Arthritis caused by *Cryptococcus neoformans* infection: A case report

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Abstract. Cryptococcal infections are uncommon in individuals with normal immune functions. These infections commonly affect the lungs and central nervous system; however, there are a few reports of infection in the bone and joint areas. The current study reported a case of knee joint infection caused by *Cryptococcus neoformans* in China. A 56-year-old man presented to The China Academy of Chinese Medical Sciences Guang'anmen Hospital Baoding Hospital (Baoding, China) with severe anemia and lung inflammation. Initially, there was no obvious cause of swelling or pain in the knee joints. However, after the patient presented with new swollen and painful knee joint symptoms, pus culture and cryptococcal antigen detection tests confirmed *C. neoformans* infection. After pus drainage and fluconazole treatment, the patient's condition substantially improved. Clinical awareness of *C. neoformans* infections should be promoted. In suspected cases, puncture fluid or tissue pathogen testing should be performed as early as possible to avoid misdiagnosis and serious consequences of delayed treatment.

Introduction

Cryptococcus, which comprises ~70 species and genera, belongs to the Cryptococcaceae family and Fungi kingdom. Currently, only *Cryptococcus neoformans* and *Cryptococcus gattii* are known to cause diseases in humans (1). Cryptococcosis is a globally widespread invasive fungal disease. Cryptococcal infections are uncommon in individuals with normal immune function (2). The lungs and central nervous system (CNS) are the most commonly affected areas by cryptococcal infections (3). Approximately 5-10% of patients with disseminated cryptococcal disease develop cryptococcal osteomyelitis; however, there are few reports of infection in the bone and joint areas and of cryptococcal arthritis in the older adult population (3,4). To the best of our knowledge, there are only nine reports of joint infection due to cryptococcal infection (5). Additional clinical data indicate that patients with compromised immunity (such as those with acquired immunodeficiency syndrome) are highly susceptible to cryptococcal infection, irrespective of sex and age (6,7). However, cryptococcal lesions of the skeletal system are rare and primarily manifest as localized swelling, pain and joint movement disorders. Certain patients also exhibit systemic symptoms, such as fever and chills (8). Imaging often reveals local or multiple osteolytic lesions that extend to the joints; some patients may also present with peripheral abscesses and soft tissue mass formation (9). The present study reported a case of knee joint infection caused by *C. neoformans* in China.

Case report

A 56-year-old man was diagnosed with primary myelofibrosis and severe anemia at the Hematology Hospital of the Chinese Academy of Medical Sciences (Tianjin, China), in October 2021. In February 2023, the patient experienced coughing after catching a cold. The inflammatory indicators of the patient revealed high-sensitivity C-reactive protein (hs-CRP) levels of 46 mg/l↑ (normal range: 0-3 mg/l) and procalcitonin (PCT) levels of 0.085 ng/ml↑ (normal range: 0.02-0.046 ng/l). A chest computed tomography (CT) scan (Fig. 1A) revealed inflammation in the middle lobe of the right lung with cord shadows, interstitial changes in both lungs and micronodules in the middle lobe of the right lung. Due to the patient's mild cough symptoms, negligible phlegm and lack of cooperation with bronchoalveolar lavage sample collection, the patient was treated with an intravenous infusion of ceftazidime (1 g q8 h) and a conventional dose of levofloxacin. After three days, the patient's cough symptoms markedly improved. After 10 days, the patient was discharged. However, due to regular blood transfusions for severe anemia, intense swelling and pain in the left knee joint (new symptoms), the patient was admitted to The General Medicine Department of Baoding Hospital, Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Baoding, China) in April 2023.

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Upon admission, the patient was conscious with a moderate mental state and mild cough symptoms. The patient did not have any recurrent fever, obvious dizziness, headache, nausea, vomiting, acid reflux, heartburn, chest tightness, chest pain, abdominal pain, diarrhea or lack of appetite. He had normal sleep at night and normal bowel movements but had severe swelling and pain in the left knee joint, limited mobility, and high skin temperature at the swollen knee joint. The patient had no history of hypertension or coronary heart disease and had not come into contact with any birds, such as pigeons, or their droppings. Admission examination revealed a body temperature of 36.2˚C, pulse rate of 86 beats/min, breathing rate of 18 times/min and blood pressure of 102/72 mm Hg, all within normal ranges. The patient had an anemic appearance and exhibited thick respiratory sounds in both lungs, audible moist rales, and no obvious murmurs in the auscultation area of each valve. The abdomen was full without any obvious tenderness, rebound pain or muscle tension. The liver was not palpable under the ribs, the spleen was enlarged and percussion pain was observed in the spleen. No edema was found in either of the lower limbs; however, there were new symptoms of severe swelling and pain in the left knee joint. Laboratory examination results were as follows: White blood cell count, $5.96x10^9$/l (normal range: 3.5-9.5$x10^9$/l); neutrophil percentage, 58.7% (normal range: 40-75%); lymphocyte percentage, 25.9% (normal range: 20-50%); monocyte percentage, 12.7% [elevated (↑), normal range: 3-11%]; red blood cell count, $1.99x10^{12}$/l [decreased (↓), normal range: 4.3-5.8$x10^{12}$/l]; hemoglobin level, 5.6 g/l (↓, normal range: 13.0-17.5 g/l); PCT level, 0.052 ng/ml (↑); hs-CRP level, 19.7 mg/l (↑); and human immunodeficiency virus (-). A chest CT scan (Fig. 1B) revealed inflammation in the middle lobe of the right lung with a cord shadow (same as previously), interstitial changes in both lungs (same as previously) and micronodules in the middle lobe of the right lung (same as previously). Magnetic resonance imaging of the left knee joint (Fig. 1C and D) revealed the following: i) Joint degeneration, ii) joint cavity and suprapatellar capsule effusion, and iii) a left anterior superior patellar soft tissue cystic lesion. Based on the patient's previous diagnosis, treatment and clinical experience, and considering pneumonia and arthritis, an intravenous infusion of ceftazidime (1 g q8 h) was administered, with a conventional amount of levofloxacin. Simultaneously, for diagnostic purposes, knee joint pus was discharged through needle aspiration (closed suction, no rupture); a gray, white purulent liquid was obtained, with a total discharge of ~20 ml. In April 2023, a sample of the knee joint pus was submitted for culture-based diagnosis. The original smear on the same day showed a moderate number of yeast-like spores (Fig. 1E). The growth status of the 48-h blood plate is presented in Fig. 1F and the ink staining result is displayed in Fig. 1H. After three days, the isolated strain was identified as *C. neoformans* using DL-96FUNGUS plate identification (DL: Zhuhai DL Biotech Co., Ltd.; equipment model: DL-96II), with an identification rate of 99.8% (Table I). The identification rate is the identification result of the instrument; it indicates the certainty of bacterial identification. A capsular antigen test for *C. neoformans* was sent to Shijiazhuang KingMed Diagnostics Laboratory Co., Ltd. for examination and the result was positive. To investigate the source of the infection, the microbiological laboratory recommended submitting lower respiratory tract samples and blood cultures for examination. The results of the sputum smear, as presented in Fig. 1G, and isolation identification were the same as those shown in Table I; however, the blood culture was negative. The pathogenic microorganism was *C. neoformans* for the knee joint and pulmonary infections. The first dose of fluconazole was 400 mg/day, which was decreased to 200 mg/day from the second day. After 10 days, knee joint symptoms had substantially improved. After 12 days of hospitalization, the patient was discharged and instructed to continue taking fluconazole 200 mg/day orally for 4 months. After 23 days of follow-up, the patient reported occasional coughing and phlegm, improved knee joint symptoms and no swelling or pain. One month later, the patient was re-examined at the hospital and was in a good mental state, the knee joint was in good condition, no swelling was detected, the patient did not report any pain, and no symptoms of cough or phlegm were present. Therefore, the treatment was deemed effective. Regarding the follow-up treatment effect and recurrence, the microbiological laboratory will cooperate with the clinician to monitor the case for 1 month. The patient continues to undergo regular follow-ups (every other month) to screen for the spread of infection in the blood, nervous system and other parts of the body via examinations including physical examination and blood culture. The patient's medication compliance will also be monitored.

Discussion

Cryptococcus comprises ~70 species and genera. At present, only *C. neoformans* and *C. gattii* are known to cause diseases in humans (1). Cryptococcal infection is uncommon in individuals with normal immune function (2) and the lungs and CNS are the most commonly affected areas (3). Immunosuppressed patients may develop disseminated *Cryptococcus* (6). Approximately 5-10% of patients with disseminated cryptococcal disease develop cryptococcal osteomyelitis, but there are few reports of infection at the bone and joint sites and few reports of cryptococcal arthritis in the elderly (4). There are also reports linking cryptococcal arthritis with immune deficiency states (7). In addition, direct hematogenous dissemination and lymphatic transmission are important sources of joint infections (10).

The patient of the present study had no obvious cause of knee joint infection with *C. neoformans* and the source of the infection remains elusive. The infection may be related to the patient's long-term use of immunosuppressants; immunosuppressed patients may acquire disseminated *C. neoformans* infections (6). The chest CT scans consistently showed pulmonary inflammation without improvement, suggesting that the lungs may have been the initial source of infection. Bloodstream or lymphatic transmission may have also occurred.

Cryptococcal infections of the joints most commonly affect the knee joint and mainly manifest as local swelling, pain and joint movement disorders. Certain patients also experience systemic symptoms, such as fever and chills (2,4-6,8,11). Imaging frequently reveals local or multiple osteolytic lesions that extend to the joints and certain patients may present with peripheral abscesses and soft tissue mass formation (8,9,12). The present case of *C. neoformans* infection of the knee joint

Table I. Antimicrobial susceptibility results of *C. neoformans*.

Antimicrobial agent	MIC, μg/ml	MIC breakpoints	Interpretive categories
Fluorocytosine	≤4	S≤4; I=8-16; R≥32	S
Amphotericin	2	S≤2; R≥4	S
Fluconazole	≤8	S≤8; SDD=16-32; R≥64	S
Itraconazole[a]	0.5	S≤0.125; SDD=0.25-0.5; R≥1	SDD
Voriconazole	≤0.125	S≤1; S-DD=2; R≥4	S

SDD, susceptible-dose dependent; MIC, minimum inhibitory concentration; S, sensitive; I, intermediate; R, resistant.

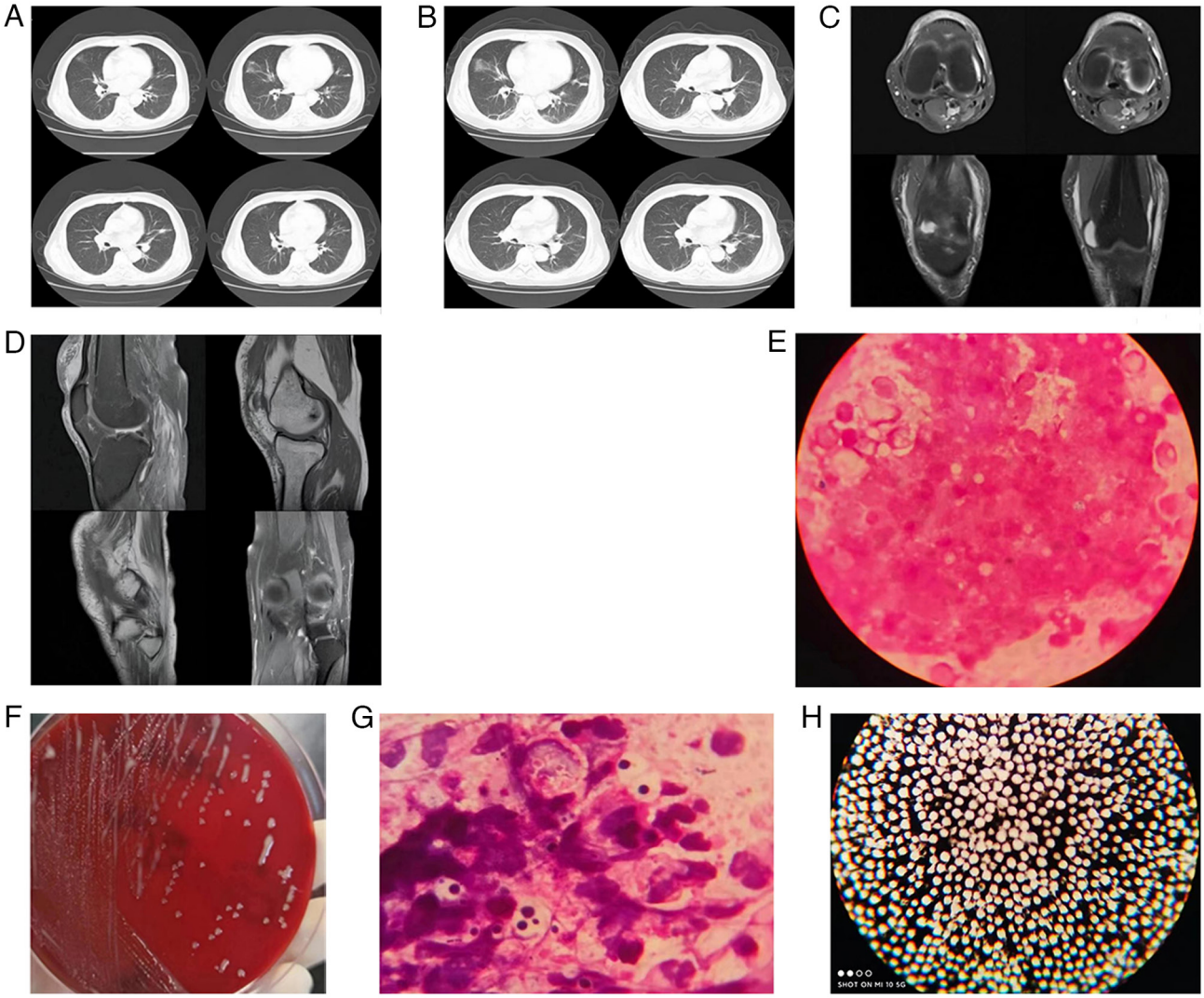

Figure 1. (A) Chest CT in February 2023. (B) Chest CT in April 2023. (C) Left knee joint MRI, transverse scan, in April 2023. (D) Left knee joint MRI, vertical scan, in April 2023. (E) Knee joint pus smear (Gram staining). (F) Columbia blood agar plate at 37˚C and 72 h; colony characteristics: Gray-white, moist. (G) Sputum smear. (H) Pure colony ink staining (light microscopy; magnification, x1,000 in E-H).

exhibited similar symptoms. Clinical practice guidelines for the management of cryptococcal disease suggest that non-meningeal, non-pulmonary cryptococcosis should be treated with fluconazole [400 mg (6 mg/kg) per day orally] for 6-12 months (11,13,14). However, drug selection and duration of therapy also depend on disease severity, response to therapy and host immune status, as studies for specific body sites, except for the lung and CNS, are unavailable (15). In the present case, considering the patient's severe anemia, surgical treatment was deemed unsuitable (16). Therefore, the treatment applied was reasonable and effective. In clinical practice, the specific medication regimen is generally personalized and

mainly determined based on the patient's basic immune status and the presence of related complications (15). Simultaneously, antifungal drugs that can eradicate infections for >6 months are necessary to prevent recurrence (11,13).

In the present case study, the patient had a left knee joint infection; given this infection, along with the pulmonary imaging data and personal medication history, the patient was considered to have a possible bloodstream or lymphatic disseminated infection caused by immune suppression. Due to the patient's severe anemia, surgical treatment was not recommended (16). According to the Expert Consultation on the Diagnosis and Treatment of Cryptococcal Infection (14), the prognosis is favorable after local puncture drainage and strict antifungal treatment. We will continue to monitor the treatment efficacy and recurrence in this patient.

In summary, the clinical and imaging manifestations of cryptococcal infection in the joints lack specificity and are difficult to differentiate from those of other diseases, such as tumors and tuberculosis. Therefore, when clinically suspected, puncture fluid or tissue pathogen testing should be performed as early as possible to avoid misdiagnosis, delayed treatment or spread to the CNS, which may result in serious consequences.

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Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

JM analyzed the study's findings, wrote the manuscript and was the main responsible person for the final approval of the pending version; YZ and JD were involved in data acquisition and analysis; YZN participated in the writing of the manuscript, critically reviewed its microbiological content and made significant contributions to the conception of the study; ZQW participated in data analysis and was responsible for conducting appropriate investigation and resolution of any issues regarding the completeness of any part of the manuscript, as well as jointly deciding with JM and YZN on the final approval of the manuscript for publication; JD and ZQW checked and confirmed the authenticity of any original data reported in the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient and his family for the publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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