



CASE REPORT

REVISED Case Report: Cryptococcal meningitis in Hodgkin’s Lymphoma patient receiving brentuximab-vedotin therapy [version 2; peer review: 2 approved]

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V2 First published: 08 Jul 2020, 9:687 <https://doi.org/10.12688/f1000research.24816.1>
 Latest published: 12 Aug 2020, 9:687 <https://doi.org/10.12688/f1000research.24816.2>

Abstract

Cryptococcus neoformans infections occur mostly in immunodeficient individuals, being the most common opportunistic fungal central nervous system (CNS) infection in HIV seropositive patients. Moreover, other conditions affecting host immunity, such as hematologic malignancies, organ transplantation and immunosuppressive drugs are implicated as risk factors.

The authors present a case of a 48-year-old male with Hodgkin Lymphoma for 26 years and submitted to several lines of treatment, diagnosed with cryptococcal meningitis while on therapy with brentuximab. The patient presented with positive cerebral spinal fluid (CSF) cryptococcal antigen plus positive blood cultures. He was put under induction antifungal treatment with liposomal amphotericin B and flucytosine, as well as corticosteroid therapy with dexamethasone with headache improvement and a favorable clinical evolution. There are no reported cases of cryptococcal meningoencephalitis under CD30-directed monoclonal antibody. Furthermore, this case illustrates the risk of *Cryptococcus neoformans* infection in immunocompromising conditions other than HIV, underlining the need of considering this differential diagnosis when physicians face an opportunistic neuroinfection.

Keywords

C. neoformans, Brentuximab-vedotin, Hodgkin Lymphoma, Meningitis

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 2 (revision) 12 Aug 2020		 report
version 1 08 Jul 2020	 report	 report

- Adriana Roque** , Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
Coimbra Institute for Clinical and Biomedical Research (iCBR), Coimbra, Portugal
 - Sarah A. Schmalzle**, University of Maryland School of Medicine, Baltimore, USA
- Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Cunha Pereira T:** Conceptualization, Writing – Original Draft Preparation; **Rb-Silva R:** Writing – Review & Editing; **Félix Soares R:** Writing – Review & Editing; **Domingues N:** Supervision, Writing – Review & Editing; **Mariz J:** Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Cunha Pereira T, Rb-Silva R, Félix Soares R *et al.* **Case Report: Cryptococcal meningitis in Hodgkin's Lymphoma patient receiving brentuximab-vedotin therapy [version 2; peer review: 2 approved]** F1000Research 2020, 9:687 <https://doi.org/10.12688/f1000research.24816.2>

First published: 08 Jul 2020, 9:687 <https://doi.org/10.12688/f1000research.24816.1>

REVISED Amendments from Version 1

As suggested by the peer review reports, grammar corrections have been made in this new version.

Any further responses from the reviewers can be found at the end of the article

Learning points

- Cryptococcal meningitis is a common opportunistic central nervous system (CNS) infection among HIV-positive patients. However, it also affects HIV seronegative patients.
- Every immunocompromising condition must be assessed and considered a risk factor for an opportunistic fungal meningoencephalitis. A therapeutic agent affecting host immunity, such as with CD30-directed monoclonal antibody, may predispose to opportunistic infections.
- Cryptococcal meningitis diagnosis may be challenging in cases presenting negative cerebral spinal fluid (CSF) cultures, but cryptococcal polysaccharide antigen titers in CSF correlate with fungal burden.

Background

Cryptococcus species have a major predilection for the lungs with potential to spread further, mainly through continuity or through hematogenic and lymphoid pathways, with possible penetration through the blood-brain barrier and CNS involvement¹⁻⁴.

Cryptococcus neoformans infections occur mostly in immunodeficient individuals, being the most common opportunistic CNS infection in HIV-positive patients, counting up to 1 million new infections annually worldwide^{3,4}. It also occurs in transplant recipients, patients with hematological malignancies, as well as patients receiving immunosuppressive medications^{1,2,4}.

This case reports an opportunistic CNS infection in a patient with Hodgkin Lymphoma under brentuximab after multiple lines of treatment for over 20 years, including an allogenic stem cell transplantation. Despite being reported as a common fungal infection in HIV-patients, neuroinfections in patients under CD30-directed monoclonal antibody therapy or other drugs besides immunosuppressants are a rare occurrence.

Case presentation

A 48-year-old Caucasian male presented at the outpatient clinic in May 2019 with holocranial headache, more intense at occipital level, lasting for 6 days, with increasing intensity over the last couple of hours, associated with photophobia and vomiting.

The patient was diagnosed in 1993 with Classic Hodgkin Lymphoma, nodular sclerosis subtype, stage IVB, achieving complete remission after first line chemotherapy. Since then, the patient suffered several relapses and underwent radiotherapy,

one autologous bone marrow transplant in 1998, as well as an allogenic stem cell transplant in 2001, followed by several lines of chemotherapy. From October 2018 to this episode, the patient was taking brentuximab due to a hepatic hilar lesion. Sequential imaging assessments showed a large left infratentorial arachnoid cystic lesion that was being monitored. (Figure 1).

At first evaluation, the patient was conscious and aware, hemodynamic stable and subfebrile, presenting general tremors and limited cervical mobility.

Blood workup revealed elevated C-reactive protein with 73.2 mg/L (normal range under 5 mg/L), without other abnormalities.

A head computed tomography (CT) scan showed the pre-existing cystic lesion in the left cerebellopontine angle with a slight right brainstem deviation, without associated edema (Figure 2A), confirmed by magnetic resonance imaging (Figure 2B). The case was discussed with the Neurosurgery Department and a lumbar puncture was postponed as it was considered a high-risk procedure. The patient started antibiotics with ceftriaxone (2 g q12h) and ampicillin. (2g q4h) At day 4, blood cultures came back positive for *Cryptococcus neoformans* sensitive to Posaconazole, Amphotericin B and Itraconazole, so that patient started Liposomal Amphotericin B (3mg/kg id) and Flucytosine (100 mg/kg per day orally in four divided doses) for 14 days and low dose corticosteroid therapy (4 mg per day). There was a progressive improvement of the symptoms and patient was discharged after 19 days with prescription of Fluconazole (400mg per day).

After one month of treatment, a ventricular puncture was performed and normal pressure cerebrospinal fluid (CSF) revealed glucose consumption and elevated levels of proteins (Table 1), as well as positivity for cryptococcal polysaccharide capsular antigen. Follow-up lumbar punctures were performed to assess



Figure 1. Head computed tomography (CT) scan revealing a large left extra-axial cystic lesion that was being monitored before current symptomatology.



Figure 2. Head computed tomography (CT) scan showed the pre-existing cystic lesion in the left cerebellopontine angle with a slight right brainstem deviation, without associated edema (2A), as confirmed by magnetic resonance imaging (MRI) (2B).

Table 1. Cerebrospinal fluid profile evolution throughout treatment. CSF – Cerebrospinal fluid. LP – Lumbar puncture. NV – Normal value.

Characteristic	LP date			
	27-06-2019	17-07-2019	31-07-2019	16-09-2019
Appearance	Clear	Clear	Clear	Clear
Nucleated cells count	104/ μ L	43/ μ L	35/ μ L	5/ μ L
Glucose (NV: 2.8 – 4.4 mmol/L)	2,3 mmol/L	3.1 mmol/L	3,4 mmol/L	3,3 mmol/L
Protein level (NV: 150 – 450 mg/L)	838 mg/L	583 mg/L	529 mg/L	544 mg/L
CSF culture	Negative	Negative	Negative	Negative
<i>Cryptococcus neoformans</i> antigen	Positive	Positive	Positive	Positive

CSF characteristics and cryptococcal antigen assessment. Patient was kept under consolidation therapy with Fluconazole for 10 weeks with a favorable clinical evolution, as well as decreasing levels of protein and nucleated cells count as seen in Table 1. Patient maintains close surveillance under regular appointments at the Onco-Haematology Clinic. However, headache complaints increased in intensity shortly after dexamethasone discontinuation with an intermittent pattern. Patient died in another hospital about 8 months after the meningitis diagnosis due to a cardiovascular event.

Discussion

Cryptococcal meningitis accounts for up to 1 million new infections annually, mainly affecting HIV-positive patients. Other immunocompromising conditions such as organ transplantation, hematologic malignancies and immunosuppressive drugs constitutes other relevant risk factors to these opportunistic fungi CNS infections¹⁻⁴.

In a recent review of *Cryptococcus neoformans* infections in patients with cancer, 82% corresponded to patients with haematological malignancies and from these patients, approximately 54% had lymphoma⁵.

The patient presented several conditions affecting host immunity due to several previous lines of treatment for over 25 years. However, *Cryptococcus* species were not considered the etiological agent for a possible opportunistic neuroinfection, emphasizing the need for an initial lumbar puncture to exclude fungal agents. This procedure was not possible at first evaluation and it delayed the start of antifungal therapy.

Although there are many published case reports of Cryptococcosis in patients with lymphoma, this is the first reported case of Cryptococcal neuroinfection in a patient with Hodgkin's Lymphoma treated with CD-30-directed monoclonal antibody.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient prior to their death.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 23 September 2020

<https://doi.org/10.5256/f1000research.28541.r69298>

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Sarah A. Schmalzle

Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA

No new comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease, HIV, cryptococcosis, Group A Strep

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 30 July 2020

<https://doi.org/10.5256/f1000research.27380.r68025>

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Sarah A. Schmalzle

Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA

This is a clinically relevant case report as it is purportedly the first report in a patient being treated with a particular immunosuppressive monoclonal Ab.

There are several minor language and grammatical improvements to be made that will strengthen

and clarify the report. It should have an additional round of editing by a native English speaker.

Examples:

1. HIV-positive should be 'people living with HIV'.
2. Abstract: 'fungi central nervous system..' should be fungal.
3. Brentuximab should be in lower case throughout. It is not explained with it is 'brentuximab-vedotin' in keywords but 'brentuximab' elsewhere.
4. End of abstract - opportunist should be opportunistic.
5. This sentence needs an English language revision: "However, these fungi neuroinfection affects HIV seronegative patients."
6. Background - it is not accurate to say crypto has a predilection for the lungs. The lungs are the route of entry, but this is a neurotropic pathogen.
7. 'penetration into' should be 'penetration through'.
8. Case presentation: "over the last couple hours" should be "over the last couple of hours" or "over the last several hours".
9. The use of 'under' to describe being prescribed a treatment is not commonly how this is stated in the US. Try "treated with" or "on treatment for ___ with ___".
10. Also not common to say patients are admitted at the outpatient clinic. Patients are seen or evaluated at a clinic, but admitted to a hospital.
11. This sentence also needs to be revised for proper grammar/syntax. "Throughout image assessments, a large left infratentorial arachnoid cystic lesion was being monitored."
12. Susceptibilities are not commonly reported in Crypto case reports. There is not known resistance and generally all therapy is empiric.
13. Corticotherapy should be corticosteroid therapy.
14. This needs to be reworded for clarity: "However, Cryptococcus species were not considered the etiological agent for a CNS infection, emphasizing the need for an initial lumbar puncture to exclude fungal agents when approaching opportunist neuroinfection. This was not possible at first evaluation in this case which delayed antifungal therapy."

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease, HIV, cryptococcosis, Group A Strep

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 July 2020

<https://doi.org/10.5256/f1000research.27380.r66704>

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Adriana Roque 

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I think that this is an interesting report that claims for attention to rare infections in patients under immunotherapy and other novel therapies, especially when they are more difficult to diagnose (due to the location and the infectious agent).

This report provides a concise and informative history of the case, mainly focus on the difficulties of the process.

I consider that it would be important to provide information about the previous therapeutics that the patient had received, including the transplantation conditioning regimen, as well as the development of graft versus host disease (GvHD) and GvHD therapeutics, because it can help to explain the subjacent immunosuppression state. Another helpful information is to understand if Hodgkin lymphoma was under control at the time of CNS infection presentation.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment

given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.**Reviewer Expertise:** Hematology, Hematology-oncology**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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