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Case Report

Anaemia Due to Amphotericin B a Double Whammy in Postoperative Mucormycosis Patients: A Case Series

Ruchi Kapoor*, Ganga Dutt Devaraj, Ajeeb Sharahudeen, Jubin Jakhar

Department of Anaesthesiology, Critical Care and Pain Medicine, University College of Medical Sciences and GTB Hospital, Delhi, India.

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ABSTRACT

Corona Virus Disease (COVID-19) which has a common association with diabetes has led to an epidemic of mucormycosis which has been mainly attributed to rampant use of steroids owing to the severity of the disease. The mucormycosis patients presented with rhino orbital mucormycosis predominantly with or without intracranial extension making it a life-threatening condition mandating urgent debridement as treatment of choice alongside antifungal medications. Injection Amphotericin B is the first-line drug that is nephrotoxic and causes dyselectrolytemia therefore administered under strict supervision.

However, we report successful management of two unique cases where patients after surgical debridement after Amphotericin B developed severe life-threatening anaemia postoperatively along with impending respiratory failure requiring Intensive care management including non-invasive ventilation. Thus, serial haematocrit monitoring is of utmost importance while the patient is being administered Amphotericin B even when a patient is receiving the relatively safe preparation that is liposomal Amphotericin B in a dose of 3.5 mg per kg body weight.

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) virus infection commonly known as Corona Virus Disease (COVID-19) has led to an epidemic of mucormycosis in India during the second wave in April 2021 [1]. The reason for COVID-19 associated mucormycosis is still unknown [2] however it is hypothesized that hyperglycaemia due to Diabetes Mellitus, a common comorbidity in COVID-19, or the steroid coupled with lymphopenia due to viremia could have contributed to the epidemic of mucormycosis. [3-4]. The propensity of SARS –Cov 2 to affect the lung tissue leading to large bilateral alveolo-interstitial infiltrates along with a reduction in the number of T lymphocytes CD4+T cells and an increase in IL-6 makes the patient prone for mucormycosis. [5]. Also, immune dysregulation along with the use of immune modulators such as Tocilizumab has been postulated to be a cause of mucormycosis [5]. Mucormycosis is an angioinvasive disease caused by mold fungi such as Rhizopus affecting eyes, sinuses, brain, and even pulmonary involvement [5] making debridement an urgent procedure to prevent its spread. The management of these patients poses a unique challenge for the intensivist as Amphotericin B which is the drug of choice for medical management has a wide array of adverse effects like nephrotoxicity, metabolic acidosis, and even severe anaemia in few patients. We report two cases of patients who were operated on for mucormycosis under general anesthesia, were extubated and maintaining vital parameters, both of whom presented on the tenth day postoperative with severe anaemia, impending respiratory failure and were successfully managed in the intensive care unit, thus emphasizing the need for strict monitoring of haematocrit in postoperative patients of mucormycosis, especially when the patient is receiving Amphotericin B.

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*Corresponding author.
E-mail address: rudoc@rediffmail.com

Case Report

A 50-year-old male presented to the ER as a referred case of suspected mucormycosis post-COVID-19 pneumonia with the chief complaint of right eye swelling. At the time of presentation, he was conscious, oriented, and haemodynamically stable, maintaining SpO2levels of 98% on supplemental O2. He was a known case of controlled type 2 diabetes who was on insulin therapy. The initial lab evaluations were normal, with Haemoglobin (Hb) being 13.1g/dL. The MRI of the brain and PNS revealed invasive fungal sinusitis with a right intra-orbital extension which was confirmed with KOH staining positive for Mucorales. A confirmatory diagnosis of rhino orbital mucormycosis was made and inj. Piperacillin-Tazobactam 4.5g tds, inj. Teicoplanin 200mg od and inj. Amphotericin-B 300mg od was advised by ENT physicians. Thereafter Hb came out to be 9.5g/dl, patient's blood group was identified as B positive and transfused with one-unit red cell concentrate preoperative to build the Hb to 12 g/dl. An HRCT of the thorax was done which showed patchy ground-glass opacities with sub-pleural fibrotic bands causing tractional bronchiectasis likely as a sequalae to COVID-19. Sinonasal debridement and exenteration were done under general anesthesia and uneventful with minimal blood loss. Post-operatively, the patient was doing well maintaining vital parameters and tolerating oral feeds. A week later, the patient's clinical condition deteriorated as he developed fever, yellowish discolouration of eyes, and shortness of breath and was transferred into the ICU. On examination, he was febrile, severely pale, and icteric with peripheral pitting oedema. He was conscious, oriented, blood pressure of 98/60 mmHg with tachycardia and tachypnea requiring supplemental O2. Blood glucose levels were within normal levels and urine output was adequate. He had the following arterial blood gas parameters: pH of 7.43, pCO2 of 24, HCO3- of 16, and a pO2 of 108. The blood investigations revealed a drastic fall in Hb levels to 4.2 g/dl with a haematocrit of 13.7, total/direct bilirubin levels of 2.4/1.2 with a normal range of KFT, liver enzymes, and cardiac enzymes. The patient's blood was sent for grouping and cross-matching however there was a discrepancy in ABO during group identification. This prompted us for further evaluation of anaemia and a Direct Coomb's test was done which came positive. Peripheral smear revealed marked anisocytosis with predominant macrocytes and few microcytic hypochromic cells. The corrected reticulocyte count was 7.4%. LDH, an indirect marker for haemolysis was raised to 950 IU/L. After consultations with the haematologist, B positive cross-matched red cell concentrate was transfused under strict monitoring after explaining the risk of transfusion reaction due to auto-antibodies. All necessary precautions were taken with emergency drugs and airway cart standby. No major transfusion reactions occurred. After transfusion of two such units, the patient had Hb of 5.5 g/dl and hematocrit of 18 with rising levels of total/direct bilirubin: 3/1.3. He continued to have respiratory distress for which non-invasive ventilation was initiated with BiPAP mode. Chest radiograph showed mediastinal widening with slight blunting of costophrenic angles. The patient was also tested for anti-nuclear antibodies which were within normal limits. The patient was screened for viral markers including hepatitis B, hepatitis C, and HIV which were negative. There was no evidence of hepato-splenomegaly. A provisional diagnosis of auto-immune haemolytic anaemia was made with the most probable cause being a therapy with Amphotericin-B. Therefore tab. Posaconazole 300mg was started after consultation with the ENT surgeon and physician. The patient required further blood transfusions and Hb improved to 7.2 g/dl, hematocrit of 22, and total/direct bilirubin of 1.8/0.6. With an increase in Hb levels, he improved clinically, tachypnea resolved and ventilator support was weaned off gradually. O2 therapy was tapered over the next few days and the patient was able to maintain SpO2in room air. Intravenous immunoglobulin was started at doses of 30g per day for AIHA since steroids are contraindicated in a patient with invasive fungal infection. Later the patient underwent revision Sino-nasal debridement under general anaesthesia when the Hb levels were 10.6 g/dl pre-operatively. After surgery, he was stable and now in recovery transferred to the ENT ward.

We report another case of a 75-year-old male who came to our ER with complaints of fever and swelling around the left eye and left side of the face with associated numbness of the area. He had no history of COVID-19 infection. He was a known case of type 2 diabetes mellitus and chronic hypertension for the past 20 years on regular treatment. At the time of presentation, he was conscious, oriented, and haemodynamically stable maintaining SpO2 levels of 97% in room air. His blood glucose levels were in the normal range on a basal-bolus insulin regimen. His blood investigations revealed Hb of 12.4 g/dl, other investigations were unremarkable. A diagnosis of rhino orbital mucormycosis made was confirmed by MRI and KOH staining. He was started on inj. Ceftriaxone 1gbd and was given peri-bulbar Amphotericin-B injections and inj. Amphotericin-B 300mg od. The patient was planned for left sub-total maxillectomy with left orbital decompression under general anaesthesia. He had a pre-operative Hb of 10.5 g/dl and hematocrit of 34. The surgery was uneventful with minimal blood loss and post-operatively, the patient was recovering in the ward. Around 10 days following surgery, the patient had a drop in Hb to 7.1 g/dl with a haematocrit of 21 and complaints of fever, shortness of breath, and swelling of lower limbs for which he was transferred to the ICU due to impending respiratory failure. On examination, he was conscious, oriented, and pale with bilateral pitting pedal oedema, haemodynamically stable with tachycardia, tachypnea, bilateral basal fine crepitus on auscultation of lung fields, and SpO2 level of 98% requiring supplemental O2. His arterial blood gas parameters were pH: 7.41, pCO2:50.4, HCO3-: 31.1, and pO2: 144. He was given non-invasive

ventilation support for few days which was later weaned off, upgraded to Inj. Piperacillin-Tazobactam 4.5gtds and inj. Levofloxacin 750mgdaily. His Hb dropped to 6.6 g/dl with a haematocrit of 20 and he was given group-specific cross-matched compatible red cell concentrate units. Peripheral blood smear revealed normochromic normocytic anaemia. With blood transfusion and supportive management, the patient's Hb levels increased to 8 g/dl and hematocrit to 24. He started to show signs of clinical improvement and was weaned off supplemental O2. He was later shifted to the ward maintaining in-room air.

Discussion

COVID-19 predisposes the patient to coagulopathies and haematologic abnormalities. Though being a relatively new clinical entity, less data is available to prove the association between anaemia and COVID -19. The massive use of glucocorticoids for management of inflammation and preexisting comorbidities such as Diabetes Mellitus has been postulated as a common cause of mucor, the common site being rhino orbital mucormycosis [1].

The standard treatment protocol advocates reversal of underlying cause where possible, surgical debridement, and the use of antifungal agents such as Amphotericin B for the management of mucormycosis [6-9]. However, even though relatively safe liposomal preparation is in vogue, yet a wide array of side effects from nausea and vomiting to metabolic acidosis, nephrotoxicity, and hypokalemia have been noted.

We encountered a rare side effect of Amphotericin B in both the patients described above that is life-threatening severe anaemia leading to impending respiratory failure in the postoperative period of exenteration and sinonasal debridement despite being on 3.5 mg per kg bodyweight of liposomal Amphotericin B, although doses of 5mg per kg body weight have been used for treatment and higher doses up to 10 mg per kg body weight are used for patients with intracranial extension. A dose of 4 mg per kg bodyweight shown to cause a drop in RBC count in 50 percent of patients has been reported [10], the same study stated that with liposomal preparation patients did not have severe anaemia, none requiring ICU admission. Therefore the exact incidence of anaemia with the liposomal preparation and the dose at which severe anaemia may be anticipated is yet unknown. Also, more studies are needed to see the incidence of anemia in mucor patients following COVID infection.

The points in favor of haemolytic anemia in the first patient were normocytic normochromic anaemia, hyperbilirubinemia, raised LDH, and Direct Coomb's test positive. The second patient too developed sudden onset anaemia and had normocytic normochromic anaemia on peripheral smear. Another observation in the case series is that both the patients had normal haematocrit preoperatively, had minimum blood loss in the intraoperative and postoperative period but developed severe anemia on the tenth postoperative day, thus a pointer to anemia due to Amphotericin B therapy. The peripheral smear picture of both the patients showed normocytic normochromic anemia pathognomonic of anaemia seen with Amphotericin B usage. Further bone marrow biopsy and iron studies can be done to make a conclusive diagnosis.

The possible explanation could be that the haematologic abnormalities caused by COVID -19 could have been further compounded by the use of amphotericin B thus leading to severe anemia. Also, since COVID 19 affects lungs leading to fibrosis, so any drop in haematocrit could present as an impending respiratory failure as seen in both the patients who presented with severe respiratory distress and needed noninvasive ventilation and immediate blood transfusion for the management of anemia.

Anaemia is known to occur with Amphotericin B on prolonged usage however very less literature is available on the impact of Amphotericin B on haematologic indices. It has been seen that with liposomal Amphotericin B, the drop in haematocrit is much less when compared to other preparations. (10) Anaemia is usually worsened when other drugs are used along with Amphotericin B or the presence of comorbidities which could explain anaemia as these were post-COVIDMucor patients.

Mechanism of anemia: A possible explanation of anaemia is the suppression of erythropoietin in renal tubular cells by Amphotericin B [11].

Management of haemolytic anaemia

Since in the first patient, Direct Coomb's test was positive and anti-A and anti-B antibodies were present, therefore autoimmune immunoglobulins were administered to the patient.

However, in the second case, the patient responded well to two transfusions of RCC and required supportive therapy in the form of oxygen by non-invasive ventilation, then weaning to room air. In both patients, Amphotericin B was stopped and patients were administered oral Posaconazole 300mg once a day.

Conclusion

Thus, to conclude, a patient with mucormycosis being managed on Amphotericin B requires strict haematocrit monitoring to avoid any possibility of a severe drop in haematocrit leading to respiratory failure. A high index of suspicion, prompt detection and intensive care therapy, oxygen supplementation, and blood transfusion, stopping the drug, and the use of alternate antifungal medications is the key to the management of these patients.

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