

Skin cryptococcosis in an immunocompromised renal-transplant recipient

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ABSTRACT

Immunosuppression after solid-organ transplantation can lead to opportunistic infections as cryptococcosis. A 69-year-old female, cadaveric renal-transplant recipient, manifested with ulcerative lesions on the 7th month of immunosuppression. Histological examination confirmed the diagnosis of cryptococcosis. Treatment with systemic and topical antifungal therapy for 7 months concluded in significant cutaneous improvement. This case presentation encourages high clinical suspicion of opportunistic pathogens such as *Cryptococcus* spp. and highlights the necessity of appropriate management.

1. Introduction

Cutaneous infectious complications are common in kidney transplant recipients because of a long term immunosuppression after transplantation. Consequently, opportunistic atypical pathogens as *Cryptococcus* spp., an encapsulated yeast found in soil, become dangerous. Cryptococcosis is an invasive fungal infection that has a worldwide distribution. For this reason it is important to maintain high suspicion for more rarely encountered pathogens and to master appropriate management in immunocompromised patients.

2. Case

A 69-year-old woman presented to the Centre of Dermatovenereology (day 0) with purple bluish coloured nodules on her right hand, which slowly enlarged and ruptured into an ulcer. The patient had a significant past medical history of long standing renal failure and hemodialysis for 18 months therefore she became cadaveric renal transplant recipient (day –793). Her immunosuppression regimen consisted of systemic tacrolimus 2 mg/day, mycophenolate mofetil 360 mg/BD and methylprednisolone 4 mg/day (day –792 to day 0). The general condition of the patient was stable, laboratory tests within the normal range. On the 7th month of immunosuppression the woman noticed skin lesions on her hand but she did not take medical advice at that time. (day –583).

Examination revealed an erythemic ulcerated nodule on her right hand. Dermoscopy showed arborising vessels and Basal Cell Carcinoma

(BCC) was suspected (day 0). Skin biopsy with Periodic acid-Schiff (PAS) staining presented epidermal and hair follicle epithelium proliferation and chronic inflammatory infiltration with possible infection of *Cryptococcus* spp. because of crypto-like insertions (day 7) (Fig. 1). Cultures were not performed as specification of the *Cryptococcus* would not result in a different management approach. Initial treatment with oral fluconazole 200 mg/day for 10 days followed by 150 mg/day for 8 weeks was prescribed (day 7). Unfortunately, the patient discontinued the treatment and did not show up for further follow-ups as planned.

Nineteen months later the patient returned to the Dermatovenereology department (day +579). The previous purple bluish coloured nodule on her right hand grew up to 2 cm and was surrounded by erythema with central ulceration and liquid exudation. Additional lesions were found on patients' right forearm and left cheek (Fig. 2 A,F).

Urine and blood analysis showed normal results, but exudate from the lesion serology examination showed colonization with *Curvularia* spp., (day +586). The fungus common in soil was an unexpected finding, but the patient admitted working in the garden recently. This secondary infection did not require additional treatment. The second histological examination of the skin lesion presented granulomatous inflammation with most possible infection – *Cryptococcus* spp. (day +594). Findings were comparable to first skin biopsy - crypto-like insertions and latent inflammatory infiltration.

Treatment of systemic itraconazole 200 mg/day and topical ketoconazole washing liquid 2–3 times/week, isoconazole-diflucortolone cream 2 times/day and clotrimazole cream 2 times/day was prescribed.

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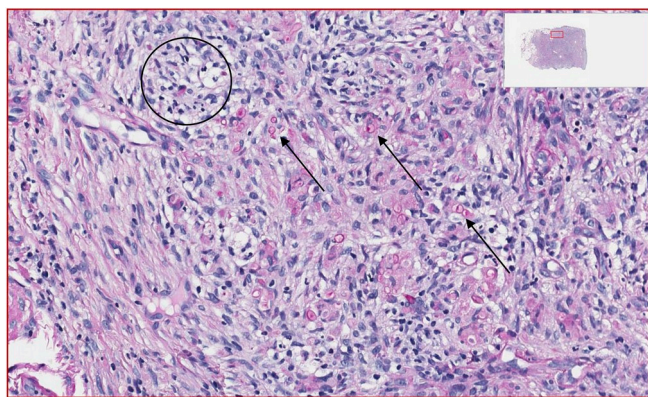


Fig. 1. Skin biopsy with PAS staining. Epidermal and hair follicle epithelium proliferation and latent inflammatory infiltration (circle) with crypto-like insertions (arrows).

Immunosuppression by mycophenolate mofetil was reduced to minimal dose of 360 mg/day.

One month later (day +624) the treatment showed slight improvement, purple bluish coloured plaques with little infiltration were seen on the face and right hand. Also multiple hematomas were observed. Systemic treatment with itraconazole and topical ketoconazole washing liquid were continued (Fig. 2B,G).

Follow up after 2 months (day +655) showed marked improvement of skin condition – the lesion on the cheek became flatter, appearing as a macule with a thin scale. Plaques and nodules with central ulceration were still noticeable on the hand and forearm (Fig. 2 C,H). Systemic treatment was discontinued because of blood indicators and isoconazole-diflucortolone cream 2 times/day was prescribed for topical use.

Follow up after 3 months (day +685) revealed worsening of the skin condition with the lesions producing an exudate due to non-compliance (Fig. 2 D,I). For this reason systemic itraconazole 200 mg/day was extended accompanied by isoconazole-diflucortolone cream 2 times/day.

After 6 months (day +777) of antifungal therapy the patient developed weakness of lower extremities, difficulty climbing upstairs and swollen face. However, skin condition was improving as ulcerations shifted to scars, only a few purple coloured plaques were still present (Fig. 2 E,J). Those symptoms were thought to be side effects of the itraconazole. Although liver enzymes analysis revealed normal results, systemic treatment with itraconazole 200 mg/day was paused for 2 weeks because of presumed side effects. Ketoconazole washing liquid 2–3 times/week and clotrimazole cream 2 times/day were continued.

Finally, 7 months later (day +808) the patient presented with only a few residual purple coloured plaques, nodules and scars on the right hand, forearm and left cheek accompanied with multiple hematomas. Repeated liver enzymes analysis showed normal liver function. Targeted systemic and topical therapy resulted in a good clinical response (Figs. 2 and 3).

3. Discussion

Cryptococcus spp. (most often *neoformans*) is an encapsulated opportunistic yeast found widely in the environment and associated with bird faeces, soil, plants, dust and infected food. Cryptococcosis may affect immunocompetent person, but typical host is under immunosuppression [1]. Prevalence of cryptococcal infection in solid-organ transplant recipients is 2–8%. Renal transplant recipients conclude the majority of cases [2]. Most patients present with pulmonary or central nervous system (CNS) infection and only 10–15% of patients with cryptococcosis develop cutaneous lesions [3].

Usually, as primary infection, cryptococcosis starts with inhalation of fungal spores and affection of the lungs. In immunocompetent host the pathogen is easily managed causing only transitory pulmonary symptoms. In immunocompromised host, the infection is followed by hematogenous dissemination to central nervous system (CNS) and other organs as bones, joints or skin [1,3]. Cryptococcosis cutaneous manifestation is mostly a sign of dissemination [4]. Although, our patient had only cutaneous lesions with no marks of internal distribution.

Following candidiasis and aspergillosis, cryptococcosis is one of the most frequent fungal infections in solid-organ transplant recipients [5]. Occurrence is often seen around the 6th month post-transplant [6]. Our case was classical, as the patient presented with cryptococcal lesions in the 7th month post-transplant.

Cutaneous presentation of cryptococcosis is polymorphous, mostly manifesting as papules, pustules, nodules, abscesses, edema, panniculitis, ulcers, cellulitis or molluscum contagiosum alike lesions [7]. Organ transplant patients may also present necrotizing fasciitis, ecchymosis, eschar, purpura, cellulitis combined with necrotizing vasculitis, pyoderma gangrenosum like lesions or purple bluish coloured plaques [2] as in the reported case. Nonspecific clinical versions can mislead to other cutaneous conditions and cause serious diagnostic difficulties.

Skin biopsy combined with Romanowsky-type staining is the diagnostic test of choice for confirmation of cutaneous cryptococcosis. Although, Periodic acid-Schiff (PAS) staining can also be used as in our case. The yeasts are surrounded by clear halos that reflect the capsule, called crypto-like insertions [8].

Targeted treatment for cryptococcosis is referred in guidelines for the management of cryptococcal disease by the Infectious Diseases Society of America (IDSA) [9]. The management varies based on disease severity, organ involvement and patients' immunological status. Treatment principles for cutaneous manifestations are the same caused by *Cryptococcus gatti* or *Cryptococcus neoformans*. In immunosuppressed patients non-CNS disseminated primary cutaneous cryptococcosis is treated with oral fluconazole 200–400 mg/day for 3–6 months or itraconazole 200–400 mg/day for 6–12 months followed by lifelong maintenance if required. Gradual reduction of immunosuppression is also recommended. In our case the antifungal treatment was started with fluconazole and later prolonged with itraconazole combined with topical medications. Lesions like this usually have an inflammatory component. Some studies show, that the addition of a topical corticosteroid to the antifungal therapy increases the bioavailability and prolongs the activity of the antifungal, while rapidly reducing inflammatory symptoms. The patient revealed good clinical response to the treatment and cryptococcosis was successfully managed.

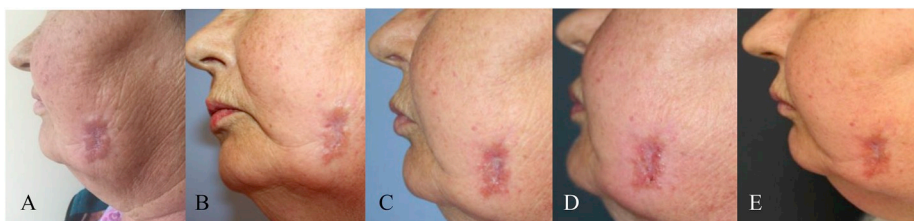


Fig. 2. Gradual clinical improvement in cryptococcal facial skin lesions from day +579 to day +777. (A) at presentation, and at 1 month (B), 2 months (C), 3 months (D), and 6 months (E) after start antifungal therapy.



Fig. 3. Gradual clinical improvement in cryptococcal skin lesions from day +579 to day +777. (A) at presentation, and at 1 month (B), 2 months (C), 3 months (D), and 6 months (E) after start antifungal therapy.

In conclusion, we would like to highlight the possibility of opportunistic pathogens such as *Cryptococcus* spp. in solid-organ transplant recipients. Only high attentiveness to cutaneous changes and appropriate treatment can lead to successful recovery from cryptococcosis in immunosuppressed transplant patients.

Declaration of competing interest

The authors declare there was no conflict of interests.

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There is no acknowledgement the authors would like to declare.

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