Jilani et al. Scr Med. 2024 Jan-Feb;55(1):119-22. DOI:10.5937/scriptamed55-47512

CASE REPORT

Metastatic Cryptococcosis as a Manifestation of Immune Reconstitution Inflammatory Syndrome in a Patient With COVID-19 Infection

Abdulhakim Jilani,[1] Mohamed Alshmandi,[2] Julia Kiernan[2]

Abstract

Disseminated cryptococcosis is an infrequent fungal illness primarily observed in immunocompromised individuals, particularly among those with human immunodeficiency virus (HIV). In this report, a case where the initiation of antiretroviral therapy revealed a previously hidden *Cryptococcus* infection in an HIV-positive male who also had COVID-19 is presented. A 30-year-old male with a medical history of HIV sought medical attention at the Emergency Department due to the presence of a widespread, non-itchy skin rash along with severe difficulty breathing. Diagnosis of unmasking immune reconstitution inflammatory syndrome (IRIS) associated with disseminated cryptococcosis, all while testing positive for COVID-19 was made based on clinical presentation and performed analyses. COVID-19 management guidelines were strictly adhered to and treatment included the administration of steroids, amphotericin B and fluconazole. Additionally, empirical coverage for *Pneumocystis carinii* pneumonia (PCP) was initiated. Regrettably, the patient's clinical condition deteriorated in the following days, ultimately resulting in his passing. The ongoing pandemic has understandably prioritised the diagnosis of COVID-19 by healthcare providers, sometimes overshadowing the exploration of alternative diagnoses. It is crucial to maintain a heightened clinical suspicion for opportunistic infections, especially among immunocompromised individuals, particularly those with HIV.

Key words: COVID-19; HIV; Cryptococcosis.

1. Department of Medicine, Tipperary University Hospital, Clonmel, Ireland.
2. Department of Medicine, Tallaght University Hospital, Dublin, Ireland.

Citation:
Jilani A, Alshmandi M, Kiernan J. Metastatic cryptococcosis as a manifestation of immune reconstitution inflammatory syndrome in a patient with COVID-19 infection. Scr Med. 2024 Jan-Feb;55(1):119-22.

Corresponding author:
MOHAMED ALSHMANDI
E: malshmandi@gmail.com
T: +353852431204

Received: 3 November 2023
Revision received: 17 January 2024
Accepted: 17 January 2024

Introduction

Disseminated cryptococcosis is an infrequent fungal illness primarily observed in immunocompromised individuals, particularly among those with human immunodeficiency virus (HIV). In this report, a case where the initiation of antiretroviral therapy revealed a previously hidden *Cryptococcus* infection in an HIV-positive male who also had COVID-19 is presented.

Case history

A 30-year-old African male, with a prior medical history of HIV, presented to the Emergency Department at Nelson Mandela Academic Hospital in South Africa. He displayed a widespread, non-pruritic skin rash and severe shortness of breath. His HIV diagnosis was established two weeks prior by his general practitioner (GP), who had initiated him on first-line antiretroviral ther-

apy using a fixed-dose combination. In South Africa, GPs have the authority to commence antiretroviral therapy. His baseline CD_4^+ cell count was measured at 2 cells/mm^3.

Upon examination, the patient was tachypnoeic and dehydrated, with an elevated heart rate and his oxygen saturation level was 84 % while breathing room air. He presented with oral thrush and a diffuse, nodular skin rash that covered his entire body (Figure 1). His Glasgow coma scale (GCS) score was 15/15 and there were no signs of neck stiffness or neurological deficits. Chest auscultation revealed clear lung fields and normal heart sounds.

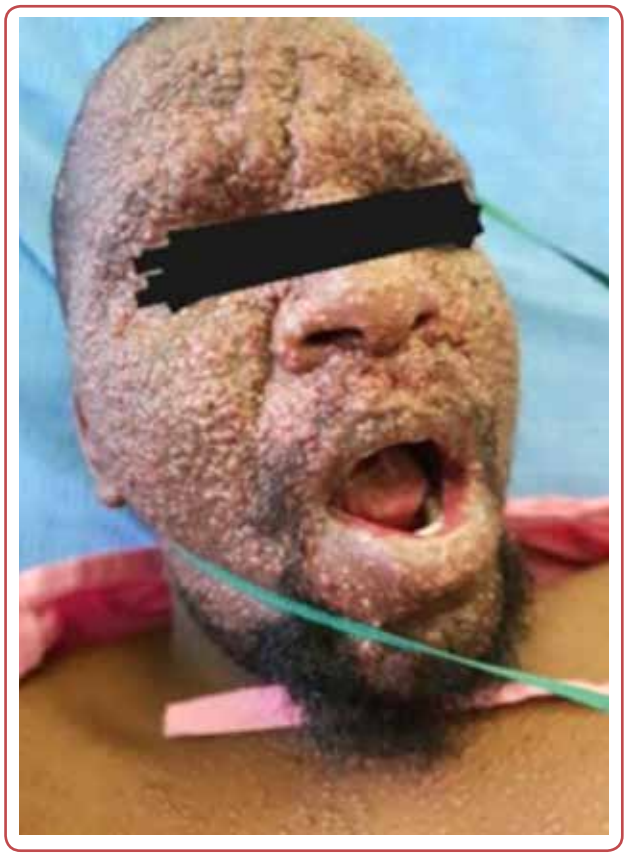

Figure 1: Oral thrush and a diffuse, nodular skin rash

Relevant diagnostic investigations were performed. Chest X-ray was within normal limits. Computed tomography (CT) and CT pulmonary angiogram (CTPA) scans showed no radiological indications of pneumonia or pulmonary embolism. Skin biopsy revealed evidence of cutaneous cryptococcosis. Lumbar puncture confirmed concomitant cryptococcal meningitis. Results of arterial blood gas analysis, serum venous sample, cerebrospinal fluid analysis and nasopharyngeal swab is shown in Table 1.

Table 1: Results of performed analyses

Analysis	Result
Arterial blood gas analysis	
pH	7.48
pCO_2	30 mmHg
O_2 saturation	87 %
pO_2	51 mmHg
HCO_3	24 mEq/L
Serum venous sample	
ALT	61 U/L
AST	66 U/L
ALP	90 U/L
GGT	361 U/L
Total bilirubin	23 µmol/L
Creatinine	206 µmol/L
Urea	17.7 mmol/L
Na^+	1387 mmol/L
K^+	5.17 mmol/L
WBC	4.35 cells × 10^9/L
Hb	14.7 g/dL
Platelets	179 cells × 10^9/L
D-dimer	1.09 mg/L
Cryptococcal Ag	+
HBV profile	-
HCV profile	-
VDRL	-
Cerebrospinal fluid analysis	
Glucose	4.2 mmol/L
Protein	0.25 g/L
ADA	0.6 U/L
Polymorphs	0
Erythrocytes	0
Lymphocytes	0
Gram stain	Moderate yeasts (+2)
RPR	-
Cryptococcal Ag	+
Culture	*Cryptococcus Neoformans*
CSF pressure	NM
Nasopharyngeal swab	
RT-PCR	+

pCO_2: partial pressure of carbon dioxide; O_2: oxygen; pCO_2: partial pressure of oxygen; HCO_3: bicarbonate; ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl-transferase; Na^+: sodium ion; K^+: potassium ion; WBC: white blood cells; Hb: haemoglobin; Ag: Latex antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; VDRL: venereal disease research laboratory (syphilis test); ADA: adenosine deaminase; RPR: rapid plasma reagin; CSF: cerebrospinal fluid pressure; RT-PCR: COVID-19 reverse transcriptase polymerase chain reaction; +: positive test; -: negative test; NM: opening pressure was not measured due to the unavailability of CSF manometer;

Diagnosis of unmasking immune reconstitution inflammatory syndrome (IRIS) associated with disseminated cryptococcosis, all while testing positive for COVID-19 was made based on clinical presentation and performed analyses. No other opportunistic infections were detected. COVID-19

management guidelines were strictly adhered to and treatment included the administration of steroids, amphotericin B and fluconazole. Additionally, empirical coverage for *Pneumocystis carinii* pneumonia (PCP) was initiated. Regrettably, despite these interventions, the patient's clinical condition deteriorated in the following days, ultimately resulting in his passing.

Discussion

IRIS is an exaggerated inflammatory response that arises when the immune system undergoes recovery. This phenomenon predominantly affects individuals with compromised immune systems, especially those with HIV and typically manifests shortly after initiating antiretroviral therapy (ART). IRIS can manifest in two distinct forms: "unmasking IRIS", which involves the re-emergence of an underlying, previously undiagnosed infection and "paradoxical IRIS" characterised by the exacerbation of a previously treated infection.[1, 2] It is important to note that IRIS can range in severity from mild to life-threatening, with an overall reported mortality rate of approximately 4.5 %.[3]

Cryptococcosis is among the opportunistic infections frequently observed in individuals with HIV and it has the potential to present as IRIS, exhibiting various clinical manifestations that can encompass cutaneous lesions and affect various organ systems. Among the manifestations, cryptococcal meningitis stands out as the most extensively documented form of the disease.

Presented patient was promptly initiated on ART by his general practitioner, even though his pre-HIV therapy screening tests were still pending. Fourteen days later, he returned with symptoms of shortness of breath (SOB) and a diffuse skin rash, which raised suspicion of a fungal infection. Unfortunately, the initial medical assessment by the hospital on-call team focused solely on the symptoms of COVID-19 pneumonia due to his respiratory distress and a positive COVID-19 polymerase chain reaction (PCR) test, however perhaps not realising the medical history and clinical signs.

During the hospitalisation, a review of his pre-screening tests revealed a positive Cryptococcal antigen latex agglutination test (CLAT). Prompt investigations were conducted, encompassing a normal chest imaging study, a skin biopsy that confirmed the presence of cryptococcosis and a lumbar puncture (LP) which definitively established the diagnosis of cryptococcal meningitis.

CT and CTPA scans conclusively ruled out the presence of concurrent pneumonia or pulmonary embolism. In the author's opinion, the apparent lack of abnormalities in the chest imaging was likely due to the significantly low CD_4^+ count, which hindered the immune response's ability to provoke and incite an inflammatory response within the lungs, rendering it undetectable on the imaging studies.

Up to the time of this case report, the literature has documented three instances of co-occurrence involving COVID-19 and cryptococcosis. One case involved cryptococcosis in a kidney transplant recipient with decompensated alcoholic liver disease and COVID-19.[4] Another case involved a patient who underwent tocilizumab treatment for a COVID-19-induced cytokine storm and subsequently developed cryptococcosis.[5] The third case described a scenario of cryptococcal meningoencephalitis in an elderly patient with SARS-COV-2 infection who was being treated with dexamethasone.[6]

Conclusion

This case underscores the challenges and complexities of dealing with multiple pathologies, particularly during the COVID-19 pandemic. It demonstrates how focusing solely on COVID-19 can sometimes overshadow other serious conditions and may diminish the significance of clinical signs pointing to other medical conditions and underlying opportunistic pathologies. A notable example is presented case of IRIS, where the presence of COVID-19 was likely incidental. In the early stages, the patient's COVID-19 status might have hindered a precise diagnosis. However, in the author's view, the patient's skin rash, medical history and a positive CLAT test should have raised suspicion of a concurrent opportunistic infection rather than COVID-19 alone.

Ethics

Our institution does not require ethics approval for reporting individual cases or case series. A written informed consent for anonymised patient's information to be published in this article was obtained from the patient's next of kin.

Acknowledgement

We extend our gratitude to the patient and his family, as well as to the entire medical team involved in providing care.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Abdulhakim Jilani (AJ):
0000-0002-8659-6989
Mohamed Alshmandi (MA):
0009-0009-5225-7821
Julia Kiernan (JK):
0009-0009-0156-1962

Author contributions

Conceptualisation: MA
Writing - original draft: AJ
Writing - review and editing: MA, JK
Supervision: MA

References

1. Bosamiya SS. The immune reconstitution inflammatory syndrome. Indian J Dermatol. 2011 Sep-Oct;56(5):476-9. doi: 10.4103/0019-5154.87114.
2. CrothersK,HuangL.Pulmonarycomplicationsofimmune reconstitution inflammatory syndromes in HIV-infected patients. Respirology. 2009 May;14(4):486-94. doi: 10.1111/j.1440-1843.2008.01468.x.
3. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M; IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010 Apr;10(4):251-61. doi: 10.1016/S1473-3099(10)70026-8.
4. Passarelli VC, Perosa AH, de Souza Luna LK, Conte DD, Nascimento OA, Ota-Arakaki J, et al. Detected SARS-CoV-2 in ascitic fluid followed by cryptococcemia: a case report. SN Compr Clin Med. 2020;2(11):2414-8. doi: 10.1007/s42399-020-00574-9.
5. Khatib MY, Ahmed AA, Shaat SB, Mohamed AS, Nashwan AJ. Cryptococcemia in a patient with COVID-19: A case report. Clin Case Rep. 2020 Dec 19;9(2):853-5. doi: 10.1002/ccr3.3668.
6. Ghanem H, Sivasubramanian G. Cryptococcus neoformans meningoencephalitis in an immunocompetent patient after COVID-19 infection. Case Rep Infect Dis. 2021 Jun 4;2021:5597473. doi: 10.1155/2021/5597473.