Surgical Management of Primary Cutaneous Cryptococcosis after Failed Medical Management

Justin Leigh McKinney • Dean Cerio • Cyrus Loghmanee • Paulo Pinho •
Rui Gomes • Mili Patel • Janeen Miraglia • Manal Youssef-Bessler •
Jonathan Zippin • Harini Rao

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Introduction

Cryptococcus neoformans is an encapsulated yeast responsible for disseminated meningitis in immunocompromised hosts. It is a saprophyte in nature and pigeons are the primary host responsible for transmitting of the fungus [1]. Although the genus *Cryptococcus* contains more than 50 species, four main serotypes exist; Serotype A and D (*var neoformans*) and B and C (*var gattii*). *C. neoformans* has been isolated from decaying wood or fruits and bird droppings, while *C. gattii* is found in decomposing wood and from the eucalyptus tree in tropical and subtropical areas [2]. *C. neoformans* (*var neoformans*) causes most cryptococcal infections in immunocompromised patients and *C. neoformans* (*var gattii*), which is considered the more virulent form, affects both immunocompetent and immunosuppressed patients.

C. neoformans is transmitted through the respiratory route. Following inhalation, the yeast spores are deposited in the alveoli and in an immunocompetent host the organism

develops a polysaccharide coat that interferes with phagocyte recognition and opsonization. In an immunocompromised host with cell mediated immune deficiency, dissemination occurs, with the central nervous system, kidneys, bone and skin being among the most commonly affected organ systems [1]. However, there have been reports of cutaneous cryptococcal infection without dissemination, termed Primary Cutaneous Cryptococcosis. [1–6]

Case Presentation

We present the case of an 87 year old male with a past medical history significant for renal insufficiency with creatinine clearance of 30–35 % and rheumatoid arthritis, for which he was treated with prednisone and adalimumab, who presented with an erythematous lesion on the dorsum of his left hand. Initial labs during the first visit revealed a WBC of 8.8 with 80.3 % neutrophils, a platelet count of 316, and ESR of 17. Blood and wound cultures were negative as also was serum cryptococcal antigen. Physical examination revealed an erythematous lesion with central induration and swelling; it was located proximal to the metacarpophalangeal joints and extended to the distal wrist. Clinically, the only other finding was axillary lymphadenopathy that was freely mobile. With minimal resolution of symptoms and multiple courses of antibiotics, the patient was referred for biopsy of the lesion. The histologic specimen revealed a “dermal inflammatory infiltrate consisting of histiocytes, neutrophils and lymphocytes with large granulomas extending into the subcutis. Gram stains were negative for microorganisms. PAS stain reveals numerous yeast forms, some of which exhibited narrow based budding and are surrounded by clear “halo” like spaces”. Fungal cultures revealed *C. neoformans*. Oral fluconazole (400 mg first dose and after 200 mg per day) was given to the patient over a 6 months period. He showed significant improvement, with reduction of hand lesion erythema and

J. L. McKinney (✉)
St. Josephs Regional Medical Center, Paterson, NJ, USA
e-mail: jmckinne@nyit.edu

D. Cerio • C. Loghmanee
East Coast Advanced Plastic Surgery, Englewood, NJ, USA

P. Pinho • R. Gomes • M. Patel • J. Miraglia
PASE Healthcare PC, Millburn, NJ, USA

M. Youssef-Bessler
Infectious Disease Center of NJ, Livingston, NJ, USA

J. Zippin
Weill Cornell Medical Center, New York, NY, USA

H. Rao
Yale University, New Haven, CT, USA

lymphadenopathy. However, due to incomplete resolution and eventual reversal back to its original condition, he was referred to the office of a plastic surgeon for further evaluation and possible excision.

The decision was made to take the patient to the operating room for excision of the mass. After circumferential dissection to normal appearing tissue, the mass was sharply dissected off the peritenon of the extensor tendon apparatus. Due to the size of the resulting defect following excision, a dorsal skin advancement flap was required to close the resultant defect. Both the advancement flap and remaining skin were closed with a 4-0 nylon horizontal mattress suture.

Final Pathology revealed a piece of fibro-fatty tissue measuring $5.5 \times 5 \times 0.6$ cm with granulomatous inflammation and microabscess formation, extending to the inked surgical margin (Fig. 1 Hand Mass Following Excision). There were fungal yeast forms noted within the necrotizing granulomas, which, were Grocott's Methenamine Silver (+), Periodic acid-Schiff (–), Mucin (+), Acid-Fast Bacillus (–); final culture subsequently revealed *Cryptococcus*.

Two months after the surgical excision, the lesion had completely healed and the patient denied any pain and had a normal full range of motion. Oral fluconazole (200 mg per day), was given to the patient for an additional 6 months.

Discussion

PCC is defined in the literature as the identification of *C. neoformans* in the skin biopsy specimen by culture, clinical criteria (chancreform lesion) and histologic criteria (lesion confined to the skin or subcutis) in parallel with the absence of dissemination [3, 6]. In 2003, Neuville, et al., reviewed cryptococcal cases associated with skin lesions from the French National Registry. They retrospectively reviewed cases reported to the National Reference Center for Mycoses (NRCM) from 1985 to 2000. Of 1974 cases of cryptococcosis reported during the study period, 108 had a positive skin culture while 28 were considered to be PCC and subsequently analyzed [3]. The analysis showed additional evidence of this

distinct clinical entity and that some distinct clinical parameters could be used to distinguish PCC from secondary cutaneous cryptococcus infections. According the Neuville *et al*, PCC occurred in male to female patients in a 1:1 ratio, the patients tended to be immunocompetent and reside in suburban areas. The skin lesions were more often solitary and confined to an unclothed area. Cellulitis, ulceration, and whitlow were the most common clinical features of PCC.

Christianson et al. [6] reviewed 73 cases of patients with PCC and investigated their clinical presentation and risk factors. According to his definition, a PCC case required evidence of cutaneous inflammation and identification of *C. neoformans* and absence of disseminated infection, validated by culture or latex agglutination in serum or cerebrospinal fluid. The mean age of patients in his review was 53.1 years (± 22.8 years) among immunocompetent patients and 59.6 years (± 18.0 years) among immunosuppressed ones. The lesions were typically painful but patients were rarely febrile or systemically ill. The lesions were protean in nature, ranging from acneiform lesions to vesicles resembling Herpes Simplex. Some presented as a cellulitis, with a presentation very similar to bacterial cellulitis. The most common risk factor identified was corticosteroid usage; nearly half of the patients in his study group who used steroids developed PCC. Less common risk factors were the use of immunosuppressive drugs after solid organ transplantation, diabetes mellitus and T-cell deficiency [2, 6].

In patients with suspected PCC, the diagnosis of cryptococcosis should be confirmed with biopsy and tissue culture [4], while the search for disseminated disease is mandatory [5]. The exclusion of systemic disease is based on a good physical examination, cryptococcal antigen detection in serum and or in CSF, and HIV testing [4]. Treatment of skin lesions consists of topical application of anti-inflammatories agents and anti-fungals [1].

In patients with nonmeningeal cryptococcosis, treatment regimens are similar to those of disseminated or CNS disease. Drug selection depends on severity of disease, response to therapy, and the host's immune status because there are no substantial specific studies for individual body sites except for the lung and CNS [7]. Induction regimens consisting of Amphotericin B are recommended but in patients with renal dysfunction it should be used with caution because significant nephrotoxicity can occur. Fluconazole alone may be used at a dosage of 800 to 1200 mg per day orally for 10–12 weeks per the current recommendations. In patients with creatinine clearance less than 30 ml/min/m², significant hepatotoxicity is a consideration, and a lower dosage to minimize such should be used. Recommendations for maintenance therapy consist of fluconazole 200 mg orally per day [7]. The treatment is typically for 3–6 months in duration. In patients who fail initial treatment, excision of the lesion may be necessary.

Fig. 1 Hand mass following excision

In summary, we present the case of an immunocompromised patient who developed an erythematous hand lesion, which, after multiple courses of antibiotics, proved to be cryptococcosis on deep tissue culture. The patient subsequently was started on fluconazole. However, due to failure of medical therapy, the patient was taken to the operating room for excisional biopsy, which proved to be curative. This case serves to highlight the entity known as Primary Cutaneous Cryptococcosis, its presentation and treatment in the immunocompromised individual with renal insufficiency and that surgical intervention can prove to be curative in the case of failed medical management.

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