

An Unusual Manifestation of an HIV Patient with Fungimea Presenting with Cryptococcal Lymphadenitis

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Abstract

Introduction: *Cryptococcus neoformans* (*C. neoformans*) is a fungus which infects the lungs, meninges, skin and the nervous system. In tropical countries prevalent with tuberculosis (TB), initial clinical presentations of a *C. neoformans* infection can normally be mistaken as a TB infection. The *C. neoformans* infection shall then form part of the differential diagnosis. Exposure to *C. neoformans* does not usually manifest as an infection however, in immunocompromised patients this results to cryptococcosis.

Case: This is a case of a 33-year-old male who was admitted due to febrile seizures. He was suspected to be in an immunocompromised state due to multiple sexual partners. A non-tender, mobile left cervical lymphadenopathy was subjected to FNAB (fine needle aspiration biopsy) surprisingly

came out to be cryptococcal in nature. He was managed as a case of disseminated cryptococcosis with meningeal extension. He was given amphotericin B and fluconazole.

Conclusion: The most common suspected cause of lymphadenitis in the Philippines is attributed to TB. The high index of suspicion based on sound medical history and physical examination can lead the clinician into considering an uncommon cause of lymphadenopathy most especially in patients with high likelihood of immunocompromised state.

Keywords: cryptococcosis, *c. neoformans*, cryptococcal lymphadenitis, cryptococcal meningitis, hiv

Introduction

Cryptococcosis is an opportunistic and often fatal fungal infection that afflicts not only persons with an advanced stage of human immunodeficiency virus (HIV) infection but also those who are immunocompetent. Since the discovery of antiretroviral therapy, cryptococcal infections have decreased substantially.¹ This is to report a case of a patient suspected in immunocompromised state presented with right cervical lymphadenopathy.

There are five major sites of involvement in cryptococcosis: the lungs, central nervous system (CNS), skin, lymph nodes and eyes.² The fungus is inhaled from an environmental source making the lungs its portal of entry and the initial site of infection. After being deposited into the pulmonary alveoli, the spores of *Cryptococcus neoformans* (*C. neoformans*) must survive the normal to high pH and the physiological concentrations of carbon dioxide before they are phagocytized by alveolar macrophages, in a

more acidic environment, and disseminated systemically after a latent period. The essential factor in the survival of *C. neoformans* in this extracellular environment is glucosylceramide synthase.³

Tuberculosis (TB), on the other hand, is the most common causative agent for lymphadenitis or lymphadenopathy in a person living with HIV.⁴ Cryptococcal infection may well be common in sub-Saharan and Southeast Asia as an important opportunistic infection in HIV patients, cryptococcal meningitis remain the most common form of CNS cryptococcosis but cryptococcal lymphadenitis as a very rare initial clinical presentation of acquired immunodeficiency syndrome (AIDS) and its clinicopathological characteristics are not well established. Cervical, axillary, inguinal, supraclavicular, hilar, retroperitoneal, and epitrochlear lymph nodes can be involved.⁵

Although cryptococcal infection involves multiple organs, cryptococcosis manifesting as lymphadenitis is very rare.⁶ Most patients with cryptococcosis and AIDS reportedly have a CD4- positive (CD4+) T-lymphocyte count of less than 100 cells/ml.⁷ Thus, the early diagnosis of cryptococcal lymphadenitis is a challenge. Disseminated cryptococcal infection may only be considered once the patient manifests an infection involving the lymph nodes, skin, oral cavity, liver, kidneys and the adrenals. Serotype A (*C. neoformans* var.

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grubii) is responsible for the majority of cryptococcosis cases in the immunocompromised host.⁸

This is to report a case of a cervical lymphadenopathy secondary to *C. neoformans* in a suspected immunocompromised Filipino patient presented with right cervical lymphadenopathy.

Case

The patient is a 33-year-old male who is working as a microfinance operator in a town near Cebu city. He sought consult due to severe headache. The patient is not a known diabetic, hypertensive nor asthmatic, but had previous admissions due to a drug-related hypersensitivity reaction and was also previously diagnosed with idiopathic thrombocytopenia occurring months prior to the patient's confinement. Patient is an occasional alcoholic drinker consuming two glasses of beer on an average and an occasional cigarette smoker consuming smokes one to three sticks of cigarette a day. He denies previous illicit drug use. Coitarche was at 18 years old with a male sexual partner. Patient was reported to have had one female and three male sexual partners, all of which involved penetrative sexual activities e.g. oral and anal sex, without use of contraceptives. He claims to have no history of urinary tract infection (UTI) nor any sexually transmitted infections.

A week prior to his admission, he noted sudden onset of intermittent, severe (pain score of 10/10) headaches at the occipital area radiating to the posterior auricular and frontal areas with associated epigastric pain, non-productive cough, and night sweats. The patient's relatives and partner noted that following his severe headaches, he had episodes of unresponsiveness, with blank stares, followed by upward rolling of eyeballs and generalized rigidity over both upper extremities. These often occurred after the patient complained of severe headache lasting approximately less than two minutes. His headaches were reportedly relieved with effervescent oil massage and were aggravated by sudden assumption of an upright position. Throughout those times he had recurring fever but no attempt to seek a consult from a physician took place.

A day prior to admission, patient noted the presence of a 3.0 cm solid round mass over the right neck. There were noticeable plaques of whitish oral lesions on his tongue, buccal mucosae and hard palate which he observed to be visible almost a fortnight, with unresolved worsening headaches, associated with nuchal rigidity.

At the time of the medical examination, the patient was hyposthenic, with systolic BP of 120-130 mmHg and diastolic BP of 80-100 mmHg with a pulse rate of 90-115 beats/min, respiratory rate of 20-21 cycles/min, and O₂ saturation of 95% at room air. He is likewise febrile with T_{max} of 41°C. He has a firm, nontender, mobile, enlarged left posterior

cervical lymph node. He has multiple whitish plaques on the hard palate, the lateral surface of the tongue and buccal mucosae. His neck was supple. Cardiac and pulmonary findings were normal. Abdominal examination revealed an enlarged spleen. He has variform skin lesions which included plaques seen usually in the lower extremities and feet (Figure 1), acneiform, superficial granulomas and umbilicated papules in most of the legs usually in the antero-lateral aspect of the right thigh (Figure 2). He was lethargic but was oriented to time, place and person. His cranial nerves were intact, and his cerebellar, sensory and motor tests were likewise normal, Brudzinski's sign was positive. Fundoscopic examination was not done due to the irritability of the patient's uncooperative nature.

In the course of the admission, a fine needle aspiration biopsy (FNAB) of the right lateral neck mass was done, cytology revealed mononuclear cells compatible with components of a lymph node and in between the lymphoid elements are numerous spherical yeast like cells surrounded by a capsule or refractile halo dispersed in patternless sheets and appears in singles which confirms cryptococcal lymphadenitis using the H and E stain (Figure 3 and 4). A



Figure 1. Skin lesions showing darkened erythematous patches of varying sizes, right foot.

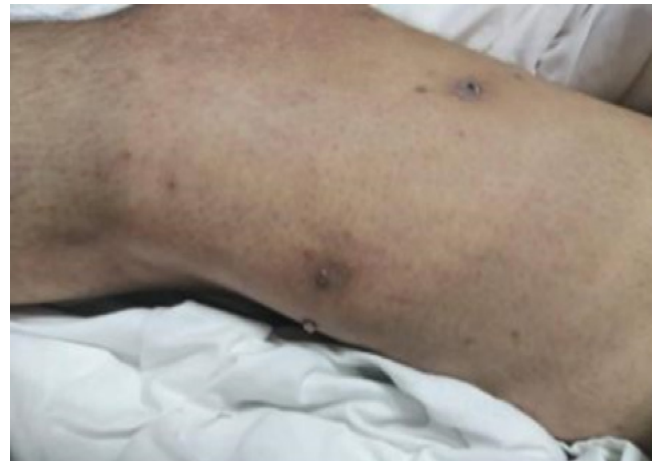


Figure 2. Darkened acneiform lesion with central umbilication on the antero-lateral aspect, right thigh.

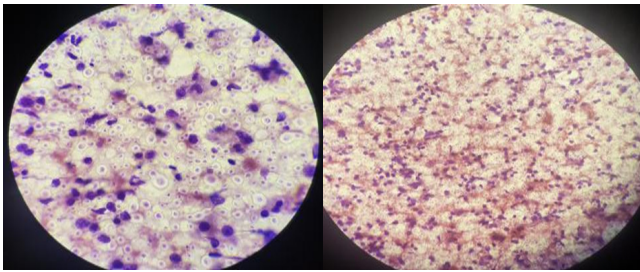


Figure 3.

Figure 4.

Figure 3 and 4: Cervical lymph node sample taken via FNAB. In between the lymphoid elements are numerous spherical yeast like cells surrounded by a capsule or refractile halo dispersed in patternless sheets and appears in singles on oil immersion field and on high power magnification (10x lens) of the lymph node tissue during FNAB using H&E staining method.

screening HIV qualitative test (One Step anti HIV 3.0 Test) was conducted after getting consent from the patient which came out positive. The hospital laboratory then informed the medical team of the confirmatory test to be sent to Manila (San Lazaro Hospital). A cranial CT-scan with contrast was done and results were unremarkable. Sputum Xpert MTB/Rif Assay was negative. Sputum culture grew *Burkholderia cepacia* which was treated with piperacillin - tazobactam 4.5 mg via IV infusion given every eight hours. Blood cultures taken had no growth after five days of incubation. Several attempts to do lumbar tap were unsuccessful due to the recurrence of seizures. He was given 50 mg amphotericin B deoxycholate and 800 mg fluconazole daily. Mannitol was also given to address the increased intracranial pressure. Seizure activities were fairly controlled with administration of leviteracetam and as needed doses of diazepam. After six days of admission, the patient expired.

Post-mortem, lumbar tap was performed and cerebrospinal fluid examinations revealed the presence of encapsulated yeast on India ink stain (Figure 5) with 1:200 titers of cryptococcal antigen. CSF fungal cultures were ordered, yet was not processed due to economic limitations. The confirmatory HIV test for HIV was positive, the result was obtained after his demise.

Discussion

The histological characteristics of *C. neoformans* infection would include gelatinous and granulomatous findings. The inflammatory reactions have been thought to be inadequate in AIDS patients presenting with cryptococcal lymphadenopathy, which could be purportedly explained by the decreased counts of CD4+ T-lymphocytes in this population.⁶

More often than not, the case of cryptococcal lymphadenopathy is overlooked at the initial presentation due to its rarity. The burden of TB mimicking and presenting the same physical manifestation should be well noted. The reason why cryptococcal infections are initially diagnosed as extrapulmonary TB is that both have similar manifestations. Despite the need for urgency for precise diagnosis, only

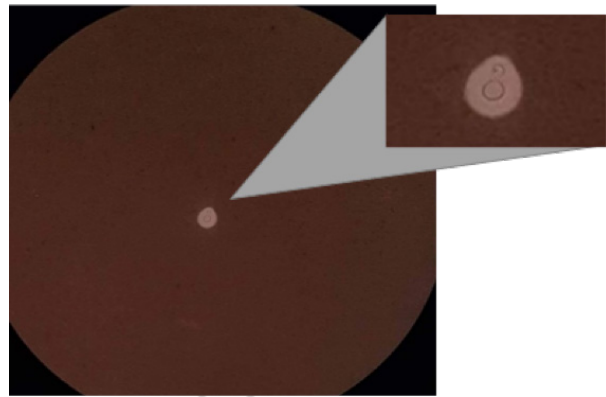


Figure 5. CSF fungal smear showing an encapsulated yeast diagnostic of cryptococcal infection.

histopathology and microbiological examinations can determine whether or not the case is TB. Both involve the cervical, axillary and inguinal lymph node regions. Both also have non-specific presentations which were seen in the patient's case that include fatigue, low grade fever, night sweats and weight loss. The results of fine needle aspiration cytology (FNAC) in both cases include evidence of granulomatous inflammation.⁹

Recent methods to exclude TB do not apply to the presented case in this paper. Takkar, et al. developed a diagnostic algorithm to indicate non-TB etiology where, in order to determine if the case is non-TB, there should be lack of resolution of clinical symptoms after two months of starting therapy.⁴

Cryptococcal lymphadenitis is one of the defining criteria of AIDS according to the Centre for Disease Control and Prevention guidelines.¹⁰ Laboratory diagnosis of this infection includes demonstration of the cryptococci by using special stains such as India ink, PAS-AB, mucicarmine stains and serological detection of cryptococcal antigens by the agglutination latex method and culture.¹¹

In a case study conducted by Pia Dogbey and Marjorie Golden, et al., it is reported that an unusual initial presentation of cryptococcal lymphadenitis of HIV infection diagnosed through lymph node biopsy and treated with Liposomal amphotericin B and 5-flucytosine for two weeks, followed by an eight-week treatment with fluconazole.¹² In a separate study conducted in India it focused on analysis of lymph node specimens from a population of HIV infected patients.¹³ These patients were then found to have had either TB or reactive lymphadenitis. It is noted that only 1.3% of the lymph node samples analyzed was found to be positive for cryptococcus.

From the above case discussion, it is apparent that the rarity of the infection and the prevalence of TB has compromised the early detection of cryptococcal lymphadenitis by the prevailing physical examination methods.

Conclusion

The setting and nature of any lymphadenopathy would warrant an obvious diagnosis of tuberculous in origin, yet this case unfolded surprisingly a different disease entity. The presentation and diagnosis of cryptococcal lymphadenitis remain elusive and difficult due to its similarity in manifestations with TB. This poses difficulties in situations where no prior consults were done as of this case and in resource-limited settings. Cryptococcal infection should be a diagnostic consideration for lymphadenopathy in any patient, regardless of known HIV status. This case features the importance of keeping a high index of suspicion in patients presenting with non-specific lymphadenopathy. A rapid, cost-efficient and precise methodology in diagnosing cases of lymphadenopathy remains to be FNAB of the involved lymph node. Since there is scarce literature on cases where the subject is immunocompetent it is also recommended that further studies in the early diagnosis of cryptococcal lymphadenitis infection be developed.

Authors' Declaration

The author of this research paper receives research support from the Visayas Community Medical Center - Department of Internal Medicine and also is a resident of the same institution. The terms of this arrangement have been reviewed and approved by the Visayas Community Medical Center Institutional Review Board in accordance with its policy on objectivity in research. This is a joint research with the co-author, Dr. Dax Ronald Librado, an Internal Medicine Consultant practicing in the same institution with no conflict of interest .

References

1. **Derek J Sloan, Paris V.** Cryptococcal meningitis: epidemiology and therapeutic options. *Clinical Epidemiology*. Vol 2014:6, pp. 169-182.
2. **Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.** Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
3. **Del Poeta, Maurizio, et.al.** Synthesis and Biological Properties of Fungal Glucosylceramide. *PLOS Pathogens*. Vol. 10 Is.1. New York. January 2.
4. **Thakkar, Karan.** Lymphadenopathy: Differentiation between Tuberculosis and Other Non-Tuberculosis Causes like Follicular Lymphoma. *Frontiers in Public Health*. Vol. 4 Is. 31. Published online. February 2016.
5. **Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al.** Clinical Practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291-322.13-5
6. **Matobogolo M. Boaz, Samuel Kalluvya, Jennifer A. Downs, Bonaventura C. T. Mpondo, and Stephen E. Mshana.** Pattern, Clinical Characteristics, and Outcome of Meningitis among HIV-infected Adults in a Tertiary Hospital in North Western Tanzania: A Cross Sectional Study. *Journal of Tropical Medicine*. Volume 2016.
7. **Radha Rajasingham, Rachel M Smith, et al.,** "Global Burden of disease of HIV-associated cryptococcal meningitis: an updated analysis," HHS Public Access. Author Manuscript. *Lancet Infect Dis*. 2017 August.
8. **Aline Z. de Azambuja, Gustavo Wissman Neto, et al.,** "Cryptococcal Meningitis: A Retrospective Cohort of a Brazilian Reference Hospital in the Post-HAART Era of Universal Access." *Hindawi. Canadian Journal of Infectious Diseases and Medical Microbiology*. Volume 2018.
9. **Marian Poley, MS, et al.,** (2019) "Cryptococcal Meningitis in an Apparent Immunocompetent Patient," *Journal of Investigative Medicine High Impact Case Reports*. Volume 7: 1-5.
10. **Filipe A. Colombo, Rogerio Brasiliense Elsemann, et al.,** (2014) "Updating: Cryptococcosis Diagnostic Aspects," *Journal of AIDS & Clinical Research*. Volume 5. Issue 12.
11. **Jitendra G. Nasit and Gauravi Dhruva,** (2016 Jul-Dec) "Cryptococcal lymphadenitis in a Human Immunodeficiency virus - infected patient: A diagnostic role of fine needle aspiration cytology and special stains" *Indian Journal of Sexually Transmitted Diseases and AIDS*.
12. **Pia Dogbey, Marjorie Golden, et al.** Cryptococcal lymphadenitis: an unusual initial presentation of HIV infection. *BMJ Case Report* 2013. Connecticut, USA
13. **Kamana NK, Wanchu A, et al.** Tuberculosis is the leading cause of lymphadenopathy in HIV-infected persons in India: results of a fine-needle aspiration analysis. *Scand J Infect Dis* 2010;42:827-30.