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Case Report

Cryptococcal Meningitis as a Fatal Complication of Sarcoidosis

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Abstract

Cryptococcosis typically affects patients infected with immunodeficiency virus (HIV), but it may also occur in individuals under immunosuppressive treatment. Since initiation of immunosuppressive therapies, there has been a constant increase of cryptococcosis cases. Therefore, clinicians should always consider cryptococcosis as an important differential diagnosis. In fact, patients who are not suffering from an underlying HIV infection or not being transplant recipients now are at the highest risk group for mortality due to cryptococcosis in resource-available countries, because of delayed diagnosis of the disease.

Keywords: Cryptococcal meningitis; Sarcoidosis; Corticosteroids; Immunosuppressive drugs

Introduction

Cryptococci are encapsulated saprophytic yeasts; Cryptococcus neoformans and Cryptococcus gatti are the principal human pathogens, mainly transmitted by inhalation. These species have been further sub-divided into several genotypes (VNI, VII, VNB, VNIV, and VGI-IV), some of them being associated with a poor clinical prognosis [1-6]. In most cases patients with deficient cell-mediated immunity are affected amongst them HIV infection is considered the main risk factor. In addition, individuals taking immunosuppressive drugs are at higher risk. The overall likelihood of cryptococcal disease does not directly depend on the immunosuppressive agent used, but especially high-dose corticosteroids increase the risk of infection [1,4,5,7]. The most common clinical presentation is Cryptococcal Meningitis (CM) with over one million cases and 600,000 deaths per year [8]. CM most commonly causes subacute headache and confusion. If Intracranial Pressure (ICP) is increased, this may then cause cranial nerve palsies or seizures. Only the minority of patients presents with features of "meningism" (e.g., neck stiffness) [9]. Altered mental state is associated with higher mortality [10-12]. Pulmonary illness may range from asymptomatic colonization to severe pneumonia and formation of cryptococcomas in the lungs.

Case Presentation

A 38-year old male with known sarcoidosis for one year, presented himself at the emergency clinic on December 18th, 2015, with the following symptoms: increasing headache for four days, as well as incremental confusion and nausea since the morning of that day. Additionally, recurrent attacks of fever and a change of personality since two months were reported by the relatives. Meningitis could not have been ruled out completely.

Patient history

Headshot injury 20 years ago with trepanation and a remaining metallic foreign body in situ, resulting in amblyopia of the left eye; sarcoidosis with multiple-organ involvement (since 2014) treated with Azathioprine, at a daily dose of 150 mg, which had to be discontinued due to pancytopenia and fever in October 2015 (odontogenic sepsis) and was replaced by Glucocorticoids (GC) (25 mg daily). A 3-stage deep vein thrombosis in May 2015 was treated with Apixaban 5 mg twice daily. Due to hypercalcaemia (as part of the underlying sarcoidosis), GC were increased to 0.8 mg/kg body weight in December 2015. From October to December 2015 the patient was treated several times by an orthodontia because of multiple tooth extractions.

Social situation

The patient is living on a farm with viniculture, is married and has two little children.

The daily medication at the time of admission comprised

Apixaban 5 mg 1-0-1; Pantoprazole 40 mg 1-0-0; Prednisolone 25 mg 3-0-0; Amoxicillin and Clavulanate 1g 1-1-1 (day 9).

Clinical and laboratory findings

Upon examination the patient was subfebrile with a temp of 37.3°C, his blood pressure was 131/65, and the patient was confused, showed questionable clinical signs of meningism (neck stiffness). Apart from the pre-existing pancytopenia,initial laboratory tests did not show any parameters indicative of infection: CRP 0.76 mg/dl; Procalcitonin (PCT) neg.; kidney function parameters were found increased (creatinine 1.36 mg/dl MDRD GFR 54 ml/min), as well as elevated liver liver enzymes. Pro BNP amounted to 1149 pg/mL (normal – 150 pg/ml) as well as hypoalbuminemia was revealed. Three consecutive

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blood cultures revealed gram positive cocci: staphylococcus hominis with a time to positivity of 15,60 h and a staphylococcus hemolyticus with a time to positivity of 14,40 h, the third blood culture did not reveal any evidence of germs. Urine analysis showed no microbial growth. HIV, HSV, VZV, CMV, Adeno virus, Influenza A, Influenza B, mycoplasma, chlamydia antibodies, Coxsackie-, enter-, measles-, mumps virus and lymphocytic choriomeningitis tested negative.

Clinical course/Progression

Due to the patient's marked confusion a CCT was carried out and did not show any significant findings. Since it was not possible to exclude meningitis and due to the continued state of arousal, the patient was sedated and transferred to an academic neurological department on the same day. The initial EEG showed signs of a diffuse brain function disorder, but neither distinct lesions nor signs of cramps have been seen. Immediately, a virostatical therapy with Acyclovir intravenously as well as an antibiotic therapy with Ampicillin-Sulbactam was implemented. Due to clinical worsening and inconclusive blood cultures results, the antibiotics were changed to Piperacillin-Tazobactam, later supplemented by Linezolid, followed by Ceftriaxone. Apart from the continuing pancytopenia, slightly increased acute phase parameters were seen in the follow-up investigations. The highest CRP value amounted to 2.3 mg/dl, accompanied by an also elevated IL 6 of 42.89 µg/mL; however, PCT at this time was negative. The pre-existing chronic renal insufficiency and the increased liver enzymes (GGT of 491 U/L, alkaline phosphatase of 358 U/L) stayed stable.

Imaging

Initially, an MRI of the brain was considered which turned out to be not feasible due to the known headshot injury with a metal foreign body (cartridge) in situ. The CCT follow-up did not show any change. The chest CT presented the known image of a sarcoidosis II. At that time point, the patient was already in a worsened general state, and in the need of permanent sedation. Considering the complex situation, the steroid dose of 75 mg was tapered to 25 mg upon agreement with the rheumatological unit, as a corticosteroid dependent psychosis was considered. Due to the absent positive virological as well as bacteriological findings in the spinal fluid the virostatical therapy was discontinued. The number of granulocytic cells in the liquor was elevated, and the lab reported suspicious cryptococci-like structures in the liquor/spinal fluid. A second lumbar puncture confirmed this suspicion. As a consequence the patient was then urgently referred to the department of infectiology of the Vienna General Hospital. Therapy with liposomal Amphotericin B 300 mg as well as Flucytosine 2.5 g, later on replaced by Fluconazole 800 mg was initiated. However, despite every effort, the patient, unfortunately, died 3 months later from Cryptococcus meningitis.

Discussion

This specific patient posed a significant diagnostic challenge, emphasizing that Cryptococcosis is grossly underrecognized. Cryptococcosis can present as a chronic, acute to subacute pulmonary, systemic or meningeal disease. Mostly, the presentation is nonspecific (low grade fever, headache, confusion, pulmonary illness and signs of meningitis), however, there may be no diagnostic symptoms at all present. Pigeons and red river gum trees harbor the Cryptococcus in nature. Our patient, a farmer, might have been infected by pigeons' feces. In this case, the main risk factor for infection could have been the high dose - corticosteroid therapy as well as sarcoidosis itself, because of the underlying T-cell defect [13].

Cryptococcosis can be regarded an important infectious disease occurring all over the world. The affected patients' majority also suffers from impaired cell-mediated immunity and/or is taking immunosuppressive drugs. In high income countries (HICs) cryptococcosis in HIV negative persons is associated with a higher mortality rate than in HIV positive individuals. As the germ is not basically suspected in HIV negative patients, this may result in a prolonged latency in diagnosis. In all patients on immunosuppressive therapy and presenting with unclear specific infectious symptoms, cryptococcosis should be seriously considered as a differential diagnosis.

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