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Primary Cutaneous Cryptococcosis in an Eight-year-old Immunocompetent Child: How to Treat?

Primäre kutane Kryptokokkose bei einem 8-jährigen immungesunden Jungen: Wie behandeln?

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Key words

- cryptococcosis
- cryptococcus neoformans var. neoformans
- skin involvement
- immunocompetence
- capsule
- treatment options

Schlüsselwörter

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- Hautbeteiligung
- Immunokompetenz
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Bibliography

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Abstract

Here we report on a case of primary cryptococcal skin infection in an immunocompetent 8-year-old boy. The infection first manifested itself as a subcutaneous abscess around the proximal joint of his right thumb after a minor injury from contact with a thorny shrub. After surgical incision and drainage was performed, *Cryptococcus neoformans* var. *neoformans* was the only pathogen cultured from the lesion. An agglutination test for the capsular antigen in serum displayed negative results and the immunological work-up revealed no underlying immunodeficiency. A “watch and wait” strategy – one without systemic antifungal treatment – was adopted and this resulted in uneventful healing. In summary, primary cryptococcal skin infections in immunocompetent hosts may be managed successfully by surgical treatment in combination with careful clinical follow-up. This approach may help avoid unnecessary antimicrobial treatments.

Zusammenfassung

Wir berichten über den Fall einer primären Hautinfektion durch Kryptokokken bei einem 8-jährigen immunkompetenten Jungen. Nach einer Verletzung in einem Dornengestrüpp manifestierte sich diese als subkutaner Abszess des rechten palmaren Daumenballens. Nach chirurgischer Inzision und Drainage konnte *Cryptococcus neoformans* var. *neoformans* als einziger Krankheitserreger aus dem Drainagesekret kultiviert werden. Ein Agglutinationstest für das Kapsel-Antigen im Serum blieb negativ wie auch Untersuchungen hinsichtlich einer systemischen Infektion oder einer zugrundeliegenden Immundefizienz. Wir verfolgten daraufhin eine abwartende („wait and watch“-)Strategie bei primärer kutaner Kryptokokkose ohne systemische antimykotische Therapie. Diese führte zur vollständigen Genesung. Eine primäre kutane Kryptokokkose beim immungesunden Patient kann durch alleinige chirurgische Therapie mit anschließenden engmaschigen klinischen Verlaufskontrollen erfolgreich behandelt werden – ein Vorgehen, das hilft, unnötige antimikrobielle Behandlungen zu vermeiden.

Introduction

Cryptococcosis is an opportunistic infection caused by yeasts belonging to the genus *Cryptococcus* [5], which is an encapsulated fungal pathogen of 4–8 μm in diameter. Among immunocompromised, often HIV-positive, adult patients in Africa it is the most common pathogen causing meningitis [5]. Infections in humans mainly are caused by 2 cryptococcal species. The first, *Cryptococcus neoformans*, includes the varieties *grubii* (serotype A), *neoformans* (serotype D) and hybrids of serotype A and D [16]; it can be found in avian excrements, especially from pigeons [22]. The second species, *Cryptococcus gattii* (serotype

B and C), more commonly is found in tropical and subtropical areas, and is associated with the presence of Eucalyptus or fir trees [2,23].

In most cases, infection occurs via inhalation of fungal cells. Therefore, disease onset can involve the lung, with symptoms including fever, cough and signs of pleuritis. Secondary stages result from lymphatic or hematogenous spread, which may lead to meningoencephalitis, meningitis, erythematous papulo-pustulous skin lesions, osteomyelitis, arthritis or chorioretinitis. Rare disease manifestations include endocarditis, renal abscesses and adrenocortical insufficiency [3]. For treatment of cryptococcal infections in immunocompromised patients, intravenous

amphotericin B combined with flucytosine, followed by oral fluconazole are recommended [1, 12].

While infections due to *C. gattii* in endemic areas are common among immunocompetent patients, infections as a result of *C. neoformans* remain rare in these patients [23]. Cutaneous cryptococcal infections can be found in immunocompetent as well as in immunosuppressed patients. However, in the latter, cryptococcosis of the skin most frequently is due to secondary dissemination. In an immunocompetent patient traumatic inoculation of the infectious agent may cause a localized cutaneous infection, which is a separate clinical entity, named primary cutaneous cryptococcosis (PCC) [6, 21, 24]. Treatment regimens for PCC range from diverse anti-fungal medications to surgery alone [17, 21, 24]. Most patients with PCC show full recovery independent of the treatment administered.

Here, we report on an 8-year-old boy without underlying disease, who suffered from an infection with *C. neoformans* (serotype D) in his right thumb. After surgical incision and drainage, he recovered fully without any additional antifungal treatment. This outcome suggests that antimicrobial therapy may not be necessary in immunocompetent patients with PCC.

Case report

An 8-year-old boy developed swelling, warmth and pain around the proximal joint of his right thumb after a minor injury that was caused by contact with a thorny shrub a week earlier. As swelling progressed, the patient began to have difficulties moving his thumb. A 5-day course of oral cefuroxime had no effect. 9 days after the onset of symptoms, the patient was referred to the surgical outpatient department of Freiburg University Medical Center. Examination revealed a fluctuating, but not erythematous swelling without localized lymphadenopathy. An X-ray of the finger showed no bone or joint abnormalities. Surgical incision revealed an abscess, which was drained (◻ Fig. 1). Due to a suspected pyogenic bacterial infection, oral cefuroxime therapy was continued. After 2 days, the drainage culture grew *Cryptococcus neoformans* as the only pathogen. The pathogen was identified on a species level by matrix assisted laser desorption/ionization and time-of-flight mass spectrometer – MALDI-TOF. The isolate was subtyped as serotype D using a microarray and gene probes based on the IGS region of rDNA of pathogenic cryptococcal species [8], that has been developed in cooperation with Chipron GmbH, Berlin. Subsequently, the patient was re-



Fig. 1 Intraoperative presentation of the primary cutaneous lesion.

ferred to our pediatric infectious diseases outpatient clinic. A detailed medical history and clinical examination revealed no other infection sites, and in particular, no respiratory or neurological symptoms. The family did not recall any direct contact with birds (especially pigeons), and had not travelled outside of Europe. Stool frequency and quality were normal. The family history was negative for autoimmune or immunodeficiency diseases and the boy had no history of frequent or unusual infections in the past. Furthermore, he had never received steroids for treatment, nor had he been hospitalized for any medical problem.

All laboratory results were normal (i.e., leukocyte count, differential blood count, liver and kidney function tests, immune globulins IgM, IgA, IgG, complement levels, total CD4 and CD8 cell number and CD4/CD8 ratio). A cryptococcal antigen test in serum was negative, as was the serology for HIV, hepatitis B and C. X-rays of the chest and the paranasal sinuses, as well as an abdominal ultrasound, did not show any abnormalities.

The patient was treated by surgery only. On the basis of the negative cryptococcal antigen test, and because there was no hint for an underlying immunodeficiency, systemic antifungal therapy was not prescribed. One month after the surgical incision, the child was healthy and had normal wound healing at the incision site. Additional control visits at 4 and 6 months revealed no signs of ongoing infection, and the serum cryptococcal antigen continued to remain negative.

Discussion

In a majority of cases, cryptococcosis is acquired via inhalation of fungal cells. Inside the alveolar spaces of the lung, the spores develop into yeast form and the process of capsulation starts. The polysaccharide capsule is a critical virulence factor protecting the cryptococci from phagocytosis and complement deposition [20, 25]. In immunocompetent patients, cryptococcal infections are controlled by a Th1-cell response with CD4⁺ and CD8⁺ T-cell recruitment accompanied by the production of inflammatory mediators. Following this, the pathogen is either eradicated or else contained in granulomas [13, 23, 25]. However, in immunocompromised patients, especially those with a T-cell defect, the infection may disseminate and spread to CNS, bones, skin and other organs. Therefore, all patients with cryptococcosis should undergo a basic immunological work-up including lymphocyte subsets (i.e. CD4⁺ and CD8⁺ T-cells as well as CD4⁺/CD8⁺ ratio), functional testing of the complement system (e.g. CH-50) and an HIV antibody test. Other potential risk factors are pregnancy, organ transplantation, lymphoma treated with cytotoxic drugs, and treatment with high doses of corticosteroids, such as those used in systemic lupus erythematosus or pemphigus. Other diseases that pose a risk for progressive cryptococcosis are sarcoidosis, hyper-immune globulin (Ig) M and IgE syndromes, CD4-positive lymphopenia not caused by HIV and other immunological defects involving interleukins or interferon-gamma pathways [23].

Cutaneous lesions like cellulitis, abscesses, or herpes-like lesions are present in 10–20% of cases with systemic cryptococcosis [24, 26]. By contrast, PCC is a particularly rare disorder that usually originates from direct inoculation of fungal cells into the skin. In the case of our patient, we presume that he acquired the disease through a minor injury caused by a thorny shrub with which he had come into contact. Whether the shrub area was

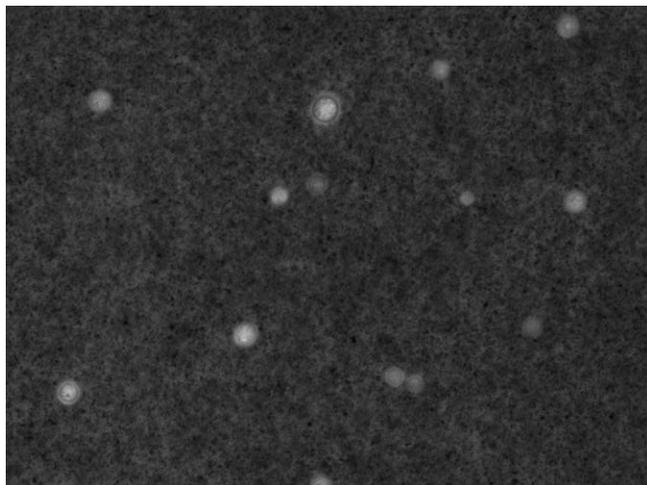


Fig. 2 Microscopy of the cultured *Cryptococcus neoformans* var. *neoformans* in Indian ink stain.

contaminated with pigeon droppings could not be verified. Interestingly, in the current case, the cryptococcal isolate expressed only a very thin capsule (as determined by Indian ink staining; ◉ **Fig. 2**). The presence of either plasma [15] or of high levels of CO₂ and HCO₃ in the alveolar environment [7,9] may promote capsule development. Nevertheless, the role of capsule thickness in pathogenesis is controversial. Several studies have found that the capsule's thickness is not necessarily directly correlated to its virulence [4, 7, 10, 27]. Additionally, acapsular cryptococcal strains have been able to be isolated from patients with systemic infections [29]. Capsule-promoting factors, such as CO₂, HCO₃ and plasma, probably are lacking in PCC [9]. Therefore, our case may support the hypothesis that primary infections outside the lung are not in fact related to a virulent, highly encapsulated cryptococcal phenotype.

Only a small number of primary cutaneous cryptococcosis cases with secondary systemic dissemination have been reported in immunocompromised hosts [28, 30]. However, in several cases it remains unclear whether the cutaneous lesions were the primary focus of infection, or whether they were secondary to dissemination, i. e., originating from a yet-to-be-detected infection. Therefore, in patients with PCC, an underlying immunosuppression and disseminated disease need to be excluded before a treatment plan is made.

The patient's isolate was identified as *C. neoformans* var. *neoformans*, which is an equivalent to serotype D. This serotype most frequently has been found in PCC [19,21], including reports from Germany [11, 14]. The slightly lower thermotolerance of *C. neoformans* var. *neoformans* isolates as compared to *C. neoformans* var. *grubii* could be another factor impacting the lower pathogenicity of *C. neoformans* var. *neoformans* [18].

Currently, there is no standard treatment for immunocompetent patients suffering from skin infection with *C. neoformans* [23]. The only case reports that have been published focus on treatment options in PCC in immunocompetent patients [21,24]. Among these, treatment regimens are highly variable, ranging from no treatment to surgical incision with or without antimycotic therapy. Controlled studies on different treatments and/or evidence-based guidelines currently are not available [23]. Accordingly, it remains unclear whether systemic antifungal treatment may be necessary in immunocompetent patients when

disease is localized. However, irrespective of the specific treatment option chosen, the outcome has been excellent in all reported cases [6,21]. In accordance with these observations, our patient showed complete local healing 4 weeks after surgical incision and local antiseptic treatment. Clinical follow-up at 1, 4 and 6 months after infection onset showed no signs of systemic spread of the yeast. Cryptococcal antigen tests in the serum consistently were negative. Despite the favorable outcome in all reported PCC cases, a thorough investigation remains necessary in order to determine the extent of the infection, as well as to rule out immunodeficiency. This recommendation is supported by Neville's report of 2 cases in which cutaneous cryptococcosis was shown to be the first sign of an underlying immunodeficiency. However, in these 2 cases, it remained unclear whether the skin was the primary site of infection, or whether skin involvement was just the first sign of a systemic cryptococcosis [21].

Based upon our own case, along with a review of related reports in the literature, we conclude that immunocompetent patients with a PCC and a negative cryptococcal antigen test in serum may not need systemic antifungal treatment. In the event of an abscess, the initial therapy should be surgical. Moreover, we strongly recommend a basic diagnostic work-up in order to rule out any underlying immunodeficiency. Meanwhile – while awaiting laboratory results – it may be valuable to consider a probative antifungal treatment, especially if or when an underlying disease or immunological defect is suspected. Follow-up controls also may be prudent in order to exclude systemic spread. In addition to the clinical evaluation, cryptococcal antigen testing in serum may be helpful in excluding secondary dissemination, although the presumed impaired formation of the polysaccharide capsule outside the alveolar environment and/or the CNS may impede the serological detection of the capsular antigen in cryptococcosis without lung involvement. Furthermore, acapsular cryptococci occasionally may cause systemic infection [29]. For these reasons, neither serology nor any other laboratory tests can be sensitive enough to replace repeat and thorough physical examinations in PCC.

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Contributor's Statement

▼ DL, PH and MH drafted the manuscript, and all coauthors carefully revised the manuscript. SMG and DW delivered patient care and initiated microbiological and immunological tests. JH and KT performed microbiological culture and identification and gave advice on microbiological issues.

Conflict of interest: The authors have no conflict of interest to disclose.

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