CASE REPORT OPEN ACCESS

DOI: 10.5281/zenodo.5495601

# SKELETAL CRYPTOCOCCOSIS IN AN IMMUNOCOMPETENT PERSON: A CASE REPORT & LITERATURE REVIEW

**Ghulam Rabbani Anwar*, Danial Tahir*, Sidra Humayun**, Muhammad Irfan***

***Ayub Medical College/Teaching Hospital Abbottabad-Pakistan, **Rehman Medical College Peshawar-Pakistan**

Cryptococcus neoformans and Cryptococcus gattii can cause a deadly opportunistic infection, called cryptococcosis. Symptomatic cryptococcosis is commonly seen in immunocompromised patients. Cryptococcus is a facultative intracellular fungus, which can exist freely in the environment or inside the soil. Similarly, it can be found inside the phagocytes or freely in body tissues and fluids. The most common sites of infection include the brain and the lungs. It also has a propensity to cause disseminated infections especially in the immunocompromised host, such as HIV patients. Symptomatic infections in people with a competent immune system are rare, but cases of localized cryptococcosis have been reported in the literature. Disseminated and skeletal cryptococcosis are the rarest forms of infection in an immunocompetent host. Here we present a case of a 65-year-old man with a prolonged fever and non-specific symptoms who was diagnosed with skeletal cryptococcosis. He was apparently immunocompetent with negative HIV and other virological markers on repeat testing. His condition was diagnosed too late due to the extremely low probability of cryptococcal infection in an immunocompetent person. A physician must have a high degree of clinical suspicion to catch the disease early in such patients. Prompt initiation of treatment early in the disease course is essential for survival.

**Citation:** Anwar GR, Tahir D, Humayun S, Irfan M. SKELETAL CRYPTOCOCCOSIS IN AN IMMUNOCOMPETENT PERSON: A CASE REPORT & LITERATURE REVIEW. THE STETHO 2021;2(8):104-08

## INTRODUCTION

Cryptococcosis is an opportunistic fungal infection. The most commonly implicated species are Cryptococcus neoformans and Cryptococcus gattii [1]. The fungus generally favors immunocompromised hosts such as HIV seropositive patients or those on immunosuppressive medications. Given the weaker host immunity, cryptococcosis can have a variety of presentations, the most common being meningitis. Although extremely rare, symptomatic cryptococcosis can present in a seemingly immunocompetent host characterized by respiratory and CNS symptoms [2]. In the immunocompetent host, skeletal cryptococcosis is the rarest presentation and can be an isolated infection or part of the disseminated disease [3]. The cryptococcal infection needs prompt diagnosis and treatment regardless of the host immune competence. Without appropriate therapy, cryptococcosis is consistently fatal [4]. Here we present a case of a 65-year-old immunocompetent male who was diagnosed with skeletal cryptococcosis after having a prolonged fever with non-specific systemic symptoms.

## CASE REPORT

A 65-year-old male presented to our outpatient department with a fever of 9 months. The fever started gradually and ranged from high grade to low grade. It was intermittent with relapses and remissions, associated with rigors and chills. It was accompanied by pain in the right hypochondrium and lower extremity, early satiety, and anorexia. He had been treated for malaria and urinary tract infection before the presentation. Apart from this, he had no contributory medical or surgical history. On examination, the patient had pallor to the palms and palpebral mucosa. No oral and cutaneous lesions were noted. Examination of the respiratory system was within normal limits. He had massive splenomegaly (spleen extended up to the umbilicus), hepatomegaly, and axillary and inguinal lymphadenopathy. The rest of the examination was unremarkable.

Based on the initial clinical assessment, our differentials included chronic infection and malignancy. His baseline investigations were requested. Also, blood, urine, and sputum specimens were collected and sent for culture. He was started on empiric antibiotics as per institutional guidelines. His chest x-ray showed no abnormal findings and an ultrasound confirmed the examination findings of hepatosplenomegaly and peripheral lymphadenopathy.

Results of his baseline investigations are given in **Table 1:**

| Investigation | Patient's reading | Investigation | Patient's reading |
|---|---|---|---|
| WBCs (4-11 x $10^3$/uL) | 15.16 | Total Bilirubin (0.1-1.0 mg/dL) | 1.65 |
| % Neutrophils (40-75%) | 74.91 | ALT (10-50 U/L) | 25 |
| % Lymphocytes (20-45%) | 6.9 | ALP (40-129 U/L) | 389 |
| % Eosinophils (0-6%) | 13.47 | Gamma GT (0-30 U/L) | 12.3 |
| Hemoglobin (11.5-17.5 g/dL) | 10.06 | LDH (80 – 35 U/L) | 273 |
| RBCs (4-6 x $10^6$/uL) | 3.62 | | |
| Hematocrit (36-54 %) | 29.03 | PT (Control: 12 seconds) | 17.6 seconds |
| Platelets (150-450 x $10^3$/uL) | 40.44 | INR | 1.4 |
| | | APTT (Control: 28 seconds) | 35.9 seconds |
| Sodium (135-150 mmol/L) | 138 | | |

| | | | |
|---|---|---|---|
| Potassium (3.5-5.1 mmol/L) | 3.82 | Dengue NS1 & Malarial Parasite | Negative |
| | | HBsAg ELISA | Non-reactive |
| Urea (18-45 mg/dL) | 55 | Anti-HCV antibody ELISA | Non-reactive |
| Creatinine (0.64-1.2 mg/dL) | 0.7 | Anti-HIV antibody by ELISA | Non-reactive |

Urinalysis was within normal limits. Repeated blood, urine, and sputum specimens grew no organisms. A contrast-enhanced CT scan was requested which showed hepatosplenomegaly (red asterisk in **Figure 1**) with few enlarged left para-aortic lymph nodes (yellow asterisk in **Figure 2**), the largest measuring 13 mm. There was no evidence of soft tissue masses.

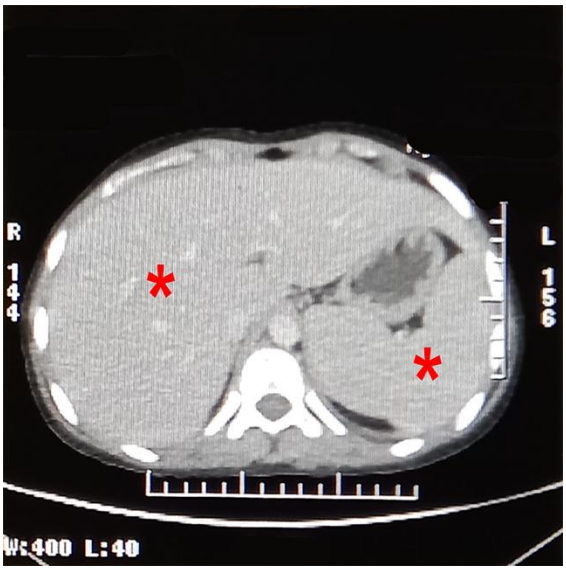


**Figure 1: Hepatosplenomegaly (red asterisks)**

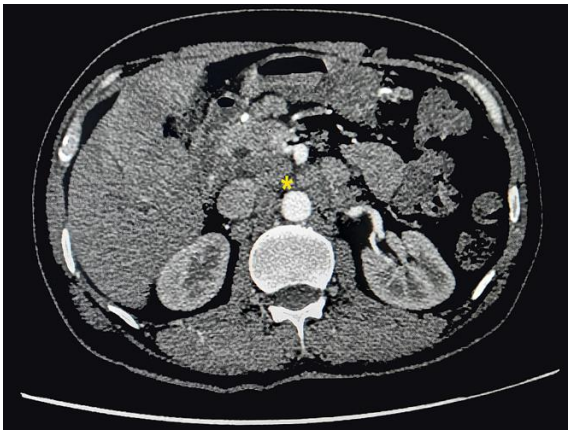

**Figure 2: Para-aortic lymphadenopathy (yellow asterisk)**

A bone marrow sample with trephine biopsy was obtained from the iliac crest and sent for histopathology and culture and sensitivity. Bone marrow study showed a reactive picture without evidence of malignant cells. The culture grew Cryptococcus neoformans after which he was started on amphotericin and fluconazole. He was scheduled for a whole-body MRI, however, on the second day of antifungals, the patient went into septic shock which proved to be fatal despite vigorous resuscitation efforts.

## DISCUSSION

Cryptococcosis is a deadly opportunistic fungal infection. The estimated global mortality of cryptococcosis is more than half a million per year [4]. The majority of the disease is caused by two species of the cryptococcus genus, namely C. neoformans and C. gattii [1] The fungus is found in the excreta of birds (C. neoformans) and some species of trees (C. gattii) and most of the cases have a history of exposure. However, our patient did not report any such exposure. It is inhaled as spores and primarily lodges in the lungs. It can cause an asymptomatic primary infection or remain dormant. The dormant form gets reactivated once the host is immunocompromised. From the lungs, it enters the circulatory system and seeds into various systems such as the central nervous system (CNS) causing meningitis [5]. Symptoms of pulmonary and meningeal cryptococcosis include chest pain, dry cough, fever, headache, nausea, confusion, fatigue, and neck stiffness. While the lungs and the CNS are the primary targets, cryptococcus infection can involve other parts of the body as well [1]. Infection outside the lungs and the CNS is considered disseminated even if confined to a single anatomic site [6]. Sites of dissemination include the skin, musculoskeletal system, the liver, lymph nodes, peritoneum, urogenital tract, and adrenal glands. Vertebrae are the preferred site of osteoarticular infection [6].

Cryptococcus neoformans infection is commonly seen in immunocompromised patients, such as solid organ transplant recipients on prolonged immunosuppressant therapies, HIV patients, patients battling cancers, and patients with diseases of the immune system [4]. C. gattii is associated with infection in the immunocompetent population [4]. Although apparently immunocompetent, these individuals may have genetic defects of the immune system making them susceptible to this infection [7].

Cryptococcosis in the immunocompetent usually remains asymptomatic. However, it can present with respiratory and CNS symptoms. Disseminated cryptococcosis in the immunocompetent is extremely rare, atypical in presentation, and often diagnosed late in the disease course [2]. Skeletal cryptococcosis in immunocompetent patients is even more rarely reported in the literature [3]. The skeletal disease can be a feature of disseminated cryptococcosis or present as primary skeletal infection without the involvement of other tissue [8]. The most likely involved in our patient were bones and the liver and spleen. Skeletal infection can occur due to hematogenous spread from a primary pulmonary source or through direct inoculation via skin [9]. Common skeletal sites of infection include the vertebrae, ribs, tibia, and femur. Presentation is non-specific with the majority of patients complaining of soft tissue swelling, bone pain, and fever [9]. Non-specific lytic lesions are the most frequently observed radiological findings. Mild periosteal reactions may or may not be present [10]. Our patient did not have visible soft tissue swelling but fever and bone pain were

the most bothersome features. Overall, our patient had an extremely unusual condition that could not be diagnosed in time because of the non-specific features and disease course.

## CONCLUSION

Cryptococcus is an opportunistic pathogen usually causing infection in the immunocompromised, such as HIV patients. Although rare, cases of infection in apparently immunocompetent persons have been reported. Skeletal cryptococcosis in the immunocompetent is an unusual presentation of the infection that is not among the top differentials due to its non-specific features. Early diagnosis is crucial to the successful treatment and survival of such patients.

## REFERENCES


1. Akaihe CL, Nweze El.: Epidemiology of Cryptococcus and cryptococcosis in Western Africa. Mycoses. 2021, 64:4-17. 10.1111/myc.13188
2. Adzic-Vukicevic T, Cevik M, Poluga J, Micic J, Rubino S, Paglietti B, Barac A.: An exceptional case report of disseminated cryptococcosis in a hitherto immunocompetent patient. Revista do Instituto de Medicina Tropical de São Paulo. 2020, 62:10.1590/S1678-9946202062003
3. Deus G, Gómez-Zorrilla S, Echeverria-Esnal D, et al.: Osteoarticular Cryptococcosis Successfully Treated with High-Dose Liposomal Amphotericin B Followed by Oral Fluconazole. Infection and Drug Resistance. 2021, 14:719. 10.2147/IDR.S294299
4. Mada PK, Jamil RT, Alam MU.: Cryptococcus. [Updated 2021 Jun 15]. StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL); 2021.
5. May RC, Stone NR, Wiesner DL, Bicanic T, Nielsen K. : Cryptococcus: from environmental saprophyte to global pathogen. Nature Reviews Microbiology. 2016, 14(2):106-17. 10.1038/nrmicro.2015.6
6. Cryptococcus neoformans infection outside the central nervous system. (2019). Accessed: 2021: https://www.uptodate.com/contents/cryptococcus-neoformans-infection-outside-the-central-nervous-system?search=dissemi....
7. Qu J, Zhang X, Lu Y.: Clinical analysis in immunocompetent and immunocompromised patients with pulmonary cryptococcosis in western China. Sci Rep. 2020, 10:10.1038/s41598-020-66094-7
8. Zhou HX, Lu L, Chu T, et al.: Skeletal cryptococcosis from 1977 to 2013. Frontiers in microbiology. 2015, 14:740. 10.3389%2Ffmicb.2014.00740
9. Ramkillawan Y, Dawood H, Ferreira N.: Isolated cryptococcal osteomyelitis in an immune-competent host: a case report. International Journal of Infectious Diseases. 2013, 17(12):e1229-31. 10.1016/j.ijid.2013.04.013
10. Qadir I, Ali F, Malik U Z, umer m.: Isolated cryptococcal osteomyelitis in an immunocompetent patient. J Infect Dev Ctries. 2011, 14(5):669-673.