Case report

Recurrent alveolar hemorrhage: How do you treat that which you cannot see?

Philipose Jobin\textsuperscript{a,b,∗}, Siddiqui Faraz\textsuperscript{b}, Wong Jiyoung\textsuperscript{a}, Wiesel Shimshon\textsuperscript{b}, Esper Ziad\textsuperscript{b}, Elsayegh Dany\textsuperscript{b,}\textsuperscript{c}

\textsuperscript{a}Department of Internal Medicine, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY, 10305, USA
\textsuperscript{b}Pulmonary Medicine and Critical Care, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY, 10305, USA
\textsuperscript{c}E-mail address: philipose.jobin@gmail.com (P. Jobin).

Abstract

Diffuse alveolar hemorrhage (DAH) is a rare and life-threatening event which is characterized by bleeding into the alveolar spaces of the lung. Etiology of DAH can be broadly divided into immune and non-immune mediated disease. In the absence of infection or malignancy, an immunological workup is required to find the cause of alveolar bleed. Rarely, there is a failure to establish a definitive etiology in patients with DAH. In those scenarios, patients who do not respond to steroids, plasmapheresis should be considered as a rescue treatment to prevent catastrophic outcomes. Herein, we present a unique case of a 48-year-old male admitted with DAH of unknown etiology completely recovered after empirical plasmapheresis.

1. Background

Diffuse alveolar hemorrhage (DAH) is a life-threatening event, caused by the disruption of the alveolar-capillary basement membrane. Pulmonary capillaritis is the most common culprit of this disruption, apart from bland pulmonary hemorrhage and diffuse alveolar damage [1]. Etiology of DAH is broad and includes immune and non-immune mediated disease. Systemic vasculitis and autoimmune diseases (AD) represent the most common cause of DAH, hence serology is the key to diagnosis. Although rare, some of these patients are affected by lack of circulating disease-specific autoantibodies in the blood which comprises the entity, seronegative autoimmune disorder [2]. Another diagnostic consideration in patients with negative serology is idiopathic pulmonary hemosiderosis (IPH) which requires confirmation with open lung biopsy. Sometimes, it is not feasible to perform extensive work up to find the etiology, and we are left in dilemma regarding the therapeutic options. Herein, we present a similar case scenario of a 48-year-old male admitted with DAH of unknown etiology who completely recovered after empirical plasmapheresis.

2. Case report

A 48-year-old male chronic smoker presented to the emergency department with hemoptysis and worsening shortness of breath for the last 1 month.

On arrival, he was in acute respiratory distress. His blood pressure was 120/58 mmHg, pulse 106 bpm, respiratory rate of 20/minute, with an oxygen saturation of 69% in ambient air. He was immediately intubated for acute hypoxic respiratory failure. He had no significant past medical history including any illicit drug use. His laboratory results revealed a white cell count of 18000/mm\textsuperscript{3} (granulocytes 78%, lymphocytes 14%, eosinophils 0.1%), hemoglobin 8 g/dl, mean corpuscular volume 85 fL and platelets 390/mm\textsuperscript{3}. His serum electrolytes, coagulation studies, renal and liver function were all normal. His serum creatinine remained normal throughout this process with no evidence of nephritic or nephrotic syndrome. The decision to cover the patient was 120/58 mmHg, pulse 106 bpm, respiratory rate of 20/minute, with an oxygen saturation of 69% in ambient air. He was immediately intubated for acute hypoxic respiratory failure. He had no significant past medical history including any illicit drug use. His laboratory results revealed a white cell count of 18000/mm\textsuperscript{3} (granulocytes 78%, lymphocytes 14%, eosinophils 0.1%), hemoglobin 8 g/dl, mean corpuscular volume 85 fL and platelets 390/mm\textsuperscript{3}. His serum electrolytes, coagulation studies, renal and liver function were all normal. His serum creatinine remained normal throughout this process with no evidence of nephritic or nephrotic syndrome. The decision to
use empiric plasmapheresis was made after he failed to respond to pulsed dose steroids. After two sessions, he made a dramatic recovery, both clinically and radiographically (Figs. 4 and 5). He was subsequently extubated and discharged on immunosuppressive therapy with oral steroids, mycophenolate mofetil and advised on smoking cessation. Of note, cyclophosphamide was declined by the patient in view of azoospermia as an adverse effect. Rituximab was also considered but given his seronegativity, it was not covered by his insurance.

Eleven months following the initial hospitalization, he returned to our emergency with the similar episode. At this juncture, a lung biopsy was scheduled immediately and revealed marked alveolar hemosiderosis, focal organizing alveolar hemorrhage, and interstitium without vasculitis. His serum again did not show any evidence of antibody-mediated disease. His serum creatinine was normal, although mild proteinuria was present. Patient was offered renal biopsy for further evaluation but was declined. Intravenous steroids was administered, but with minimal response. He received a session of plasmapheresis and improved again without complications. The fact that he responded to plasmapheresis, seronegative autoimmune disorder likely anti-glomerular basement membrane disease (anti-GBM) was added as a differential diagnosis along with IPH on discharge. He was sent on azathioprine as outpatient by the rheumatologist but was unfortunately lost to follow up.

3. Discussion

DAH is a severe syndrome with in-hospital mortality ranging from 20 to 100% [3–5]. Failure to identify the etiology of DAH may lead to delay in initiating appropriate treatment and worse prognosis. In our case, seronegative autoimmune disorder likely anti-GBM disease was strongly suspected due to lack of circulating autoantibodies and
response to plasmapheresis. Few plausible explanations for undetectable antibodies in case of seronegative autoimmune disorders are serum dilution, immunofluorescence substrate, prozone phenomenon, low immunoglobulin levels and hidden antibodies deposited in the tissue [2]. Similarly, in the case of anti-GBM disease, technical limitations of the routinely available assay and low levels of antibodies from previous immunosuppressive therapy might be the reason for seronegativity [6,7]. Standard ELISA testing for anti-GBM is performed for the immunoglobulin G1 (Igg-1) subtype, but more recent cases have introduced an immunoglobulin G4 (Igg-4) subtype implicated in atypical presentation [8]. IPH was also considered in the differential in view of negative serology and lung biopsy results. In concern for minimal response to steroids and high mortality with this condition, empirical plasmapheresis was started as a salvage treatment of DAH with unclear etiology.

Plasmapheresis is an extracorporeal treatment that selectively removes large molecular weight substances such as immune complexes and autoantibodies from the plasma. Role of plasmapheresis in DAH has been well described in previous literature as a rescue therapy in various autoimmune disorder including anti-GBM disease [9–11]. In contrast, use of plasmapheresis has not been established in IPH. Although, F Pozo-Rodriguez et al. reported a case of IPH in 1980 which was successfully treated with plasmapheresis suggesting a link to immunological pathogenesis of this disorder [12]. Thus, in the above clinical setting a single definitive diagnosis was difficult to establish.

In conclusion, alveolar hemorrhage can be a devastating manifestation of many disease processes. Defining and controlling the underlying cause of the disease is integral to both short-term management and long-term suppression. Additionally, as seen in this case, empirical plasmapheresis should be considered as a salvage treatment in DAH of unclear etiology to prevent fatal outcomes. As lengthy workup and potential false negatives may hinder therapy and subsequent recovery.

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Declarations of interest

None.

Ethics

We hereby, confirm that informed consent was obtained from the patient for publication of the case details.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2018.09.002.

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Fig. 5. Repeat CT scan showed complete resolution of ground glass opacities after plasmapheresis.