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CASE REPORT

Disseminated Cryptococcosis in an HIV-Negative Young Malay Female with Underlying Mediastinal Hodgkin Lymphoma: Case Report and Review of Literature

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ABSTRAK

Kriptokokosis biasanya disebabkan oleh Cryptococcus neoformans dan Cryptococcus gattii, yang membentuk kompleks Cryptococcus. Jangkitan ini berkait rapat dengan pesakit berstatus positif-'human immunodeficiency virus' (HIV) dan sering menyebabkan pesakit berstatus negatif HIV terabai. Keadaan ini lebih ketara apabila pesakit mempunyai penyakit serentak lain yang boleh menyembunyikan gejala meningitis kriptokokus yang kelihatan tidak begitu ketara. Hasilnya ialah kelewatan diagnosis yang membawa kepada kelewatan rawatan dan prognosis yang lebih buruk untuk pesakit ini. Selain itu, pesakit limfoma yang menjalani kemoterapi menghadapi cabaran berganda, kerana kedua-dua penyakit dan rawatan menyumbang kepada kelemahan sistem imun, menyebabkan mereka terdedah kepada jangkitan patogen dan oportunistik. Dalam laporan kes ini, kami membentangkan kes seorang wanita Melayu berusia 36 tahun, tanpa sejarah jangkitan HIV tetapi menghidapi penyakit limfoma Hodgkin mediastinal. Beliau mengalami jangkitan Cryptococcus neoformans yang merebak secara serentak dan akhirnya meninggal dunia akibat jangkitan tersebut.

Kata kunci: *Cryptococcus; HIV-negatif; limfoma Hodgkin; meningitis*

ABSTRACT

Cryptococcosis is mainly caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, which form the Cryptococcus complex. The infection is closely related to the human immunodeficiency virus (HIV)-positive status of the patient and often leaving HIV-negative patients overlooked. This is particularly noticeable when patients have other concurrent illnesses that mask the seemingly inconspicuous symptoms of cryptococcal meningitis. The result is a late diagnosis, which leads to delayed treatment and a poorer prognosis for these patients. In addition, lymphoma patients undergoing chemotherapy face a double challenge, as both the disease and the treatment contribute to a weakened immune system, leaving them vulnerable to pathogenic and opportunistic infections. In this case report, we presented a 36-year-old Malay female, with no history of HIV infection but with underlying mediastinal Hodgkin lymphoma. She concurrently developed disseminated Cryptococcus neoformans infection and eventually succumbed to the infection.

Keywords: Cryptococcus; HIV-negative; Hodgkin lymphoma; meningitis

INTRODUCTION

Cryptococcosis is mainly caused by C*ryptococcus neoformans* and *Cryptococcus gattii*, which form the Cryptococcus complex. It mainly occurs in immunocompromised patients, i.e. acquired immunodeficiency syndrome (AIDS) and other cellular immunodeficiency diseases such as lymphoma, leukaemia and systemic lupus (Kwon-Chung et al. 2000). However, infections in immunocompetent individuals have also been reported (Syazana & Hing 2018; Varghese et al. 2024). In people living with human immunodeficiency virus (HIV), cryptococcosis has undergone a biphasic evolution, starting with an increase in cases in the early 1980s, when HIV had just been discovered, to the decline of this infection in HIV-positive patients after the introduction of highly active antiretroviral therapy (HAART) (Mirza et al. 2003). However, this particular wave of change was not observed in HIV-negative cryptococcosis patients. In patients with underlying lymphoma, both the disease and chemotherapy treatment significantly affect the immune network (Mancuso et al. 2022). We reported the case of an HIV-negative, 36-year-old Malay female with underlying mediastinal Hodgkin lymphoma (HL) and concomitant disseminated *Cryptococcus neoformans* infection.

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A 36-year-old Malay woman with a history of bronchial asthma and eczema, was first diagnosed with primary mediastinal HL (mixed cellularity stage IIB) in 2018. She completed Adriamycin-Bleomycin-Vinblastine-Dacarbazine (ABVD) chemotherapy in August 2018 but relapsed during her first pregnancy in 2020. After further ABVD therapy in 2021, she discontinued planned salvage therapy and was last seen in June 2022.

In June 2023, she presented with cough and cervical lymph node swelling. Diagnosed with recurrent HL with obstructive signs and pneumonia, she was treated with intravenous antibiotics and later referred for further management. Computed tomography (CT) imaging revealed enlarging necrotising lymph nodes causing tracheal stenosis and superior vena cava obstruction. A lymph node biopsy confirmed HL, and she began Escalated Bleomycin-Etoposide-Adriamycin-Cyclophosphamide-Oncovin-Procarbazine-Prednisolone (ESC-BEACOPP) therapy. Blood cultures showed methicillin-resistant coagulase-negative *Staphylococcus* species. During hospitalisation, she experienced occasional headaches and vomiting, which subsided with paracetamol.

After discharge, her symptoms worsened, with severe headaches, vomiting and altered consciousness. She was readmitted and developed focal seizures. A plain CT scan revealed a white matter lesion without hydrocephalus or oedema. Ceftriaxone, (2 g intravenously every 12 hours) was started, later switched to meropenem (2 g intravenously every 8 hours). A lumbar puncture was performed and the cerebrospinal fluid revealed Gram-positive rounded yeast cells and encapsulated yeast cells on India ink preparation (Figure 1). Other tests including for HIV, Hepatitis B, Hepatitis C and tuberculosis were negative. Amphotericin B 1 mg/kg/day intravenously plus flucytosine 100 mg/kg/day orally were started immediately.

Unfortunately, despite prompt amphotericin B and flucytosine treatment, she experienced worsening seizures and declining Glasgow Coma Scale (GCS). On day-3 of antifungal therapy, she was intubated and transferred to the Intensive Care Unit (ICU), where CT imaging showed hypoxic-ischemic brain injury with tonsillar herniation. With deteriorating clinical status, her family was informed of her prognosis, and she succumbed to her disease following episodes of supraventricular tachycardia and poor GCS recovery.

DISCUSSION

Cryptococcus neoformans predominantly affects immunocompromised individuals, especially those with HIV/AIDS. It causes cryptococcal

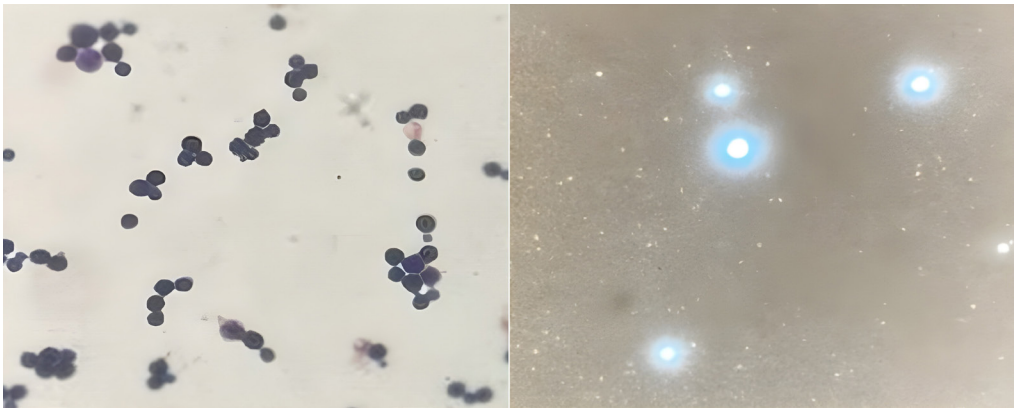

FIGURE 1: Left: Gram stain showing round yeast cells with budding; Right: India ink preparation positive for encapsulated yeasts

meningitis, a serious condition leading to respiratory and neurological complications, with symptoms like headache, fever and altered mental status. While *Cryptococcus neoformans* is the most common cause, other species, such as *Cryptococcus humicolus* (Ramli et al. 2012) and *Cryptococcus laurentii* (Ding & Kamarudin 2018) have also been reported. In HIV patients, antifungal treatment and antiretroviral therapy (ART) are vital for preventing opportunistic infections. The advent of highly active ART (HAART) in the 1990s significantly reduced cryptococcosis cases in HIV patients, but it remains a concern, with an estimated 152,000 annual cases of cryptococcal meningitis leading to 112,000 deaths globally (Rajasingham et al. 2022).

Cryptococcosis also occurs in non-HIV conditions like cerebral lupus (Khoo et al. 2020), pontine infarcts (Sakthiswary et al. 2015) and hypogammaglobulinemia (Zainal et al. 2011), yet these cases are often underdiagnosed. This neglect can lead to diagnostic delays, as seen in patients initially misdiagnosed with space-occupying lesions, intracranial haemorrhage or tuberculosis. Prompt recognition and appropriate treatment of cryptococcal infections are critical, regardless of HIV status, to improve patient outcomes.

A PubMed search for *Cryptococcus neoformans* infection in lymphoma patients (2011-2023) identified 12 reports involving 13 individuals aged 6-79 years. Among these, one (7.7%) were HIV-positive, six (46.2%) HIV-negative and six (46.2%) had unknown HIV status. Headache was the predominant symptom, and blood and cerebrospinal fluid (CSF) were the main diagnostic samples. Most patients had received chemotherapy for lymphoma, and treatments for cryptococcosis included amphotericin B, liposomal amphotericin B, fluconazole, with occasional use of flucytosine and voriconazole. Survival was reported in 9/13 (69.2%) of cases after antifungal treatment. Detailed case summaries were provided in Table 1.

Lymphoma and its treatment suppress the immune system, increasing susceptibility to infections. Lymphoma originates in the lymphatic system, disrupting lymphocyte function, which compromises the immune response. Cancerous lymphocytes proliferate uncontrollably, crowding out healthy cells and reducing immunity (Pace et al. 2007). Bone marrow infiltration by lymphoma further reduces the production of white blood cells, weakening the body's ability to fight pathogens (Mancuso et al. 2022). Additionally, chemotherapy exacerbates white blood cell

TABLE 1: Summary of reported cryptococcosis cases with underlying lymphoma (sorted by year of publication).

References	Age, Gender	Type of Lymphoma	HIV Status	Symptoms & signs	Samples Positive for *Cr. neoformans*	Chemotherapy	Antifungal Received	Patient Outcome
Wong et al. (2011)	58, F	Enteropathy-associated T-cell lymphoma	Negative	Abdominal pain, weight loss	Lymph node tissue	Given (Methotrexate, ifosphamide, L-asparaginase, etoposide)	FLU	Alive
To et al. (2012)	66, M	Nodal marginal zone B-cell lymphoma	Negative	Right-sided rib pain, headache, fever	Rib bone, serum	Given (Rituximab, cyclophosphamide, vincristine, prednisolone, etoposide, procarbazine, cyclophosphamide)	LAMB, FLU	Alive
Nandennavar et al. (2014)	45, M	Follicular lymphoma	Negative	Right neck swelling, headache, reduce vision, fever, vomiting, cervical lymphadenopathy	CSF	Given (Cyclophosphamide, adriamycin, vincristine, prednisolone)	AMB, FLU	Alive
Wang & Kelley (2015)	27, M	CNS lymphoma	Positive	Headache, diplopia, malaise	CSF	Not stated	FLU	Alive
	70, M	Mantle cell lymphoma	Not stated	Altered mental status, visual hallucination, headache	CSF, serum	Given (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, bortezomib, ibrutinib, lenalidomide)	AMB, FLC, FLU	Alive
Sun et al. (2018)	78, M	Mantle cell lymphoma	Not stated	Imbalance, headache, double vision	CSF	Given (R-CHOP regime, bortezomib, rituximab, bendamustine,Bexxar, lenalidomide, ibrutinib)	AMB, FLC, FLU	Not stated
Swan & Gottlieb (2018)	79, M	Diffuse large B-cell lymphoma	Not stated	Left-sided chest pain, dyspnoea	Serum, pleural fluid	Given (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, ibrutinib)	LAMB, FLU	Alive

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References	Age, Gender	Type of Lymphoma	HIV Status	Symptoms & signs	Samples Positive for *Cr. neoformans*	Chemotherapy	Antifungal Received	Patient Outcome
Pereira et al. (2020)	48, M	Nodular sclerosis Hodgkin lymphoma	Negative	Headache, photophobia, vomiting	Blood, CSF	Given	LAMB, FLU	Alive
Hengeveld et al. (2020)	59, M	Follicular lymphoma	Negative	Fatigue, fever	Blood, CSF	Given (Rituximab, cyclophosphamide, vincristine, prednisolone, bendamustine, lenalidomide, idelalisib)	LAMB, FLC, FLU	Alive
Khursheed et al. (2022)	6, M	Suspected lymphoma	Not stated	Fever, abdominal pain and distension, vomiting, skin lesion, cervical lymphadenopathy	Lymph node tissue, blood, CSF, skin tissue	Not stated	AMB, FLU	Passed away
Mundada & Ahmed (2022)	67, M	Hodgkin lymphoma	Negative	Cervical lymphadenopathy, fever, headache	IHC of lymph node tissue	Not stated	Not stated	Not stated
Silva et al. (2020)	72, M	Non-Hodgkin lymphoma	Not stated	Fever, vertigo, lack of appetite, nausea, epigastralgia	Blood	Given	FLU	Passed away
Zhang et al. (2022)	20, M	Lymphocyte-rich Hodgkin lymphoma	Negative	Headache, nausea, vomiting, cervical lymphadenopathy, cervical rigidity	CSF	Given (Doxorubicin, bleomycin, vinblastine, dacarbazine)	LAMB, FLC, VOR	Alive

AMB: Amphotericin B; CNS: Central nervous system; CSF: Cerebrospinal fluid; F: Female; FLC: Flucytosine; FLU: Fluconazole; IHC: Immunohistochemistry; HIV: Human immunodeficiency virus; LAMB: Liposomal amphotericin B; M: Male; VOR: Voriconazole

suppression, impairing lymphocyte and antibody production, which are crucial for pathogen recognition and neutralisation. Enlarged cancer lymph nodes also lose their filtering function, making patients more vulnerable to infections (Menzel et al. 2020). These combined factors significantly weaken the immune defenses in lymphoma patients.

Chemotherapy is a key lymphoma treatment administered intravenously or orally in cycles, combining drugs like the doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) regimen to kill cancer cells (Ullah et al. 2023). While effective against cancer, its cytotoxic effects also harm healthy cells, disrupting normal functions, particularly immune defenses. This increases vulnerability to pathogens and opportunistic infections, such as *Cryptococcus neoformans*. The treatment's impact on immunity highlights the balance needed to manage both cancer and infection risks.

Accurate sampling is crucial for detecting microorganisms, requiring proper sample selection, timing and techniques. Deviations can cause false negatives, hindering accurate diagnoses. The patient's initial respiratory symptoms, asthma history and headache resolving with paracetamol further delayed recognition of cryptococcal meningitis. These factors highlight the importance of precise sampling and thorough clinical evaluation.

During the patient's second admission, worsening symptoms of increased intracranial pressure prompted a lumbar puncture for CSF sampling. However, cryptococcal infection was initially overlooked, likely due to the patient's HIV-negative status. As noted by Pappas (2013), cryptococcal infections in non-HIV, non-transplant patients represent a diverse group, including individuals with chemotherapy-induced immunosuppression, organ dysfunction or congenital immunodeficiencies. This heterogeneity complicates the understanding of epidemiology, clinical presentation and outcomes, making it challenging to establish a universal treatment regimen for this subgroup.

Cryptococcal infection is definitively diagnosed using culture and sensitivity tests, the gold standard in diagnostics, though they take at least 48 hours for results. Faster genotypic methods, like polymerase chain reaction (PCR), provide rapid and specific results but require sophisticated equipment, trained personnel, and are mostly limited to reference laboratories. In this case, multiplex PCR provided meningitis/encephalitis panel results within 2 hours, and serological testing via latex agglutination detected cryptococcal antigens in 1 hour, though postzone phenomena can cause false negatives (Malik et al. 2021). India ink staining allowed immediate detection of encapsulated cryptococcal yeasts, prompting timely antifungal therapy. This highlights the value of combining phenotypic, genotypic, serologic and rapid tests for accurate, efficient diagnosis and treatment.

CONCLUSION

In summary, it is crucial to maintain a high clinical suspicion of cryptococcal meningitis in immunocompromised patients, regardless of their HIV status. This is particularly important when these patients present with symptoms suggestive of increased intracranial pressure.

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