



Case report

Disseminated cryptococcal infection in a patient with treatment-naïve chronic lymphocytic leukemia (CLL)

Adam Suleman^a, Ruth Padmore^b, Carolyn Faught^c, Juthaporn Cowan^{d,e,*}^a Faculty of Medicine, University of Ottawa, Canada^b Division of Hematopathology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Canada^c Division of Hematology, Department of Medicine, The Ottawa Hospital, Canada^d Clinical Epidemiology Program, the Ottawa Hospital Research Institute, Canada^e Division of Infectious Diseases, Department of Medicine, The Ottawa Hospital, Canada

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ABSTRACT

We report a case of disseminated cryptococcosis in a treatment-naïve chronic lymphocytic leukemia (CLL) patient. A 60-year-old man presented with a two-week history of intermittent fevers, frontal headaches, night sweats, weight loss and multiple pink papules on hands and face. Cryptococcosis was found by blood culture unexpectedly. Further investigation confirmed cryptococcal meningitis and skin disease. He responded to two week amphotericin B and flucytosine followed by four-week amphotericin B and fluconazole, three-month high dose fluconazole (800 mg/day), and maintenance fluconazole (400 mg/day) thereafter. CSF pleocytosis persisted until day 203 while cryptococcal antigen in the CSF persisted at day 334 of treatment.

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Introduction

Cryptococcosis is an opportunistic infection caused by encapsulated yeast, mainly *Cryptococcus neoformans*, or less commonly *C. gatii* [1]. The majority of patients with symptomatic cryptococcosis have a clearly identified underlying immunocompromised condition. The most common underlying condition is human immunodeficiency virus (HIV) infection. The global burden of cryptococcosis in HIV-infected patients was estimated to be 6.0% in people with a CD4 cell count of less than 100 cells/ μ L [2]. Moreover, the incidence of cryptococcal meningitis in HIV-infected patients was estimated to be close to one million person per year [3]. The mortality rate per 100 person-years is 15.3 [95%CI, 12.2–18.4] in the combined antiretroviral treatment era [4].

Non-HIV conditions that may be associated with predisposition to cryptococcosis include corticosteroid therapy [5], cytotoxic chemotherapy, immunotherapy agents [5,6], idiopathic CD4 lymphocytopenia [7], organ transplantation [8], and decompensated liver cirrhosis [9]. In a retrospective series of 302 patients

with cryptococcal infections, 39 (12.9%) of patients had no obvious risk factors for developing the infection [10].

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in the Western hemisphere [11]. An initial course of illness is relatively benign. Treatment for advanced CLL disease is generally comprised of cytotoxic chemotherapy such as fludarabine, cyclophosphamide and rituximab [12]. Newer agents such as ibrutinib are also emerging [11]. It is well-known that infection represents a major cause of death in patients with CLL. The majority of infections affect the lower respiratory tract, and are usually caused by bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* [13]. Patients with CLL are known to have hypogammaglobulinemia, suppression of helper T-cells, T-cell subset imbalances, diminished T-cell response to proliferative signals, inverted CD4/CD8 T-cell ratios, with a decreased CD4 T cells count and high level of cytotoxic CD8 T cells were also previously described in patients with CLL [14–17], which have been associated with an increased rate of infection.

Opportunistic infections have been reported sporadically in patients with advanced CLL on treatment [13,18]. In most of these cases, it is thought that the treatment for CLL predisposes to opportunistic infections. However, untreated CLL is not typically seen as a risk factor for cryptococcosis. We report an atypical case of disseminated cryptococcosis, and aim to review previous case reports of cryptococcosis in untreated CLL.

* Corresponding author at: Division of Infectious Diseases, Department of Medicine, The Ottawa Hospital, Canada.

E-mail address: jcowan@toh.ca (J. Cowan).

Case report

A 60-year-old man with untreated B-cell chronic lymphocytic leukemia (CLL), under a watchful waiting strategy, presented to a primary-care hospital with a two week history of intermittent fevers, mild frontal headaches, night sweats, weight loss, multiple papular pink skin lesions on his hands and face, and fatigue. Two weeks prior to presentation he had spent a week in Jamaica; while there he noticed an asymptomatic skin-colored firm papule on the dorsum of his right hand, which gradually developed over two weeks to papules on his other hand, arms, posterior neck and face. On physical exam, he had palpable bilateral axillary lymph nodes and one palpable right inguinal lymph node. His rash consisted of multiple skin-colored to pink round papules with an erythematous rim, primarily over the patient's dorsal hands (Fig. 1a), face and posterior neck. His cardiac, respiratory, gastrointestinal and genitourinary exams were unremarkable. His blood work showed a white blood cell count of 1 190 cells/ μL , a hemoglobin of 9.5 g/dL and platelet count of 201 000 cells/ μL . A CT chest showed no change in the size of previous pulmonary nodules, which prior biopsy had shown to be due to CLL infiltrates, as well as stable hepatosplenomegaly, axillary, mediastinal and hilar lymphadenopathy. Human immunodeficiency virus (HIV) serology was negative.

On day six of incubation, the patient's blood cultures became positive with *Cryptococcus* spp. The patient was referred to our hospital, a tertiary-care hospital, on the same day and we report this as day 1 of admission. He was immediately started on liposomal amphotericin B (5 mg/kg IV q24 h). Flucytosine was not readily available because a special request was required. A biopsy of the skin lesion was performed on day 2 of admission (pathology shown in Fig. 1b and c). Lumbar puncture was performed to rule out meningitis. The cerebrospinal fluid (CSF) analysis showed 1 385

cells/ μL total nucleated cells, 41% lymphocytes, 21.6 mg/dL glucose, 60 mg/dL protein, and the CSF culture showed growth of *Cryptococcus neoformans*, confirming cryptococcal meningitis.

Repeat CSF on day 14 showed evidence of infection with presence of yeast cells visible by microscopy (Fig. 2a). Fluconazole 800 mg daily was added while waiting for flucytosine. Three weeks into the patient's treatment, fluconazole was stopped and flucytosine was started at 2 g orally every 6 h. However, this was interrupted for few days due to cytopenia. The dosage was subsequently adjusted to 2 g every 12 h to enable completion of 2-week induction treatment with dual therapy of amphotericin B and flucytosine.

Due to the extent of the disease, the treating team decided to give dual therapy for an extended duration, but flucytosine was changed to fluconazole. This dual therapy was continued until day 40 of treatment before transitioning to high-dose fluconazole monotherapy. Repeated CSF analysis at that time demonstrated persistent pleocytosis with total nucleated cells of 69 cells/ μL , and cryptococcal antigen at a titer of 1:2048. During which time, the patient developed headache and floaters in his right eye. An MRI revealed multiple high T2 signal foci throughout the basal ganglia, thalamus and midbrain with associated edema, and new significant bilateral edema of the optic nerves extending to the optic discs; small cryptococcomas could not be ruled out. A neuro-ophthalmologist concluded that the patient's symptoms were due to increased intracranial pressure. Subsequent lumbar puncture on day 100 of treatment showed 62 total nucleated cells/ μL with further reduction in the cryptococcal antigen titer to 1:1024. The CSF opening pressure was unfortunately not measured. His ocular symptoms improved gradually over four weeks and remained asymptomatic over the course of this treatment. Therefore, the treating team was comfortable in starting the patient on maintenance therapy with fluconazole 400 mg daily on day 126.

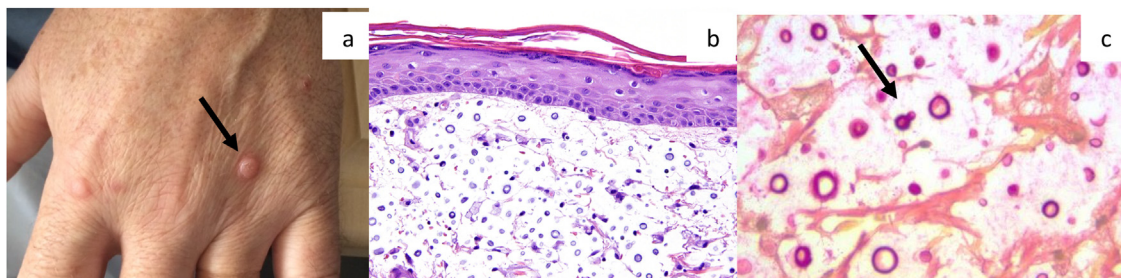


Fig. 1. A. Rash on the patient's hand upon initial presentation. B. Section of skin biopsy with hematoxylin and eosin stain, original magnification $20\times$. C. Photomicrograph of the skin biopsy showing large numbers of yeast forms surrounded by a clear space, typical of the thick capsule of *Cryptococcus*. (Mucicarmine, magnification $63\times$, courtesy of Dr. Bruce Burns).

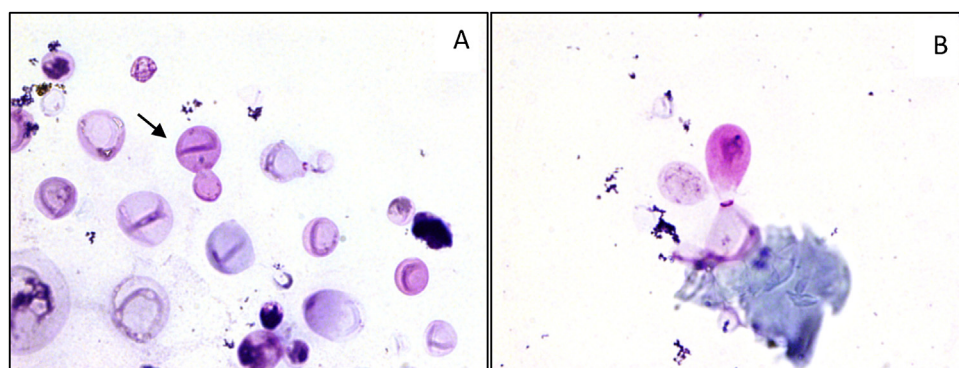


Fig. 2. Cerebrospinal fluid A. Yeast cells on day 14 of treatment and B. Degenerating yeast cells on day 334 of treatment. (May-Grünwald-Giemsa, original magnification $100\times$ oil immersion).

Interestingly, a repeat CSF analysis on day 334 of treatment showed a reduction in total nucleated cells to 3 cells/ μ L but cryptococcal antigen was still detected at a titer of 1:128 (Table 1).

Meanwhile, the patient developed transfusion-dependent anemia, thrombocytopenia, and increased lymphadenopathy which were likely related to his underlying CLL. His hematologist therefore started the patient on ibrutinib, a Bruton tyrosine kinase inhibitor, for the treatment of CLL on day 342. Due to potential drug-drug interaction between ibrutinib and fluconazole through CYP3A4, reduced dose of ibrutinib at 140 mg daily was recommended. He has done dramatically well without worsening cryptococcosis at two-year follow-up. We plan to continue fluconazole for life as a secondary prophylaxis.

Discussion

We conducted a search for case reports or case series of cryptococcal infection in patients with CLL. We found 52 cases reported previously. Of 52, two occurred in treatment naïve CLL patients. Together with our case report, there are thus three cases in total (Table 2). All cases had documented *C. neoformans*, not *C. gatii* infection. All patients were male. The average age was 72 years old (range 60–84). CLL disease stage was not reported in two other cases [19,20]. The patient from our case was diagnosed with RAI Stage I previously, however, at the time of his presentation with cryptococcosis, he appeared to progress to RAI Stage II, subsequently needing CLL treatment. All patients had disseminated disease. Two had CNS involvement [19] including our case who had a severe and prolonged CNS infection with pleocytosis and high titer of cryptococcal antigen and visible degenerating cryptococcal yeast cells in the CSF on day 334 of treatment (Fig. 2b).

All presented subacutely. Fever and headache are the most common symptoms (66.7%) while none presented with alteration of consciousness. Skin lesions of our case were nodular while lesions of the other reported case were ulcerative [20]. None had cryptococcal pneumonia. All patients received fluconazole but two also received amphotericin B during induction phase. Flucytosine was only used in our case. The patient developed significant cytopenia but responded well to a decreased dose. There was no

death with average follow up time of 12 months (range 2 weeks to 24 months).

A key component of the immune response in combating a cryptococcosis infection consists of cell-mediated immune responses through CD4+ and CD8+ T-cells, as described in a review by Perfect and Bicanic [21]. This has been validated in mice, where depletion of CD4+ T-cells has been shown to exacerbate CNS infection of *Cryptococcus* [22]. Epidemiologically, idiopathic CD4+ lymphopenia is the highest risk factor for *Cryptococcus* infection in non-HIV patients [23]. In a recent study by Allahmoradi et al., T-cells were isolated from twenty five untreated CLL patients and found to have a significantly lower percentage of CD4+ T-cells when compared to healthy controls [17]. This study also found that CD4+ T-cells from CLL patients had impaired proliferation and cytokine production when compared to healthy controls. Forconi and Moss described in their review how T-cells are functionally impaired in CLL, with impaired synapse between T-cells and antigen presenting cells [24]. It can be hypothesized that patients with CLL who have impaired function of their CD4+ T-cells are at a higher risk for infection by pathogens such as *Cryptococcus*, which are typically recognized by a cell-mediated immunity. The decrease in immune response is also supported by the decreased response in untreated CLL patients to the conjugated pneumococcal vaccine. Pasiarski et al. described how 58.3% of CLL patients produced an adequate response to vaccination as compared to 100% of the control healthy patients [25]. The antibodies created by the proliferating B-cells in CLL have been characterized as pathogenic and target-restricted, suggesting that patients with CLL have defective humoral immunity in addition to the inadequate cell-mediated immune response [26].

While HIV-infected patients with cryptococcosis typically present with headache, fever, and altered mental status, CLL patients present with symptoms that may not initially suggest a cryptococcal infection, such as weight loss and cough [27,28]. As a result of the atypical presentation, patients were often treated with antibacterials for a bacterial infection before the true diagnosis was revealed [28–30]. Our case highlights the importance of recognizing the broad spectrum of infections that can present in patients with CLL.

Table 1

Characteristics of the cerebrospinal fluid (CSF) throughout the course of the cryptococcal infection.

Time from first treatment	Day 1	Day 14	Day 42	Day 100	Day 203	Day 334
CSF total nucleated cells (cells/ μ L)	1385	77	69	62	10	3
CSF percent neutrophils	0%	2%	0%	1%	Not available	Not available
CSF percent lymphocytes	41%	92%	98%	97%	Not available	Rare lymphocyte on scanning
CSF glucose (mg/dL)	21.6	10.8	18	23.4	52.2	55.8
Serum glucose (mg/dL)	99	93.6	93.6	Not available	95.4	Not available
CSF protein (mg/dL)	60	66	55	73	34	30
CSF Gram Stain	Not available	Many white cells Moderate yeast cells	Moderate white cells No organisms seen	Many white cells No organisms seen	Not available	Few white cells (but yeast cells noted in hematology cytospin prep)
CSF culture	Light growth <i>Cryptococcus neoformans</i>	No growth	No growth	No growth	No growth	No growth
CSF cryptococcal antigen titer	Not available	Not available	1:2048	1:1024	1:512	1:128
Antifungal treatment	IV fluconazole 800 mg, transitioned to Amphotericin B 400 mg q24h	Fluconazole 400 mg daily and Amphotericin B 400 mg q24h	Fluconazole 800 mg daily	Fluconazole 800 mg daily	Fluconazole 400 mg daily	Fluconazole 400 mg daily

Table 2
Summary of reported *Cryptococcus neoformans* infection cases in untreated patients with CLL (N = 3).

Paper	Age/ Sex	CLL Stage	Clinical Presentation	Time from Presentation to Diagnosis	Extent of disease	Treatment for Cryptococcus	Outcomes	Cryptococcal CSF titers
Johannsson et al. 2009 [19]	84 M	Not reported	Insidious left groin pain for several months not limiting activity. Weight loss and intermittent nausea for several months. Two-week history of sudden onset fever and sharp left groin pain. Mild frontal headache with decreased and painful range of motion of left prosthetic hip.	Presumably within one week	Hip joint and CNS	Induction: Amphotericin B for 12 days (total dose of 800 mg). Maintenance: Oral fluconazole 400 mg daily continued for greater than 10 months.	Resolution of symptoms after 12 days of treatment. Resection and arthroplasty performed after 10 months of medical treatment. Evidence of chronic inflammation.	1:1 in undiluted CSF
Muller et al. 2010 [20]	73 M	Not reported	Three-month history of an asymptomatic, ulcerated, rapidly growing nodule/mass on the left temporal region with severe left eyelid edema. Vision was not affected.	Presumably within one week	Skin and blood.	Fluconazole 400 mg daily followed by voriconazole 400 mg daily for a total of 2 weeks.	50% reduction of the skin lesion after 2 weeks of treatment.	LP not done.
This report	60 M	Rai stage II	Two-week history of intermittent fevers, mild frontal headaches, night sweats, weight loss and pink papular nodular lesions on his hands and face.	Six days.	Skin, CNS and blood.	Induction: Amphotericin B and flucytosine with a transition to Amphotericin B and high dose fluconazole (800 mg/d) due to cytopenia for six weeks. Maintenance: Fluconazole 800 mg/d transitioned to 400 mg/d.	High intracranial pressure seven weeks after treatment. Infectious symptoms resolved while on maintenance therapy. Asymptomatic at one year.	1:2048 on Day 42 of treatment.

Abbreviations – CLLchronic lymphocytic leukemia, CSFcerebrospinal fluid, LP lumbar puncture, CNScentral nervous system.

Conclusion

Our case highlights the rare disseminated cryptococcosis in a fully treatment-naïve CLL patient, suggesting that hematologic malignancies predispose patients to a variety of opportunistic infections. Presentations are non-specific but outcome is favorable. Persistent CSF cryptococcal antigen can be seen. Physicians should be aware of possibility of disseminated cryptococcosis in patients with treatment-naïve CLL.

Conflicts of interest

We have no conflicts of interest to declare.

Author contribution

JC – supervised Adam Suleman, edited and reviewed the manuscript.

AS – reviewed the case, literatures and wrote original draft.

RP – performed literature search, provided input from histological aspect and reviewed manuscript.

CF – provided input from hematology aspect and reviewed manuscript.

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