Primary cutaneous cryptococcal infection due to fingolimod – Induced lymphopenia with literature review

Sachin M. Patil[a],*, Phillip Paul Beck[a], Niraj Arora[b], Bran Andres Acevedo[a], Dima Dandachi[a]

[a] Infectious Disease Department, University of Missouri Hospital and Clinic, 1 Hospital Dr, Columbia, MO 65212, USA
[b] Neurology Department, University of Missouri Hospital and Clinic, 1 Hospital Dr, Columbia, MO 65212, USA

ARTICLE INFO

ABSTRACT

Cryptococcus. Neoformans (C. neoformans) is an encapsulated heterobasidiomycetous fungus responsible for opportunistic infections worldwide in immunocompromised patients. Clinical presentation ranges from asymptomatic respiratory tract colonization to disseminated infection in any human body part. The central nervous system (CNS) and pulmonary diseases garner most of the clinical attention. Secondary cutaneous cryptococcosis is an uncommon manifestation seen as a sentinel sign commonly in disseminated cryptococcal infection. Primary cutaneous cryptococcosis (PCC) is a rare manifestation seen in both immunocompromised and immunocompetent patients. It is a discrete infection with different epidemiological trends. Immunosuppressive therapy (corticosteroids, tacrolimus) predisposes a patient to acquire this clinical entity. We present a case of an elderly Caucasian male on fingolimod for relapsing-remitting multiple sclerosis with nonhealing scalp lesions for four years. He was a referral to our healthcare center for the presence of fungal elements seen on a scalp biopsy fungal stains. Final cultures returned positive for C. neoformans susceptible to fluconazole (MIC = 8 μg/mL). The CD4 count was 13 cells/uL, and workup for CNS and disseminated cryptococcal infection were negative. Fingolimod is an immunomodulator that acts on sphingosine 1-phosphate receptors, affecting the lymphocytes. Pubmed literature review revealed few case reports (< 5) with PCC in patients on fingolimod. To our knowledge, ours is the first case with scalp cryptococcosis, with the lowest CD4 count while being on fingolimod. No randomized controlled trial data exist for the treatment of PCC. Therapy initiated with oral luconazole for six months with significant improvement at three months.

Introduction

Cryptococcus. neoformans is a saprophytic yeast responsible for infections in both immunosuppressed and immunocompetent patients. The most commonly affected organs are the central nervous system (CNS), followed by lung and skin. The incidence of cryptococcosis in the pre-AIDS era was 0.8 cases per one million persons per year, and it increased to fifty cases per one million persons per year in several large cities in 1992. By the mid-1990s, due to the widespread use of fluconazole for oral candidiasis, the incidence rate diminished and stabilized to approximately 1 case per 100,000 persons per year [1]. The initiation of highly active antiretroviral therapy in HIV infected patients has further decreased the incidence. Cutaneous cryptococcosis (CC) accounts for 10 % of total cases and frequently as a manifestation of disseminated cryptococcosis (DC) [2]. Clinical diagnosis of Primary cutaneous cryptococcosis (PCC) can be challenging due to its varied skin manifestations [3].

Immunosuppression due to HIV is responsible for most of the cases, whereas medication (corticosteroid) induced immunosuppression accounts for lesser cases [2]. Both result in a diminished cell-mediated immune response. Apart from corticosteroids, other medicines associated with CC are tacrolimus and fingolimod. A Pubmed literature search on fingolimod-induced cryptococcal infections revealed approximately 10 cases. Of 10 cases, only two had PCC. Fingolimod is the first oral disease-modifying agent for relapsing-remitting multiple sclerosis (MS) approved by the FDA in September It modulates sphingosine 1-phosphate receptor causing CNS lymphopenia and a decrease in inflammation. Here we report the first case of biopsy and culture-positive PCC on the scalp (caused by C. neoformans) in an MS patient who was on fingolimod for seven years. This case report highlights the importance of medication-induced cryptococcosis and its management.

* Corresponding author.
  E-mail address: drssmp1@gmail.com (S.M. Patil).

Case report

A 63-year-old male presented to his dermatologist with a history of multiple nonhealing left occipital scalp lesions for four years. On clinical examination, the patient had two nonhealing lesions over the left occipital scalp and one over the right occipital scalp. Right occipital scalp (Fig. 1) revealed a 1.4 cm pink plaque lesion, left superior occipital scalp lesion (Fig. 2) revealed a 1 cm pink plaque, and the left inferior occipital scalp lesion (Fig. 3) revealed 1 cm ill-defined papule. Examination of the face revealed 1 cm pink plaque with central depression located over the right parietal scalp, a 5 mm erythematous papule over the right superior helix, and an ill-defined 2 cm pink plaque over the right preauricular cheek. Shave biopsy of all three scalp lesions performed and specimens sent to histopathology for further examination. The right occipital scalp lesion revealed solar elastosis and vascular ectasia at the margins, whereas the left superior occipital scalp lesion revealed an ulcer with numerous fungal yeast forms and granulomatous dermatitis at the margins. The left inferior occipital scalp lesion revealed an ulcer with multiple fungal yeast forms present at the margin.

Due to the abnormal histopathology report, two weeks later, he underwent a repeat biopsy of the left superior occipital scalp lesion for fungal tissue culture. Due to the presence of numerous fungal yeast forms on the biopsy patient referred to our University medical center for management. After reviewing his clinical history, a decision made to admit him to the internal medicine inpatient service for additional work-up. Past medical history was significant for MS diagnosed more than 30 years back, osteoarthritis of right knee status post right knee arthroscopy, and degenerative disc disease of low back status-post surgery. For MS, the patient was on fingolimod for seven years. The patient admitted receiving high-dose corticosteroids for MS exacerbation previously but none in the length of the fingolimod use. His last MS exacerbation was 18 years ago. He denied any other clinical symptoms. He denied any exposure to birds or farm animals and no recent significant travel history and was a retired lineman. Clinical concern was to rule out acute DC, as the patient was on fingolimod for MS. Morphology and histochemical properties of the organisms seen on histopathology specimens were consistent with Crypto-coccus spp.

On the day of admission due to a lack of neurological symptoms and signs, CT head was not performed. Two sets of blood cultures obtained at the admission were negative. Complete blood counts, comprehensive metabolic panel, and prothrombin time were within normal limits. HIV 1–2 serology, hepatitis C serology, serum cryptococcal antigen, andCD4/CD8 lymphocyte subset were ordered. Cerebrospinal fluid (CSF) analysis was clear, colorless; the protein was 52 mg/dL; glucose was 59 mg/dL; White cell count was 0 cells/uL and red cell count was 19 cells/uL. CSF specimens sent for fungal and bacterial culture. On day three, serum
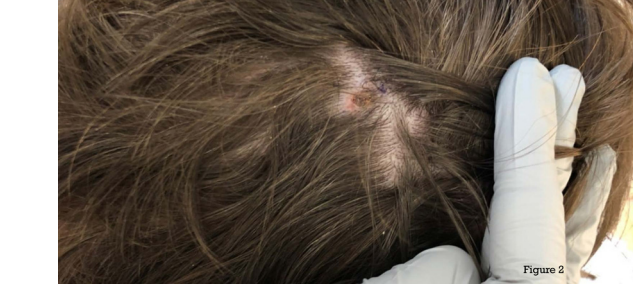
cryptococcal antigen, HIV, and hepatitis C serology were nonreactive. CSF cryptococcal antigen testing was negative, and CSF bacterial and fungal cultures were negative for growth. He received no antifungal therapy during his hospitalization and was discharged on day three. Post-discharge day 1 CD4/CD8 lymphocyte subset results revealed CD4 of 13 cells/μL (5.1 %) and CD8 of 147 cells/μL (57.1 %). Due to low CD4 count, Sulfamethoxazole/ trimethoprim double strength once a day started for pneumocystis prophylaxis, and fingolimod discontinued. A clinical diagnosis of PCC made due to a lack of CSF involvement, negative HIV serology, and fingolimod administration with lymphocytopenia. His neurologist notified so that he could resume treatment with an alternative medication for multiple sclerosis. For PCC, he was initiated on therapy with six months of oral fluconazole 400 mg daily. Five days post-discharge biopsy culture returned positive for C. neoformans (susceptible to fluconazole, MIC = 8 μg/mL) confirming the diagnosis. At three weeks follow up, an improvement in his scalp lesions(decreased itchiness and drainage) seen with no change in face lesions. In the tenth week, scalp lesions were healing (Fig. 4) with no new lesions. At three months, the CD4

Fig. 2. Left superior occipital scalp lesion.

Fig. 3. Left inferior occipital scalp lesion.

Fig. 1. Right occipital scalp lesion.

Fig. 4. Left occipital lesions at 3 months of therapy.

count increased to 209 cells/μL, and Sulfamethoxazole/trimetho-prim doublestrength was stopped.

Discussion

In cryptococcosis, 80 % of cases are due to immunosuppression, whereas the remaining 20 % have no underlying disease or risk factor [4]. Clinical presentation in classic cryptococcosis is dependent on a host's immune response to inhaled cryptococci. An efficient immune system eliminates it or produces a dormant small pulmonary lymph node complex via Th1 response, whereas immunosuppression leads to proliferation, dissemination result-ing in disease [1]. The infection ranges from asymptomatic respiratory tract colonization to the spread of infection into any human body part. CC can be primary or secondary as in disseminated cryptococcosis [2]. Secondary cutaneous cryptococ-cosis (SCC) is an uncommon manifestation in 10–15% of disseminated cryptococcal infections attributed to hematogenous dissemination [2].

PCC is a rare manifestation in both immunocompromised and immunocompetent patients. It is a separate clinical entity with different epidemiological trends. The clinical definition includes identification of the C. neoformans in the skin lesion biopsy specimen or by culture and either clinical criteria or histological criteria together with the absence of dissemination [3]. It results from direct inoculation via preceding trauma or occupational/ hobby exposure to environmental sources with a predisposition to skin injury [2,3]. Skin lesions are solitary or confined to a limited area and located in unclothed areas in PCC; however, in SCC, they are multiple scattered, situated on both exposed and clothed areas. In both, the infection presents as a new skin lesion refractory to conservative or antibacterial therapy. Most typical skin lesions are nodular or granulomatous, followed by ulcerative lesions. In SCC, almost every type of skin lesion is seen, most often being umbilicated papules or cellulitic patterns. Overall the most common site of infection is the upper extremities. Lesions are located over the finger and face in immunocompetent, whereas they are on the trunk and lower extremities in immunocompro-mised patients [2]. Around one-half of patients with PCC were

immunocompetent, whereas in the remaining, the most common risk factor being corticosteroids [2]. Significant geographical variation persists concerning the causative strain. In France, serotype D was responsible for 71 % of cases whereas, in Australia and New Zealand, it was serotype A and C. gatti in subtropical areas [2,5,6]. In the United States clinical series, serotyping done on only five patients returned positive for serotype D [2]. In solid organ transplant (SOT) patients, serotype A was responsible for most of the cases [7]. In PCC risk of dissemination of infection to other areas exists in immunocompromised patients. In immunocompetent patients, only one case of dissemination in a laboratory accident has been described [1].

Competent local immune response at the skin, underdiagnosis, or misdiagnosis can explain the lower incidence of PCC [3]. The average human skin temperature is 33 °C. Serotype D is dermatotropic due to its inability to grow at higher temperatures compared to serotype A. Calcineurin is essential for the growth of the cryptococcus at 37 °C. Tacrolimus (FK506) has an intrinsic antifungal activity due to calcineurin inhibition after binding to FKBP12 (FK506 binding

protein). It predisposes stable SOT patients to PCC as this activity is ineffective at lower skin temperatures [8]. Tacrolimus does confer protection against cryptococcal meningoencephalitis at an average body temperature of 37 °C [8]. Cyclosporine inhibits the growth of the cryptococcus by binding to cyclophilin A resulting in calcineurin inhibition at 37 °C but no effect at 24 °C. In vivo, the potent immunosuppressive effect of cyclosporine negates the anticryptococcal activity [9]. Corticosteroids alter the local cytokine milieu by repressing IL-12 and stimulating IL-4, IL -10 & IL-13, resulting in a Th2 response rather than a Th1 response. A Th1 response occurs due to an increase in IL-12 rich local cytokine milieu stimulating CD4 production of IL-2, IFN-ɣ & TNF-β conferring protection against fungal infections (Fig. 5) [10].

Fingolimod (FTY720) is an oral disease-modifying agent approved by the FDA for relapsing-remitting MS. The FREEDOMS ‖ trial unfolded a single case of asymptomatic pulmonary cryptococcosis in a patient five months after discontinuation of the drug [11]. Clinical trials reported a marginal increase in the rate of lower respiratory and Herpes virus infections. Numerous AIDS-
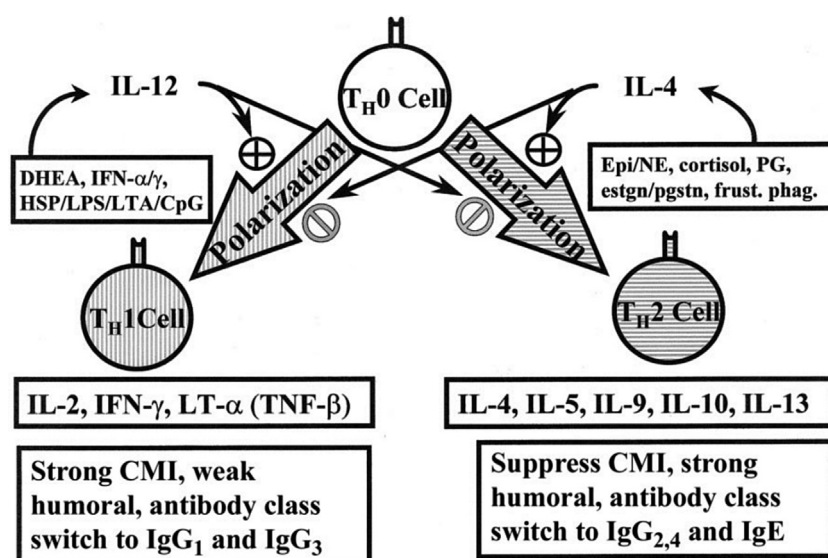
Fig. 5. Summary of Th1/Th2 induction. Cytokines, hormones, and microbial antigens stimulate the innate immune system to produce either IL-12 or IL-4 in the local microenvironment around a newly activated T cell. IL-12 induces Th0 polarization to the Th1 phenotype and inhibits polarization to the Th2 phenotype, whereas IL-4 acts reciprocally. CMI, cell-mediated immunity; CpG, purine-purine-C-G-pyrimidine-pyrimidine DNA hexamer; DHEA, dehydroepiandrosterone; Epi/NE, epinephrine/ norepinephrine; HSP, heat shock protein; LTA, lipoteichoic acid; LPS, lipopolysaccharide; PG, prostaglandin; estgn/pgstn, estrogen/progesterone; frust.phag., frustrated phagocytosis *(Type 1/Type 2 Immunity in Infectious Diseases Brad Spellberg1 and John E. Edwards, Jr.) reproduced with permission from* [10].

defining illnesses have occurred in patients on fingolimod, including cryptococcosis, histoplasmosis, PML (Progressive Multi-focal Leukoencephalopathy), atypical mycobacterial infections, and Kaposi's sarcoma [12]. Cryptococcal infections seen with fingolimod are meningoencephalitis, disseminated cryptococcal infection, and PCC. The mean age at diagnosis was 56 years. The possibility of cryptococcal infection is higher after two years of therapy with fingolimod [11]. Natalizumab is the only other MS medication associated with cryptococcal infection.

Fingolimod binds with a high affinity to sphingosine 1 phosphate receptors (S1P1,3,4,5) with initial activation of Lymphocyte S1P1 followed by downregulation resulting in receptor internalization and lymphocyte entrapment in lymph nodes. Lymphocyte redistribution results in peripheral lymphopenia with sparing of the effector memory T cells. Autoreactive lymphocyte infiltration into the brain subsides due to lesser cells crossing the blood-brain barrier. Fingolimod dwindles circulating CD4 + T cells and, to a lesser extent, CD8 + T cells with no effect on antigen presentation, T or B cell activation, proliferation, differentiation, or effector function. It alters the Cytokine milieu and abates NK cell subsets resulting in switching the host immune response from Th1 to Th2 in cryptococcal infections [11]. Th1 immune response is crucial for fungal infection control. Long term fingolimod (51–64 months) culminates in a reversal of a healthy 2:1 ratio of CD4 to CD8 also seen in HIV AIDS patients and immunosenescence (elderly) [11]. The recommendation is to hold therapy if the lymphocyte count drops below 200 cells/uL for the immune rebuild before the reinitiation of therapy [12]. Immune system impact due to fingolimod does not return to normalcy immediately after cessation. Post cessation lymphocytes exceed the lower limit of normal by 6–8 weeks and recover to 80 % of their baseline level by three months [11]. A case of meningoencephalitis was described at eight weeks post discontinuation, as was a case of asymptomatic pulmonary cryptococcosis at five months after stopping (FREE-DOMS ‖ trial). We concur with the likelihood of potentiation of fingolimod effects by a senescent immune system. Treatment span with fingolimod and age are important risk factors for the development of cryptococcal infection.

HIV negative patients present with sparse signs and symptoms, insensitive serological testing, an occurrence leading to valuable hindrance in diagnosis and therapy institutions [4]. Nonmeningeal nonpulmonary cryptococcosis has the highest percentage of failed therapy and the worst prognosis [2,4]. Among these patients, fluconazole, when used alone, had a successful outcome. Mortality in PCC was 9.2 %, higher in immunocompetent compared to immunocompromised patients [2]. In SOT clinical series, the overall mortality of cutaneous cryptococcosis was 15.4 % (4/26),12.5 % in PCC (1/8) & 16.7 % (3/18) in DCC [7]. Predictors for mortality in PCC include male gender and organ failure syndrome [4].

In our case, the patient did not receive any high dose corticosteroids for the seven years he was on fingolimod. Other than his scalp lesions, he had no other clinical signs or symptoms which attests to the above-mentioned atypical presentations.

In the absence of other clinical manifestations, DC and meningoencephalitis evaluations were negative. The CD4 count was the lowest yet seen at 13 cells/uL. Biopsy and culture confirmed the diagnosis, and it was susceptible to fluconazole. After a PUBMED literature review, this is the second case with scalp involvement and the first case while being on fingolimod. The patient is a retired lineman, and environmental source exposure is a high possibility. Due to low CD4 count patient was placed on oral Sulfamethoxazole/trimethoprim double strength once a day for the next three months for Pneumocystis prophylaxis until CD4 counts were greater than 200 cells/uL. In a recent systemic review of PCC in immunocompetent patients [5], all cases treated with itraconazole, had a successful outcome. Due to the lack of randomized controlled clinical trials, expert opinion (based on clinical experience, descriptive studies, and case reports), the current clinical consensus is to follow IDSA guidelines for nonmeningeal nonpulmonary cryptococcosis treatment, which recommends using fluconazole at 400 mg per day for 6–12 months [13].

Conclusion

Although fingolimod is a safe and effective drug for MS, there has been a recent increase in case reports of cryptococcal infection in patients on fingolimod. A literature review revealed less than 15 patients reported to date. Recommendations on how to screen or monitor these patients for infections are scant. Due to higher mortality in PCC, whether screening these patients regularly with serum cryptococcal antigen and CD4 counts will help in detecting these patients earlier is an unsolved dilemma currently. As several AIDS-defining illnesses have occurred in these patients, our suggestion is to monitor the CD4 counts regularly, and if they are less than 100 cells/uL, then obtain a serum cryptococcalanti-gen. Monitoring might cut short the unreasonable delays in diagnosis and institution of therapy. Monitoring will be an excellent additional supplement to the clinical questionnaire related to cryptococcosis and clinical examination. In PCC, itraconazole was successful in a few patients; we suggest to use fluconazole as per IDSA guidelines for at least 6–12 months.

Acknowledgments

References

[1] Mandell Perfect JR. Douglas, and Bennett's principles and practice of infectious diseases, cryptococcosis (Cryptococcus neoformans and Cryptococcus gattii). 9th ed. Philadelphia: Elsevier; 2020. p. 3146–61.

[2] Christianson JC, Engber W, Andes D. Primary cutaneous cryptococcosis in immunocompetent and immunocompromised hosts. Med Mycol 2003;41 (3):177–88, doi:http://dx.doi.org/10.1080/1369378031000137224.

[3] Neuville S, Dromer F, Morin O, Dupont B, Ronin O, Lortholary O. Primary cutaneous cryptococcosis: a distinct clinical entity. Clin Infect Dis 2003;36 (3):337–47, doi:http://dx.doi.org/10.1086/345956.

[4] Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 2001;33(5):690–9, doi:http://dx.doi.org/10.1086/322597.

[5] Du L, Yang Y, Gu J, Chen J, Liao W, Zhu Y. Systemic review of published reports on primary cutaneous cryptococcosis in immunocompetent patients. Mycopathologia 2015;180(1-2):19–25, doi:http://dx.doi.org/10.1007/s11046-015-9880-7.

[6] Marques SA, Bastazini I, Martins ALGP, et al. Primary cutaneous cryptococcosis in Brazil: report of 11 cases in immunocompetent and immunosuppressed patients. Int J Dermatol 2012;51(7):780–4, doi:http://dx.doi.org/10.1111/j.1365-4632.2011.05298.x.

[7] Sun H-Y, Alexander BD, Lortholary O, et al. Cutaneous cryptococcosis in solid organ transplant recipients. Med Mycol 2010;48(6):785–91, doi:http://dx.doi.org/10.3109/13693780903496617.

[8] Kanj SS, Welty-Wolf K, Madden J, et al. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. Medicine (Baltimore) 1996;75(3):142–56, doi:http://dx.doi.org/10.1097/00005792-199605000-00004.

[9] Cruz MC, Del Poeta M, Wang P, et al. Immunosuppressive and nonimmunosuppressive cyclosporine analogs are toxic to the opportunistic fungal pathogen Cryptococcus neoformans via cyclophilin-dependent inhibition of calcineurin. Antimicrob Agents Chemother 2000;44(1):143–9, doi:http://dx.doi.org/10.1128/aac.44.1.143-149.2000.

[10] Spellberg B, Edwards JE. Type 1/type 2 immunity in infectious diseases. Clin Infect Dis 2001;32(1):76–102, doi:http://dx.doi.org/10.1086/317537.

[11] Grebenciucova E, Reder AT, Bernard JT. Immunologic mechanisms of fingolimod and the role of immunosenescence in the risk of cryptococcal infection: a case report and review of literature. Mult Scler Relat Disord 2016;9:158–62, doi:http://dx.doi.org/10.1016/j.msard.2016.07.015.

[12] Grebenciucova E, Pruitt A. Infections in patients receiving multiple sclerosis disease-modifying therapies. Curr Neurol Neurosci Rep 2017;17(11):88, doi:http://dx.doi.org/10.1007/s11910-017-0800-8.

[13] Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. Clin Infect Dis 2010;50(3):291–322, doi:http://dx.doi.org/10.1086/649858.