Primary Cutaneous Cryptococcosis and Secondary Antigenemia in a Patient with Long-Term Corticosteroid Therapy

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Abstract

We report a case of a 71-year-old male who developed severe cellulitis of his right forearm and hand after he had an accidental injury from the sharp edge of a metal plate of a birdhouse. The patient suffers from chronic asthma and has been treated with systemic corticosteroids for years. Culture of aspirates from two sites of the wound area revealed growth of *Cryptococcus neoformans* in one and *Acinetobacter lwoffii* in the other. After combined treatment including antibiotics, antifungal therapy with fluconazole 400 mg/d and surgical debridement followed by a mesh graft, the patient achieved complete healing of the wound. Five months after the infection, the patient was still positive for cryptococcal antigen at a titer of 1:64 despite oral treatment with fluconazole 50 mg/d, and maintenance therapy with fluconazole 200 mg/d was recommended for 6 months, or longer depending on further results. The clinical and microbiological characteristics of this patient as well as therapeutical and epidemiological aspects of primary cutaneous cryptococcosis (PCC) are discussed.

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Introduction

Cryptococcus neoformans is an opportunistic encapsulated yeast and the most frequent *Cryptococcus* species found as a human pathogen. The capsular serotypes A (var. *grubii*), D (var. *neoformans*) and AD can be distinguished from *C. gattii* with the serotypes B and C. *C. gattii* is mostly restricted to tropical and subtropical areas while *C. neoformans* has been isolated from decaying wood, fruits, vegetables, hay, and dust [1-3]. Bird droppings, especially of pigeons are an important source for cryptococcal infection [4, 5]. Other wild and pet birds like canaries and parrots also represent a potential source of infection [6]. More recently, *C. neoformans* has been isolated from the litter of starling nests [7]. The infection occurs mainly in immunosuppressed humans, e.g. HIV-infected patients or patients with chronic immunosuppressive medical treatment. However, there are also some reports of cryptococcosis in immunocompetent individuals [8, 9]. The infection is usually transmitted via airborne organisms and initially affects the respiratory tract. From there, dissemination can occur to other organs like the central nervous system, the urinary tract, and the skeleton. Approximately 15% of the patients with systemic dissemination show secondary involvement of the skin. In contrast, primary cutaneous cryptococcosis (PCC) without systemic infection after inoculation of infectious matter has turned out to be a distinct clinical entity [10].

Case Report

A 71-year-old farmer presented with swelling and erythema of his right hand and arm, fever of 39 °C and severe pain. The hand and forearm exhibited blistering and necrosis (Figure 1A). Upon general examination, he revealed a regional lymphadenopathy at the right axilla, but no involvement of other skin sites or organs. Inflammatory markers were increased (CRP 212 mg/l, blood sedimentation rate 16/40 mm after 1 h/2 h). The patient suffers from chronic asthmatic disease and has been treated with triamcinolone acetonide 8 mg/d p.o. for years. Ten days before presentation in our clinic, he had an accidental injury caused by a metal plate of a birdhouse, resulting in a banal graze of his right hand. In the birdhouse usually wild birds like finches and tits were fed. After 1 week of apparently normal wound healing (the wound was covered by a crust), he disseminated moldy hay with his unprotected hands. The next day the first signs of inflammation started at the site of the former lesion, and 2 days later the patient presented himself in our clinic.

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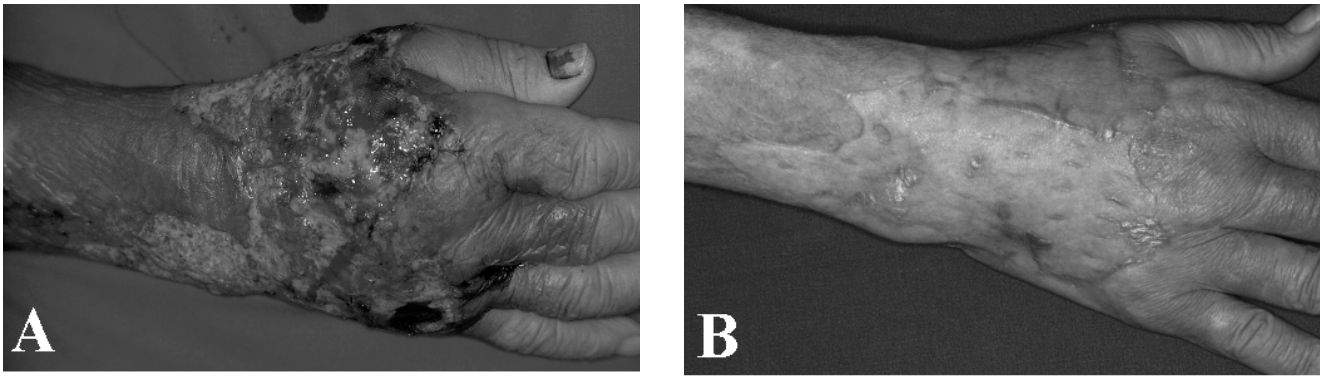

Figure 1. Primary cutaneous cryptococcosis of the right hand resembling a necrotizing fasciitis at the time point of initial presentation (**A**) and 3 months after surgical debridement and closure of the skin defect with a mesh graft (**B**).

Aspirates from two sites of the wound area including one blister, and blood cultures (20 ml) were taken. The patient was started on intravenous piperacillin 3 × 4 g/d, sulbactam 3 × 1 g/d and clindamycin 3 × 600 mg/d for the empirical treatment of bacterial cellulitis. The CRP value slightly decreased the following days but did not normalize, and the clinical symptoms did not improve. Unfortunately, nuclear magnetic resonance imaging could not be performed because of a long-standing metallic implant in the right scaphoid bone of the patient. Computer tomographic imaging showed an edema of both the subcutis and the muscles of the hand and the forearm, but no involvement of the bones. However, no necrosis could be detected in the deeper compartments, therefore a necrotizing fasciitis was excluded.

Microbiology Findings

Initial microscopy from aspirate 1 demonstrated gram-negative rods, later identified as *Acinetobacter lwoffii*, sensitive to the administered antibiotics. From aspirate 2, colonies of mucoid growth were noted after 48 h on chocolate agar. Microscopy of the colonies demonstrated budding yeast cells with a capsule. *Cryptococcus neoformans* was suspected and subsequently confirmed by a positive latex agglutination test, biochemical profile (ID-YST card, VITEK II, bioMérieux, Inc., Durham, USA), and sequencing of 18S rDNA after PCR using universal primers [11]. The MIC for fluconazole was 2 mg/l (Etest®, AB BIODISK, Solna, Sweden). PCR fingerprinting with the single primer $(GACA)_4$ revealed a genotype VND1, which belongs to the serotype D [12]. No bacteria were detectable in the second aspirate, neither by culture nor by PCR using two sets of broad-range primers hybridizing to conserved regions within the 16S rDNA gene of bacterial organisms [13, 14].

Antimycotic therapy with intravenous fluconazole 400 mg/d was then applied from day 7 on for 11 days in addition to the antibiotics. From that time on, the patient improved remarkably and the inflammation parameters decreased continuously. The antifungal treatment with 400 mg/d fluconazole was continued orally for another 14 days. The corticosteroid administration was also continued. Intravenous piperacillin 3 × 4 g/d and sulbactam 3 × 1 g/d were administered for 16 d in total as a therapy of choice for *A. lwoffii*. In addition, intravenous clindamycin 3 × 600 mg/d was given for 16 d for empirical therapy. After 4 weeks from hospitalization, surgical debridement of the necrotic areas on the right hand and forearm was performed and the skin defect was closed with a mesh graft (Figure 1B). After his discharge, the patient continued with fluconazole 50 mg/d. From serum samples taken 6 weeks and 5 months after the trauma, cryptococcal antigen at a titer of 1:64 was detectable (Latex-Crypto® Immunomycologics, Norman, OK, USA). Therefore, a maintenance therapy with fluconazole 200 mg/d was strongly recommended for 6 months or longer, depending on further results.

Discussion

For a long time the entity of PCC was discussed controversially, because a primary skin infection might be difficult to separate from a single focused skin manifestation due to a systemic cryptococcosis. However, during the past years, it became obvious that local cutaneous infections by *C. neoformans* may occur without any simultaneous systemic infection [15–18]. *Neuville* et al. [10] have proposed criteria to distinguish primary and secondary cutaneous cryptococcosis. According to them, our patient fulfills the following criteria for PCC: solitary site of the skin lesion at an unclothed area (limb), presentation as a whitlow/cellulitis, regional lymphadenopathy, history of a prior injury and occurrence of the following cryptococcosis at the site of the former lesion, exposure to a possible contaminated source (avian faeces or hay), living in a rural area, identification of serotype D, and no signs of extracutaneous manifestation of cryptococcosis. Both the birdhouse (contaminated with avian faeces) and the hay represent possible sources of infection for our patient; however, the beginning of inflammation made us favor the birdhouse (about 1 week incubation period) rather than the hay (about 1 day incubation period) [18]. Environmental studies to isolate *C. neoformans* from the birdhouse were negative; unfortunately the suspicious source of the cryptococcosis had already been cleaned.

PCC can develop independently of the immunocompetence of the host [18] and is preferentially found in elderly patients [8]. The long-term usage of systemic corticosteroids, the most common risk factor for immunosuppression in patients with cutaneous cryptococcosis [18], probably

was responsible for the rapid and severe clinical course resembling necrotizing fasciitis in our patient. As already shown, *C. neoformans* by itself is capable of causing a necrotizing fasciitis [19, 20]. However, computer tomographic imaging demonstrating intact fasciae, as well as a biopsy excluded this entity. *A. lwoffii* also might have contributed to the course of the infection being a common inhabitant of the skin; however, wound infections are rare and the clinical course showing no remarkable improvement until administration of antifungal medication does not favor this possibility. In our patient, *A. lwoffii* was present in aspirate 1 in sufficient number to be detected by microscopy; however, culture and PCR were negative in aspirate 2. Therefore, colonization or even contamination cannot fully be excluded.

Antigen detection in the serum is not a typical feature of PCC according to the review of *Neuville* et al. [10]. However, in this retrospective study seven of the 28 patients with PCC revealed positive results of serum antigen tests. Positive antigen titers in PCC patients have also been reported from other authors [9, 15, 21]. In a first serological screening 6 weeks after the putative day of infection, *C. neoformans* antigen was detectable in our patient, indicating antigenemia due to the large infected area rather than fungemia. Systemic cryptococcosis with dissemination into the skin is very unlikely because of the patient`s antecedent trauma at the identical site of the cutaneous infection. Our patient did not show any obvious signs of infection of other organs during his hospitalization and at the 6-month follow-up. Some authors excluded patients with positive serum antigen titer from the diagnosis of PCC [18]. However, our case report indicates that secondary antigenemia might not be unusual in a subset of PCC patients. Therefore, detection of antigen in the serum should not be considered as an exclusion criterion for PCC if the other criteria are fulfilled (especially if there is a history of a former injury at the site of the cutaneous infection). Further studies have to define risk factors for patients leading to a secondary antigenemia. The possible risk for a recurrence or even a dissemination of the cryptococcosis in these patients has to be clarified. Thus, 5 months after the infection, our patient was still positive for cryptococcal antigen with a titer of 1:64, and maintenance therapy with fluconazole 200 mg/d was recommended for 6 months or longer, pending further results. If this antigen titer persists, an inapparent colonization of the metal implant in the right scaphoid bone or organs like the prostate [22], which might serve as a reservoir for a future relapse, should be excluded.

Interestingly enough, the patient's isolate belongs to the genotype VND1, an equivalent of a subtype of serotype D. Genotyping can discriminate more accurately the different subtypes of *C. neoformans* than serotyping, and a genotype-based nomenclature has previously been suggested [12]. The serotype D turned out to be most prevalent in several reports on cutaneous cryptococcosis [10, 17, 23]. In the French study group even 71% of the *C. neoformans* isolates from patients with primary cutaneous manifestation belonged to serotype D [10]. This might correlate with the slightly lower thermotolerance in *C. neoformans* serotype D isolates compared to serotype A isolates [24].

Our patient received treatment with fluconazole 400 mg/d for 25 days. Fluconazole is the preferred antifungal drug for cryptococcosis. In the retrospective study of the French group the median duration of antifungal therapy was 32 days [10]. Four immunocompromised patients of this study received lifelong maintenance therapy with fluconazole (200–400 mg/d). Apart from fluconazole, the use of amphotericin B, itraconazole, ketoconazole, and 5-fluorocytosine has been reported for the treatment of PCC. As in the present case, the majority of the patients need additional surgical treatment [10].

The presented case demonstrates that a posttraumatic cutaneous cryptococcosis due to inoculation of contaminated material (avian excrements, hay, soil, etc.) may have a foudroyant course of infection in patients under long-term therapy with corticosteroids. As the number of immunocompromised persons is steadily increasing (AIDS, organ transplantation, systemic steroid treatment, etc.), this problem has some epidemiologic relevance. Patients should be aware of unprotected contact or handling of bird's excrements or gardening. In addition, PCC can be complicated by secondary antigenemia, requiring antimycotic maintenance therapy and follow-up controls of the serum antigen titer. PCC should be included into the differential diagnosis of patients presenting with erysipelas or cellulitis of the limbs, responding weakly to antibiotics, and a history of an antecedent trauma with simultaneous contact to possibly contaminated material.

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