylitis (Figure 1). The intravenous pyelogram showed displacement of the right ureter and deformation of the right psoas outline by a paravertebral mass

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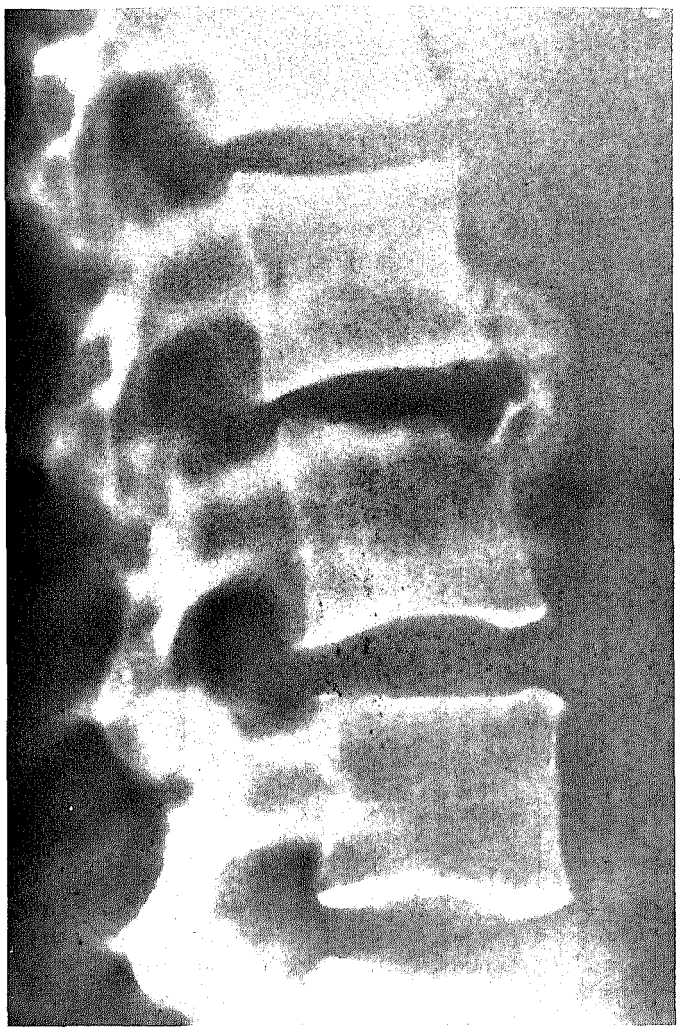

Figure 1: Lateral tomogram of the lumbar spine showing sclerosis and cortical destruction of the third vertebral body. Soft tissue calcifications can be seen, with the bridging of a narrowed interspace.

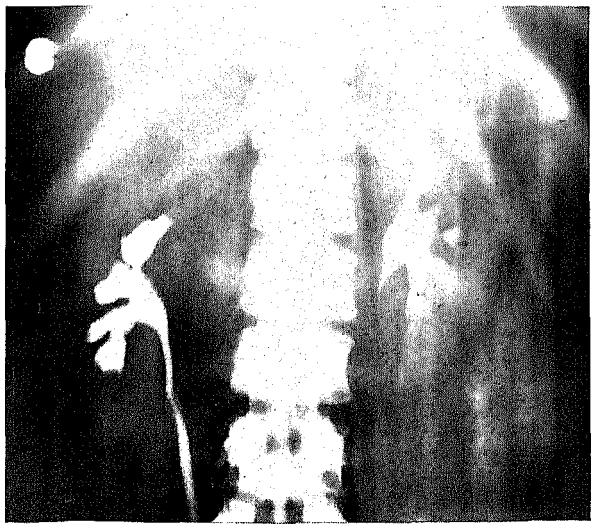

Figure 2: Intravenous pyelography. Tomographic section through the kidneys shows displacement of the right ureter and deformation of the right psoas outline by a paravertebral mass.

(Figure 2). Computer tomography of the lumbar region confirmed these findings (Figure 3a). A gallium scan revealed increased uptake in the L2-L3 area with extension toward the right side. Enteroclytic examination of the small bowel revealed swollen mucosal folds in the terminal ileum.

The third lumbar vertebra was punctured twice; Gram staining showed yeasts on both occasions, and *Candida albicans* was cultured from the material punctured. The strain was sensitive to ketoconazole. Exposure to a concentration of 0.1 μg/ml ketoconazole in Sabouraud broth resulted in inhibition of >50% after 14 days (7). Complete inhibition only occurred with ketoconazole concentrations of ≥ 16 μg/ml. When the strain was cultured in Eagle's minimal essential medium (EMEM) with 10% fetal calf serum, pseudomycelia formation was completely inhibited at concentrations of < 0.008 μg/ml ketoconazole (8).

We diagnosed candida vertebral osteomyelitis with inflammation of the surrounding structures, probably due to hematogenous spread. The intestinal abnormalities were attributed to a reflectory mechanism. Because of impaired renal function, the administration of amphotericin B was considered to be too hazardous. On April 14th, treatment with miconazole was started (600 mg i. v. once daily). After seven days, the patient refused further intravenous therapy, and ketoconazole (400 mg per os four times daily) was started on April 22nd. Serum concentrations of the drug, which were determined microbiologically as described elsewhere (9), were low, even at this high dose (Table 1). Withdrawing the antacid drug improved resorption slightly, but the concomitant administration of 15 ml of

Table 1: Serum concentrations of ketoconazole.

Time* (h)	During antacid therapy (mg/l)	Without antacid (mg/l)	With hydrochloric acid (mg/l)
1	1.1	2.3	1.6
2	1.2	2.1	7.1
3	N.D.	1.3	6.1
4	0.2	N.D.	3.2
8	< 0.2	N.D.	0.7

* after administration
N.D. = not determined

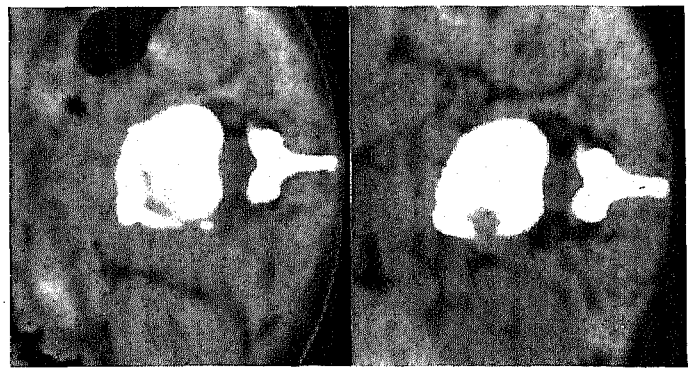

Figure 3: CT scan of the third vertebral body at the level of the intervertebral foramen.
Figure 3a: Before treatment: inflammatory swelling of the right psoas with thickening of Gerota's fascia. Marginal destruction of the vertebral body and soft tissue calcifications.
Figure 3b: After treatment: the right psoas is normal in size.

0.03 mol/l hydrochloric acid solution produced much higher levels of ketoconazole in the serum (Table 1).
Despite increased activity of the underlying illness, the clinical condition (pain, vomiting) related to the osteomyelitis and the soft tissue inflammation improved dramatically. After seven months of therapy, there were no signs of active infection, and a computerized tomogram showed that the right psoas was normal in size (Figure 3b); ketoconazole was therefore withdrawn in November 1980. Follow-up to the time of writing (November 1981) revealed no evidence of recurrence.

Discussion

Although *Candida* species are frequently implicated in systemic and local infections, they are seldom mentioned as etiologic agents of osteomyelitis (10). As far as we know, only eight well-documented cases of vertebral osteomyelitis due to *Candida* species have been reported (11–16). The most important factors predisposing to systemic *Candida* infection in these patients were hyperalimentation, previous use of antibiotics, bowel surgery and heroin addiction.
Three of the patients reported to have *Candida* vertebral osteomyelitis were treated with amphotericin B, two were treated with amphotericin B combined with 5-flucytosine, one with 5-flucytosine, one with potassium iodine and one with bed rest without fungostatic therapy. The osteomyelitis was cured in all but one patient, i. e. the patient treated with potassium iodine (15).
At present, the recommended treatment for disseminated *Candida* infections is amphotericin B alone or in combination with 5-flucytosine (17, 18, 19). The efficacy of imidazole derivatives in the treatment of disseminated *Candida* infections has not been proven (17, 19, 20).
We started to treat our patient with oral ketoconazole because she refused intravenous therapy. High plasma levels were only obtained when the drug was given in an acidified solution; this confirms the finding in volunteers that good absorption of ketoconazole requires a sufficiently low gastric pH (21).
The therapeutic results obtained in our patient suggest that there is a place for ketoconazole in the treatment of disseminated *Candida* infections; in some cases this may enable us to avoid the use of toxic amphotericin B.

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