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Case Report

Mucormycosis and SARS-CoV-2 Infection-A Diagnostic and Management Challenge in Low Resource Settings

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ABSTRACT

Mucormycosis is currently termed as one of the mortal angioinvasive fungal diseases in the world, affecting those with diabetes mellitus, especially in acidotic states. With the current Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, there has been a surge of mucormycosis cases being documented from Asian countries and a few from Sub-Saharan Africa. Herein, we present two cases of mucormycosis from Kilimanjaro, Tanzania, both with history of uncontrolled Diabetes mellitus type-1. One patient was confirmed to have Coronavirus disease-19 by Polymerase Chain Reaction (PCR). These are the first known documented cases of mucormycosis from Tanzania during the SARS-CoV-2 pandemic. We also have narrated on the challenges in diagnosis and management of patients with mucormycosis in our setting.

Keywords: Mucormycosis; Diagnosis and management challenges; Low resource setting

INTRODUCTION

Mucormycosis, an opportunistic angio-invasive fungus with high mortality and morbidity; and has recently received increased attention due to a change in epidemiology. Before the Coronavirus pandemic, the global epidemiology had already started to change with more cases being reported among diabetic patients in Asia [1]. Even though mucormycosis is common among uncontrolled diabetic patients, reports in Africa are scanty [2]. As an example, in a review of 851 case reports in the pre Coronavirus-19 (COVID-19) era, only 3% of published reports were from Africa [3]. A high prevalence of uncontrolled diabetes mellitus in sub-Africa and low reported burden of mucormycosis suggest under estimated mucormycosis burden. With the advent of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) affecting patients with diabetes mellitus disproportionately, we are bound to encounter increasing cases with mucormycosis, as diabetes is an independent risk factor for both infections.

Herein, we present two fatal cases of mucormycosis and discuss diagnostic and treatment options in a low resource setting. Because of the high fatality rate, we hope this will improve detection and treatment of these cases. It is also our hope that this will help guide policy and decision-making regarding the availability and accessibility of recommended therapies.

CASE PRESENTATION

Case 1

A-35-year-old male patient was admitted in our center because of confusion and occasional episodes of epistaxis for 2 days, which were preceded by headache. The patient had a positive history of hypertension and diabetes type 1 with poor compliance to insulin. He was discharged 4 days ago after recovery from Diabetic Ketoacidosis (DKA). He worked as a carpenter with four children.

On examination, he was semiconscious, Glasgow Coma Scale (GCS) 13/15, afebrile with body temperature 35.8°C, pulse rate 117 beats/minute, Blood Pressure (BP) 122/86 mmHg and respiration rate of 26 breaths/min with normal power, tone and reflexes. Oral examination revealed a black necrotic tissue on soft palate. Review of other systems was essentially normal.

On admission, he had ketonuria of 4+, Random Blood Glucose (RBG) was >30mmol/l, with normal Electrocardiogram (ECG) findings. The diagnosis of DKA was suggested and DKA protocol was initiated. Head Computed Tomography (CT) scan showed areas of infarction on the frontal and temporal regions (Figure 1A and Figure 1B). The Ear, Nose and Throat (ENT) surgeon was consulted due to suspicion of oral mucormycosis. Surgical debridement was done and the specimen was submitted for histopathology. The

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histopathology report confirmed the diagnosis of mucormycosis as an offending agent, (Figure 2A and Figure 2B). The patient received medical management including Amphotericin B.

Unfortunately, he passed away shortly afterwards. To better understand the disease process, a clinical post mortem was requested, however, the family denied authorizing consent.

Case 2

A-21-year old female, presented to us with 2 weeks' history of cough, lower abdominal pain and vomiting for 3 days. The cough was dry and it was associated with a runny nose. The abdominal pain was associated with vomiting which was of recently eaten foodstuff. The patient was diagnosed with diabetes type 1 about 1 year ago and was out of medications for the past 3 months. Socially, she was separated from her husband; she had a 2-year old child living with her grandmother. On examination day 1, she was ill looking, not dyspnoeic, had dry mucous membranes. Her vital signs were BP 108/69mmHg, Pulse Rate (PR) 91 beats per minute, body temperature 36.7°C, RBG 24.7 mmol/l, and urinalysis had ketones 3+. Laboratory tests indicated White Blood Cells (WBC) count of 11.22 × 10^9/L, Erythrocyte Sedimentation Rate (ESR) of 69 mm/h, creatinine of 145 micromol/l, urea of 12.99 mmol/l. Electrolytes sodium of 147.38 mmol/l, potassium 2.61 mmol/l, serum lipase 94.47 U/l, amylase 123 U/l, and normal transaminase. Her RBG was challenging to control with 105 units of total soluble insulin per day. She was kept on DKA treatment as per local treatment protocol. On day 2, the patient started experiencing spiking fever where blood culture was done.

On day 3 patient had controlled blood glucose level but had unilateral left sided facial swelling with proptotic eye, conjunctiva hemorrhage and epistaxis of the same side. She also developed multiple cranial nerves palsies I, II, IV, VI. On day 4, Chest X-ray showed bilateral peripheral opacifications suspicious for coronavirus disease-19 (COVID-19). A nasal swab for the COVID-19 Polymerase Chain Reaction (PCR) testing was taken and was isolated. In the isolation ward, she was kept on COVID-19 cocktail which included dexamethasone and heparin. On day 7, Blood culture results showed gram-positive cocci in clusters Methicillin-Resistant Staphylococcus Aureus (MRSA) negative. On day 10, the PCR SARS-CoV-2 test result came positive. While in the ward, she developed a black necrotic tissue on the soft palate. She underwent a brain CT-scan, which demonstrated brain infiltration and thrombophlebitis of the cavernous sinus suggestive of brain extension of the mucormycosis, (Figure 1C and Figure 1D). The palate lesion was biopsied and she was initiated Amphotericin B. The steroids were stopped. During surgical debridement, she

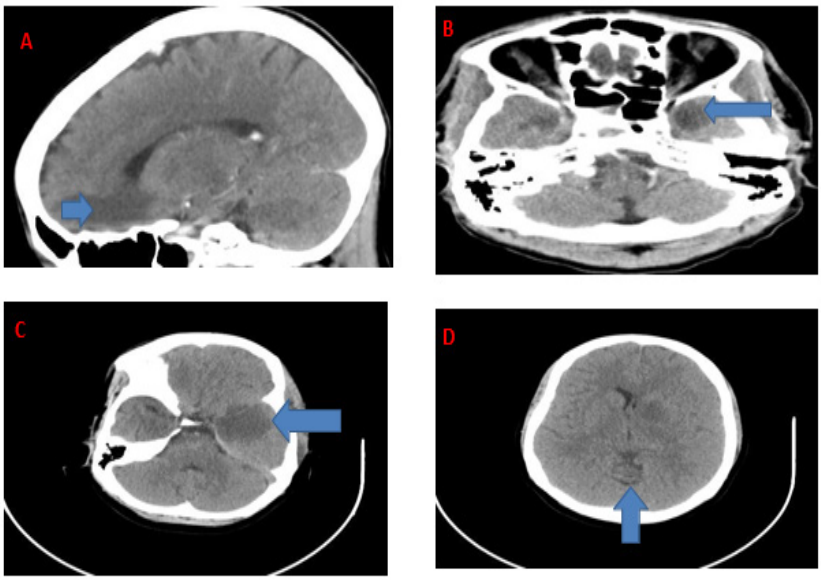

Figure 1: (A,B): CT-scan of the brain studies highlighting areas of infarction of the frontal and temporal lobes in case 1; (C): The presence of thrombophlebitis of the cavernous sinus; (D): An intracranial extension in case 2.

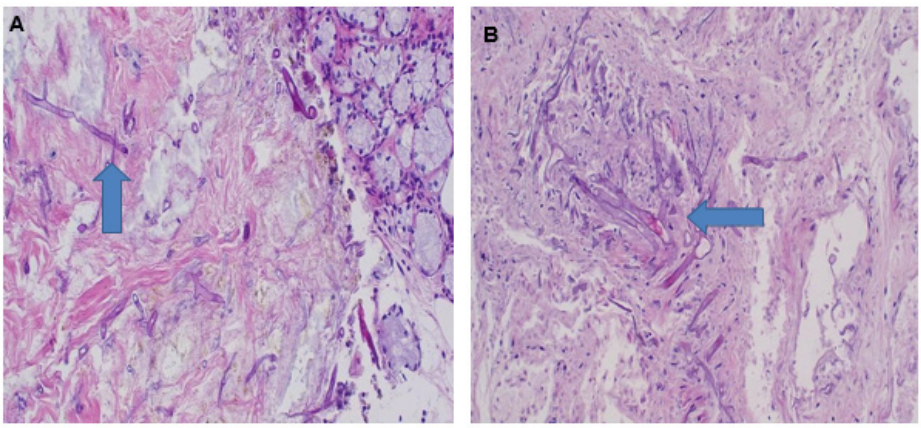

Figure 2: (A) Histopathology of mucormycosis of the palate demonstrating invasive pauciseptate ribbon-like or non- septate fungal hyphae spearing minor salivary gland of the hard palate, H&E stained section 100X original magnification; (B): Invasive fungal hyphae with necrotizing inflammation, H&E stained section 40X original magnifications.

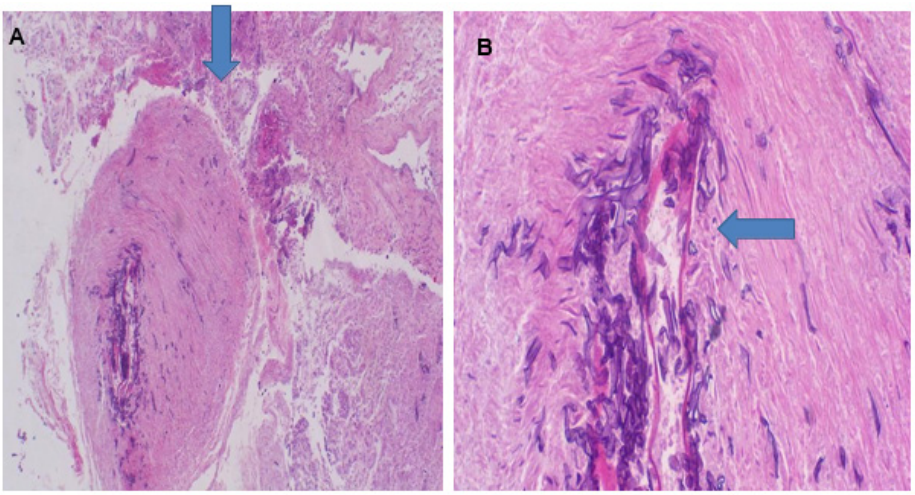

Figure 3: (A) Photo microscopy of palate showing invasive fungal hyphae associated with extensive necrosis demonstrated by the arrow; H&E stained section 20X original magnifications; (B): Angio-invasion the broad and aseptate hyphae, 100X original magnification.

passed away. Histopathology of the soft tissue lesion highlighted an invasive necrotizing fungal hyphae spearing minor salivary gland of the hard palate consistent to murcomycosis (Figure 3A and Figure 3B).

CASE DISCUSSION

We have described interesting two fatal cases of mucormycosis in northern Tanzania. Published cases in sub-Saharan Africa are limited, even during the COVID-19 era compared to Asia [4]. A possible reason might be a low index of suspicion. In both cases, diabetes was not immediately diagnosed even though some features were present. Case 1 initially presented with confusion, history of epistaxis and an eschar on the palate. While case 2 on admission had no suggestive features. The patient developed features of mucormycosis while in the ward. These included unilateral facial swelling with predominance of periorbital edema. Later on multiple cranial nerve palsies and epistaxis. Although there are no specific diagnostic criteria, an algorithm was proposed by Corzo, et al., [4] to promptly diagnose Rhino-orbital-cerebral mucormycosis in patients with diabetes. Such signs and symptoms include; cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling and ulcers of the palate.

Invasive murcomycosis is relatively rare and highly morbid fungal infection mostly affecting immune-suppressed patients particularly at risk of complications and fatality in the setting of SARS-CoV-2 infection [5]. To the best of our knowledge, these are the first reported autochthonous cases of invasive mucormycosis in Tanzania during the SARS-CoV-2 pandemic [1-3]. The clinical presentations and forms of the mucormycosis disease have been described based on anatomical sites as Rhino-orbital-cerebral, Pulmonary Mucormycosis, Gastrointestinal, Cutaneous, Central Nervous System (CNS), Disseminated and Miscellaneous [3-6]. Rhino-orbital-cerebral mucormycosis is the commonest clinical presentation amongst diabetic patients predominantly with ketoacidosis. It is also the most evident presentation acknowledged largely in Africa and Asia [6]. In early stages, patients present with features of periorbital edema, cellulitis, sinusitis, proptosis, vision loss that may be acute, ophthalmoplegia and headaches. Fever may be absent in almost half of the patients and if present may be prolonged [4-5]. Hematogenous spread to other organs can easily occur which would result in disseminated form of mucormycosis.

To complement our clinical suspicion, we were able to perform brain CT scans. In both cases, there were multiple areas of infarction as depicted in Figure 1 A-D. Other case reports have also demonstrated multiple areas of infarction [7-9]. Other described features include presence of tissue edema to bony destructions. Presence of cavernous sinus thrombosis or involvement of internal carotid arteries can profoundly be picked by the contrast MRI [8].

Diagnostic advancements of the disease using quantitative multiplex qPCR-based 18S rRNA detects the presence of Rhizopus, Lichtheimia and Rhizomucor in three days [10-12]. Unfortunately, this was not present in our setting. In our patients, diagnosis was made through evaluation of the clinico-pathological features including radiological imaging as well as demonstrating invasive non-septate hyphae in histopathological examination of the infected tissue (Figures 1-3). Early diagnosis and treatment is important in view of the high mortality. Successful treatment of mucormycosis requires multiple steps according to Cornely and coworkers [7]. These include early diagnosis, reversal of underlying predisposing risk factors, if possible, surgical debridement where applicable; and prompt antifungal therapy.

For the patients infected with SARS-Cov-2, the timing of treatment with antifungal medication is very crucial; early initiation of antifungal therapy within 6 days of diagnosis may lead to a good outcome [13,14]. Both of our patients had late presentation and unfortunately succumbed shortly after hospitalization despite receiving Amphotericin B as per the Standard treatment guideline of Tanzania [15]. Surgical interventions with conservative and radical approaches have also been documented with favorable outcome. It is obviously impossible in disseminated cases; hence should be individualized [10-12].

In summary, mucormycosis is an aggressive life threatening fungal infection mostly associated with DKA, poor glycemic control or immunosuppression. Further attempts should be made for the early diagnosis of this disease and prompt management so as to improve the treatment outcome.

LEARNING POINTS

- Mucormycosis is an important contributor of morbidity and mortality among diabetic patients during the era of SARS-CoV-2 pandemic.
- Diagnosis is mainly clinical. Based on history, particularly a history of epistaxis, sinusitis, headache, confusion and on examination an ischemic lesion on the nose and palate.

- A high index of suspicion is needed for early diagnosis, as the prompt use of antifungals, surgical debridement and control of hyperglycemia are important for a good outcome.

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Authors' contributions

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Formal analysis: Anneth Marandu, Hilary Chipongo, Alex Mremi, Kajiru Kilonzo.

Investigation: Crispin Moshi, Patrick Amsi, Gilbert Nkya, Alex Mremi.

Methodology: Anneth Marandu, Hilary Chipongo, Alex Mremi, Kajiru Kilonzo

Project administration: Sarah Urasa.

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Writing-review and editing: Alex Mremi, Kajiru Kilonzo.

Declaration of competing interest

All authors have declared that no competing interests exist.

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Ethics approval

There was exemption of ethical clearance.

Consent

Written informed consent was obtained from the patients' legal guardians for publication of this case report and accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal on request.

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