

Pubis Cryptococcal Osteomyelitis in an Immunocompetent Patient: A Case Report and Recent Literature Review

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Aim: Skeletal involvement of *Cryptococcus neoformans* is rare and normally associated with disseminated cryptococcosis or potential predisposing factors. Here, we report an atypical case of osteoarticular cryptococcosis in an immunocompetent patient.

Case Presentation: We report a case of cryptococcal osteomyelitis in a 45-year-old female who presented with swelling and pain in the left inner thigh. After a biopsy of the pubic bone and surrounding soft tissue, the pathological results and bacterial culture of the biopsy tissue confirmed *Cryptococcus neoformans* infection. After draining the pus by aspiration and administering oral fluconazole (400 mg/d) treatment, the patient's symptoms disappeared.

Conclusion: *Cryptococcus neoformans* is a rare etiology of infection of the entire pubis, and oral fluconazole and pus aspiration could benefit some cryptococcal osteomyelitis patients with soft-tissue cryptococcal infection.

Keywords: cryptococcosis, pubis infection, antifungal therapy, immunocompetent

Introduction

Cryptococcus neoformans is an encapsulated yeast organism that can cause severe illness or death in immunocompromised patients.¹ Cases most frequently involve the central nervous system or the lungs, but multiple other sites of infection have been documented, including the skin,² kidneys,³ prostate,⁴ eyes,⁵ sinuses⁶ and colon.⁷ Approximately 5% of all cryptococcal infections present with osteomyelitis.^{8,9} Predisposing factors for cryptococcal osteomyelitis include solid organ transplant, immunosuppressant medication use, diabetes mellitus and HIV.⁸ The symptoms, signs and imaging findings of patients with cryptococcal infection are often difficult to distinguish from tumors and bacterial infections. Here, we report a case of *Cryptococcus neoformans* infection of the pubic bone and soft tissue without involvement of the lung and central nervous system and with normal immune function. To the best of our knowledge, this is the only case of cryptococcal osteomyelitis of the pubis reported in the past 5 years. Written informed consent of the patient was obtained for the publication of this case report and the accompanying images. Ethical approval was also acquired.

Case Report

A 45-year-old female was hospitalized due to pain and swelling in the medial left thigh for one month. The patient is a farmer, and the neighbors raise pigeons. One month prior, she had no obvious inducement for the unbearable pain and swelling of the left thigh. Cupping and acupuncture methods had no obvious effect. The size of the mass gradually increased, so she came to the hospital. A physical examination showed that the skin temperature on the surface of the mass was increased, and the tenderness was obvious. The patient had no fever, a normal heart rate and cardiac examination, and she had high blood pressure for more than 10 years.

After entering the hospital, the laboratory examination revealed WBC: $10.89 \times 10^9/L$, RBC: $4.50 \times 10^{12}/L$, and albumin: 33.9 g/L. The immune function of the patient was normal, and she had no history of HIV, immunosuppressive therapy or diabetes. MRI of the pelvis suggested that the soft tissue mass in the left inguinal region and the bone destruction of the left inferior pubic branch should be considered malignant tumors, and infectious lesions should not be excluded (Figure 1). CT imaging of the lesion also suggested that the patient suffered from a tumor, and the lesion contained some pus. Subsequently, we carried out a soft tissue biopsy under the guidance of B-ultrasound, and a small amount of tissue and a large amount of blood-red sticky fluid were obtained in the process. We gave the patient cephalosporin antibiotics, but her symptoms did not show a significant improvement. Re-examination of the indicators of inflammatory infection revealed CRP: 36.4 mg/L, ESR: 54 mm/h, PCT: 0.06 ng/mL, and IL-6: 12.95 pg/mL. We also performed a biopsy of the pubic lesions, and *Cryptococcus neoformans* was found in the bacterial culture of the biopsy tissue. The drug sensitivity results showed that the lesion was sensitive to AMB, 5-FC and fluconazole. Pathology after biopsy showed a fungal infection with mild dysplasia of histiocytic cells (Figure 2). After an imaging examination of the brain and lungs, no special lesions were found, so cryptococcal infection in the central nervous system and lungs was excluded. After receiving the bacterial culture results, fluconazole (400 mg/d) was taken orally for 4 weeks. During the 4-week oral fluconazole treatment, the wound was broken (Figure 3A), so pus aspiration was performed on the tumor on the inside of the thigh, and cephalosporins were used to control the infection. Four weeks after taking fluconazole, re-examination MRI showed that the mass on the medial side of the left thigh and the pubic lesions had decreased in size (Figure 4).

The patient continued to take fluconazole (400 mg/d) orally for 12 weeks after discharge. Then, she went to the hospital for re-examination and found that the medial thigh and pubic lesions had basically disappeared (Figure 5), and the swelling of the patient's left thigh had disappeared (Figure 3B). At the 2-year follow-up, the patient was doing well. There were no complications or recurrences, the WBC count was normal, and the ESR and CRP were normal. After 12 weeks of oral fluconazole (400 mg/d) treatment, the pubic lesions and surrounding soft-tissue lesions disappeared.

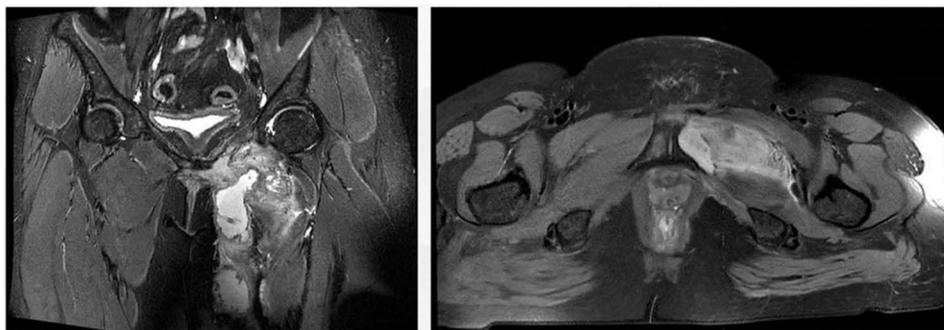


Figure 1 MRI presented lesions of the pubis and surrounding soft tissue.

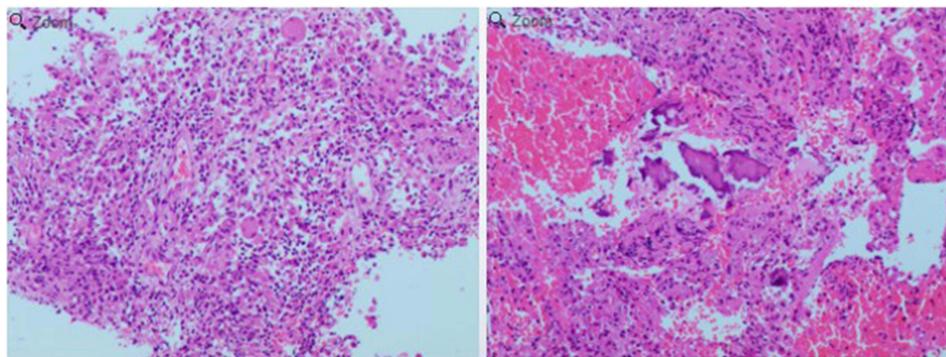


Figure 2 Pathology results showed fungal infection with mild dysplasia of histiocytic cells.

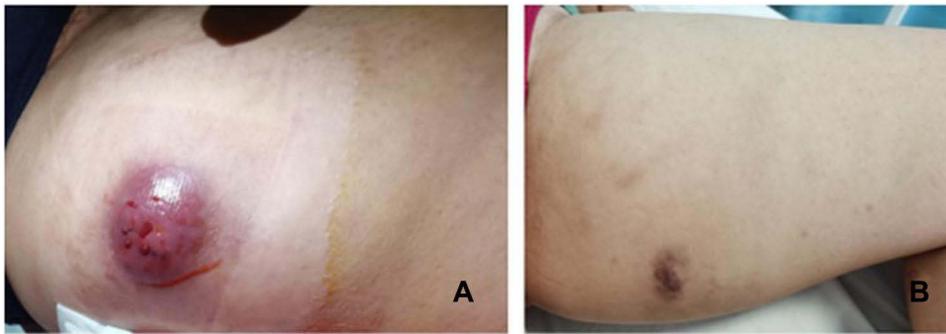


Figure 3 The appearance of the affected limb between different periods. (A) Broken biopsy wound, oozing viscous liquid. (B) After 12 weeks of treatment with oral fluconazole, the patient's symptoms disappeared.

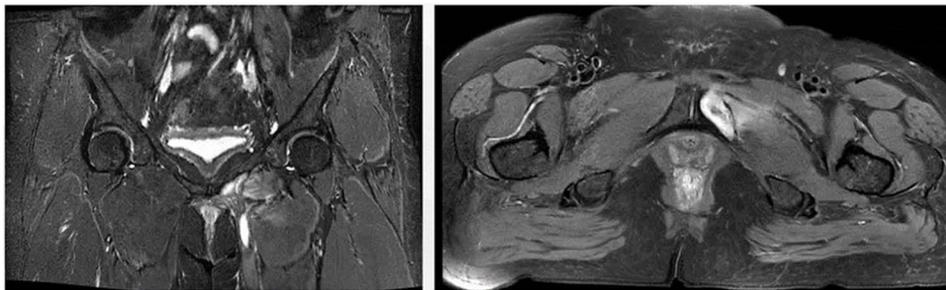


Figure 4 After 4 weeks of oral fluconazole treatment, the pubic lesions decreased in size.

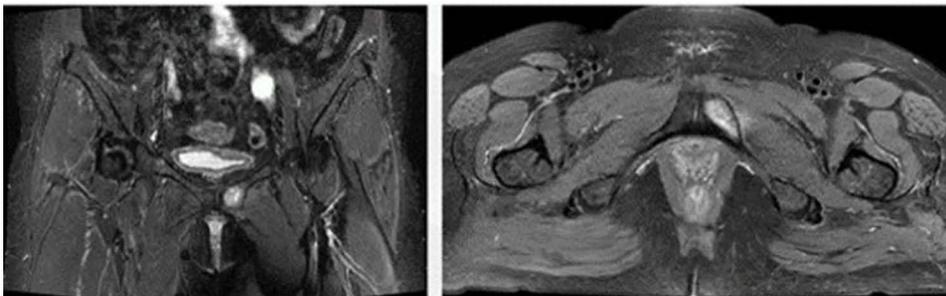


Figure 5 After 12 weeks of oral fluconazole treatment, the pubic lesions basically disappeared.

Discussion

While the capsule produced by virulent strains of *Cryptococcus neoformans* under appropriate conditions is an important virulence factor, capsule material would not cause the disease on its own. There are two kinds of common pathogenic *Cryptococcus*, namely, *Cryptococcus neoformans* and *Cryptococcus gattii*, among which *Cryptococcus neoformans* infection is the most common.^{10,11} Because *Cryptococcus* is an opportunistic pathogen,¹² with the gradual increase in the population base of the so-called “vulnerable population”, *Cryptococcus* infection has become an important infectious disease. *Cryptococcus neoformans* can cause opportunistic infections in immunocompromised patients; however, 10% to 40% of infections occur in patients without known immune deficiencies.¹³ *Cryptococcus neoformans* mainly lives in pigeons and weathered feces in soil, but fungi are not normal flora in soil.¹⁴ Detection of *Cryptococcus neoformans* mainly uses etiological detection. There are three main methods: ink staining, fungal culture and identification and cryptococcal antigen detection.

Cryptococcosis is an infectious disease caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. The lung and central nervous system are prone to *Cryptococcus neoformans* infection, while other less common body infections include skin, eyes and bones/joints.¹⁴ The site of infection can be transmitted through blood, continuous transmission or

direct vaccination. Apart from direct vaccination, animal-to-human or human-to-animal transmission is not known.¹⁵ In the case we reported, pigeons were raised in the neighbor's home; furthermore, the patient often had low back pain due to lumbar disc herniation, which sometimes resulted in cupping and acupuncture performed on her back and legs. We suspect that the skin barrier was damaged after cupping or acupuncture, so cryptococcus infection occurred after possible contact with soil contaminated by birds such as pigeons.

Bone invasion of cryptococcosis is usually characterized by localized osteolytic lesions of any piece of bone in the body, but the most common is the spine.^{14,16} Adjacent bones or joints and infected soft tissue can spread continuously. The clinical symptoms and radiological manifestations of skeletal cryptococcosis are nonspecific. Fungal bone infection can show a wide range of symptoms and onset times, depending on the pathogenicity of the potential organism, the site of infection and the potential health status of the patient. It has been reported that cryptococcal bone infection can lead to subperiosteal new bone formation, periosteal reaction and imaging manifestations of osteomyelitis.¹⁷ However, the imaging findings of cryptococcal osteomyelitis usually have no typical features and can also show well-defined osteolytic lesions, similar to malignant tumors.^{14,16–18} Meanwhile, most patients with cryptococcal osteomyelitis show soft tissue swelling and tenderness.¹⁷ Since cryptococcal infections are rare and generally subacute, the most important aspect of diagnosing these infections is to include them in differential diagnosis, especially in patients with normal immune function. It is worth noting that as many as 20% of cryptococcosis cases occur in patients with a “normal” phenotype or obvious immunity, and there are no known risk factors for infection.¹⁹ Therefore, an accurate diagnosis of cryptococcosis could require various methods, such as imaging, histopathology, and microbe examination of lesion specimens. As cryptococcosis tends to occur in patients with abnormal immune function, some patients must have their immune function detected for diagnosis. The tests include an examination of autoantibodies, the complement system, and liver and kidney function.

Although *Cryptococcus neoformans* is distributed across most of the globe, the limited history of the treatment of *Cryptococcus neoformans* remains a major challenge. Apart from lung and central nervous system infections, there is no standardized treatment for cryptococcal infections in specific body parts. The combination of antifungal therapy and surgical debridement has been used to treat many patients with bone cryptococcal infections.^{15,17,20,21} According to the American Society for Infectious Diseases, oral fluconazole (400 mg/d for 6–12 months) is the first choice for nonmeningeal, nonpulmonary cryptococcosis patients with normal immune function.^{16,17,22} Patients with disseminated diseases (involving at least two nonadjacent sites) should be given amphotericin B liposomes (3~4 mg/kg/d) plus flucytosine 100 mg/kg/d 4 times orally for at least 2 weeks. This is followed by a consolidation phase, with fluconazole 12 mg/kg taken daily for 8 weeks. Maintenance therapy includes fluconazole 200–400 mg/d for at least one year. Although the prognosis of disseminated cryptococcosis is usually poor, patients with isolated osteomyelitis with normal immune function have a good prognosis.^{17,23}

It has also been reported that there is a very restricted number of antifungal drugs that are currently clinically available for the treatment of invasive fungal infections—polyenes, azoles, echinocandins, and flucytosine.²⁴ Most antifungal drugs have few side effects and complications during long-term antifungal therapy. The major drawback of amphotericin B has always been its toxicity, particularly its nephrotoxicity, which can lead to kidney failure.²⁴ Azoles are some of the most commonly used antifungal drugs for the treatment of a variety of fungal infections, but some fungal species display intrinsic (or primary) resistance to fluconazole. A major problem with flucytosine is the extremely common occurrence of the development of resistance, and because of this, it is never used in monotherapy but rather in combination with other antifungals.²⁵ In addition, hepatotoxicity and hematological toxicity are common adverse effects at target concentrations.²⁶

A literature review was performed by searching PubMed and Web of Science for articles in the last five years containing the terms ‘Cryptococcus’ and ‘osteomyelitis’. We found approximately 28 cases of cryptococcal osteomyelitis, and the clinical characteristics and treatments are listed in Table 1.

After our case was diagnosed as a tumor in the early stage, we performed a biopsy and found that there was a large amount of fluid in the tumor. Then, we extracted the fluid from the tumor for bacterial culture, and finally, *Cryptococcus neoformans* was cultured. The pathological results also confirmed that the pubic focus was fungal infection. In our case, we used oral fluconazole treatment (400 mg/d); however, the puncture wound of the patient was broken, so we emptied the pus by aspiration and did not operate on the pubic lesion. After 3 months of oral fluconazole (400 mg/d) and pus

Table 1 Summary of 28 Cases of Cryptococcosis of the Bones in the Last Five Years

Case no./ Reference	Age/Sex	Location	ESR (mm/h)	CRP (mg/L)	Underlying Diseases	Treatment	Outcome
1 ²⁷	51/F	Rib	101	109	Normal	Flu	Response
2 ²⁷	47/M	Rib	41	10.3	DM, Hepatitis B, TB	Flu	Response
3 ²⁸	79/F	Ulna	66	74.26	Normal	Surgery+Flu+Vor	Response
4 ²⁹	36/M	Skull	NA	Normal	Liver transplantation	Surgery+AMB+5-FC +Flu	Response
5 ³⁰	69/F	Calcaneus	28	NA	renal transplantation	Surgery+AMB	Response
6 ³¹	70/M	Humerus	NA	52.8	Normal	Flu	Response
7 ³²	42/M	Ilium	NA	NA	DM	AMB+Flu	Response
8 ³³	63/M	Phalange	NA	NA	LPL	Surgery+Flu	Response
9 ³⁴	29/M	Ankle and elbow joint	43	29.5	Normal	Surgery+Flu	Response
10 ³⁵	25/M	Spine	62	44	Osteosarcoma	Surgery+AMB	Response
11 ³⁶	35/M	Spine	NA	NA	HIV	AMB+Flu	Death
12 ³⁷	18M	Scapula and Tibia	93	NA	TB	Surgery+AMB+5-FC+Flu	Response
13 ³⁸	25/M	Rib	Normal	Normal	TB	AMB+5-FC+Flu	Response
14 ³⁹	48/M	Skull	NA	NA	HIV	AMB+5-FC+Flu	Response
15 ⁴⁰	46/F	Ilium	Normal	Normal	Normal	Surgery+AMB+5-FC+Flu+Vor	Response
16 ⁴¹	78/M	Zygomatic	35	Normal	Cancer radiotherapy	Flu	Response
17 ⁴²	31/M	Mandible and Clavicle	NA	38	Normal	Surgery+AMB+5-FC+Flu	Response
18 ⁴³	11/M	Rib	NA	NA	Lung transplantation	Flu+5-FC	Response
19 ⁴⁴	17/F	Spine	NA	NA	Normal	Flu+5-FC	Response
20 ⁴⁵	41/M	Spine	62	NA	Normal	Flu	Response
21 ⁴⁶	53/M	Patella	NA	NA	Liver transplantation, DM	AMB+5-FC+Flu	Response
22 ²⁰	36/M	Scapula	NA	NA	Normal	AMB+Flu	Response
23 ²⁰	57/M	Femur	NA	NA	Normal	AMB+Flu+Surgery	Response
24 ²⁰	57/F	Ulna	NA	NA	SLE	Flu	Response
25 ²⁰	51/M	Humerus	NA	NA	Sarcoidosis, corticosteroid therapy	Flu	Response
26 ²⁰	52/F	Skull	NA	NA	Normal	Surgery+Flu	Response
27 ⁴⁷	42/F	Metatarsal	NA	NA	Normal	Surgery+Flu	Response
28 ⁴⁸	65/M	Spine	41	17.2	Renal transplantation, DM	AMB+Flu +Surgery	Response

Notes: There are 28 Cryptococcal Osteomyelitis cases in the recent years, involving clinical characters, therapy, outcome et al.

Abbreviations: NA, not available; 5-FC, 5-fluorocytosine; Flu, fluconazole; Vor, Voriconazole; LPL, lymphoplasmacytic lymphoma; TB, tuberculosis, SLE, systemic lupus erythematosus; DM, diabetes mellitus.

aspiration, the symptoms of the patient almost completely disappeared, and after follow-up, there were no more symptoms.

In summary, we report the first case of isolated cryptococcal osteomyelitis of the pubis with surrounding soft-tissue cryptococcal infection in an immunocompetent patient in recent years. Patients with isolated cryptococcal osteomyelitis of the pubis and surrounding soft-tissue cryptococcal infection may be cured with oral fluconazole and surgery, especially in some special cases; for example, in patients presenting only soft-tissue swelling and plentiful pus. Cryptococcosis therapy should be aimed at multiple factors, such as the size of the lesion and host immune conditions. We suggest that it is necessary to culture biopsy specimens, even in clinical cases in which a tumor is often suspected. This case can serve as a reminder of the many ways cryptococcal infection may be disguised and the usefulness of proper diagnostic procedures.

Abbreviations

NA, not available; 5-FC, 5-fluorocytosine; Flu, fluconazole; Vor, Voriconazole; LPL, lymphoplasmacytic lymphoma; TB, tuberculosis, SLE, systemic lupus erythematosus; DM, diabetes mellitus.

Data Sharing Statement

All data (image and table) used in this study are included in this published article. We do not have metadata sharing, thus, it is not applicable to this article.

Ethics Approval

The ethical approval was acquired by applying for the medical ethics committee of Zhongnan Hospital.

Consent for Publication

The patient gave written informed consent to the publication of her history and photographs.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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