Case report

Macrophage activating syndrome causing decompensated right heart failure

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ABSTRACT

Background: Macrophage activating syndrome (MAS) is a form of hemophagocytic lymphohistiocytosis (HLH), a rare complication of autoimmune disease that is characterized by cytokine storm and multiorgan failure.
Case summary: A 32-year-old male presented with acutely decompensated pulmonary arterial hypertension and right heart failure secondary to MAS. The patient was immediately started on inhaled and intravenous epoprostenol, vasopressors and dexamethasone and anakinra were administered. Despite the therapies given, the patient's condition continued to decline, and he was placed on veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support. Over a few days, his clinical condition improved, and he was decannulated from VA-ECMO and later transitioned oral treprostinil and was discharged home. Due to its non-specific clinical manifestations, the diagnosis of MAS depends on high clinical suspicion and initial laboratory work up such as thrombocytopenia, transaminitis, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, etc. In our patient, MAS led to decompensated Pulmonary Arterial Hypertension (PAH) leading to right heart failure that was refractory to inhaled and intravenous epoprostenol and vasopressors and required VA-ECMO as a bridge to recovery while his MAS was managed by anakinra and dexamethasone.
Conclusion: MAS can result in acute decompensation of PAH and right heart failure. Besides RV failure management, immunosuppressants such as anakinra, etoposide, etc. should be utilized early in the management of MAS. In refractory right heart failure, VA-ECMO can be considered as a bridge to recovery. There is a paucity of literature supporting the utilization of VA-ECMO in the management of refractory right heart failure caused by MAS in adults and much of the data stems from pediatric studies. This case serves as a fine example of successful use of VA-ECMO in adult population.

1. Introduction

Macrophage activation syndrome (MAS) is a potentially fatal inflammatory disease associated with autoimmune diseases that is characterized by cytokine storm and multiorgan failure (1). We present here a case of decompensated pulmonary arterial hypertension and acute right heart failure secondary to MAS.

2. Case description

A 32-year-old male with a past medical history of systemic juvenile idiopathic arthritis (SJIA) and a well-controlled pulmonary arterial hypertension (PAH) on dual oral therapy with Tadalafil and Macitentan,

presented to the hospital with a two-week history of fever, malaise, and rapidly worsening exertional dyspnea. For the past year, the patient had no access to therapy for his SJIA due to loss of insurance but was still able to get his PAH therapy.

His initial vitals showed a blood pressure of 90/30 mmHg, respiratory rate of 20/min, pulse rate 110/min, oxygen saturation of 95% on 40L and 50% high flow nasal cannula, and a temperature of 39.8′C (103.6′F). Pertinent physical examination showed a lethargic and disoriented man with tachypnea, right parasternal heave, loud P2, anasarca, hepatosplenomegaly, and cold extremities.

His laboratory results were notable for pancytopenia, acute renal failure, transaminitis, elevated international normalized rate (INR), hyperferritinemia, hypofibrinogenemia, and lactic acidosis (Table 1).

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Table 1
Laboratory results on admission.

Variable	Result
White blood cell count (4.0–10.0 THOU/mm^3)	3.5
Hemoglobin (13.0–16.5 G/DL)	7.6
Platelet (150–450 THOU/mm^3)	58
Creatinine (0.51–1.18 MG/DL)	2.91
Aspartate aminotransferase (0–37 IU/L)	11,140
Alanine aminotransferase (0–50- IU/L)	3064
Total bilirubin (0.0–1.0 MG/DL)	2.5
Alkaline phosphatase (40–150 IU/L)	183
Arterial Ammonia (18–72 MCMOL/L)	457
Ferritin (24.0–336.0 NG/ML)	8630
Triglycerides (50–149 MG/DL)	109
Fibrinogen (173–454 MG/DL)	156
Lactic acid (0.3–1.5 mmol/L)	4.1
International normalized ratio (0.8–1.1 seconds)	6

Chest radiograph showed cardiomegaly with right atrial enlargement. Transthoracic echocardiography revealed normal left ventricular systolic function, with a severely dilated right atrium, a moderately dilated and severely dysfunctional right ventricle with right ventricular systolic pressure (RVSP) of 55–60 mm Hg, and a tricuspid annular plane systolic excursion of 13 mm (normal >17mm) (Fig. 1).

Based on the clinical features and the diagnostic workup, a diagnosis of decompensated pulmonary arterial hypertension and acute right heart failure secondary to MAS was made and the patient was admitted to the intensive care unit. He was immediately started on intravenous and inhalational Epoprostenol, Vasopressors and Dexamethasone and Anakinra were given. In addition, the patient was emergently placed on VA-ECMO support with the goal of stabilizing and recovering right ventricular function while optimizing treatment of PAH and MAS. The patient's soluble interleukin (IL)-2 receptor alpha resulted at 9958.2 (normal 175.3–858.2 pg/mL) that furthered our diagnosis.

With this multifaceted approach, the patient's clinical condition gradually improved and on day 9, he was decannulated from VA-ECMO support. The patient was eventually transitioned from parenteral epoprostenol to oral treprostinil and discharged home on triple oral PAH therapy and anakinra after a prolonged hospital course.

3. Discussion

MAS is a form of hemophagocytic lymphohistiocytosis (HLH), a rare complication of rheumatological diseases, that carries high mortality of approximately 40% in adults [1]. The most common disease associated with MAS is SJIA but it has also been reported in other rheumatological
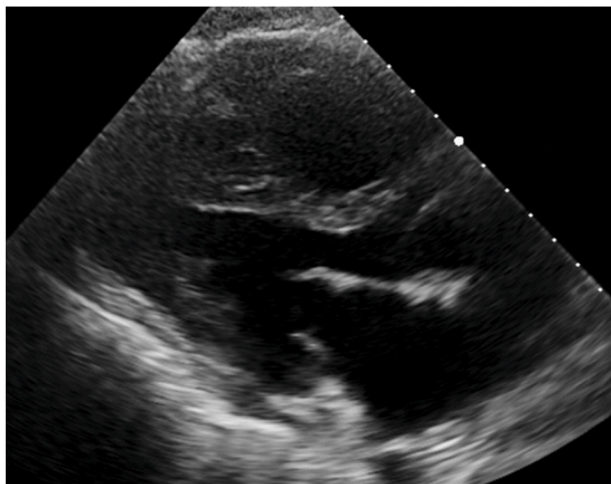

Fig. 1. Parasternal long view of transthoracic echocardiogram on admission demonstrating dilated right ventricle.

diseases such as adult rheumatoid arthritis, dermatomyositis, and systemic lupus erythematosus [2].

The pathophysiology of MAS involves a defect in CD8 T cells and natural killer cells lysis of the activated antigen-presenting cells, and therefore the resolution of the inflammation. A defect in cytolytic activity leads to uncontrolled and self-sustaining cytokine storm and multiorgan failure. Typical histopathology of MAS is characterized by the presence of numerous, well-differentiated histiocytes that exhibit the phagocytic activity of hematopoietic elements on bone marrow examination [3].

Diagnostic criteria of MAS include fever, a known or suspected juvenile idiopathic arthritis, ferritin >684 ng/mL and any two of the following platelet counts ≤181 × 10^9/Liter, aspartate aminotransferase > 48 units/liter, triglycerides >156 mg/dL, fibrinogen ≤360 mg/dL[1] [4].

The management of MAS is challenging due to nonspecific clinical manifestations of this syndrome leading to a delay in diagnosis. Furthermore, there is no established treatment protocol. The current treatment of MAS includes using broad immunosuppressive medications such as glucocorticoids, calcineurin inhibitors such as cyclosporine, and etoposide or cytokine specific therapy such as anakinra-an IL-1 receptor antagonist [5]. Each treatment modality poses its own challenges. Etoposide's side effects include marrow suppression, hepatic, and renal toxicity, as such it was not a good choice in this patient with hepatic and renal failure. Similarly, cyclosporin has a significant renal toxicity side effect. Additionally, achieving therapeutic trough takes days which makes the use of calcineurin inhibitors in acute settings unfavorable. Since IL-1 plays a central role in cytokine storm and pathogenesis of MAS, Anakinra, an IL1-receptor blocker has been used successfully in the management of MAS [6]. Additionally, treatment with anakinra has been associated with a better survival outcome compared to etoposide. Furthermore, anakinra has additional benefits when treating MAS in the context of being less myelosuppressive and hepatotoxic, has a short half-life, and being an IL-1 selective blocker, it does not suppress markers of infection such as C-reactive protein and fever as seen with the use of IL-6 blockers. Elevated cytokines, like IL-1, have been shown to predict survival in patients with idiopathic and familial PAH. In animal models of PAH, IL-1 receptors blockade reduces pulmonary hypertension [7].

MAS leading to decompensated PAH and acute right heart failure (RHF) is characterized by anatomic and/or physiologic right heart dysfunction despite adequate preload. It may result from intrinsic right heart insults such as ischemia or increased RV afterload resulting from an increased pulmonary vascular resistance. Management of RV failure generally follows a three-pronged approach: reducing afterload, optimizing preload, and increasing contractility. However, despite maximum medical therapy, some patients go into refractory RHF that requires mechanical circulatory support such as Extra Corporeal Membrane Oxygenation (ECMO). A veno-arterial ECMO (VA-ECMO) withdraws blood from the venous system and returns oxygenated blood to the arterial system to provide both respiratory and circulatory support and is used in cases of cardiopulmonary failure. The primary challenges to the use of VA-ECMO, in this case, were the patient's coagulopathy as evidenced by thrombocytopenia and elevated INR and a lack of supporting literature of VA-ECMO use in such cases. The presence of renal and liver failure made the patient an unsuitable candidate for a heart transplant and therefore we resorted to VA-ECMO as a bridge to recovery while optimizing treatment of MAS and PAH.

VA-ECMO in the management of HLH/MAS has exclusively been studied and reported in pediatric populations, and the literature for its successful use in the management of RHF secondary to MAS in adults remains scarce [8,9]. This case highlights the successful use and potential of VA-ECMO in adults for the management of MAS leading to decompensated PAH and multiorgan failure.

4. Conclusion

MAS can rarely result in acute decompensation of PAH and right heart failure. Besides RV failure management, immunosuppressants such as anakinra, etoposide etc. should be utilized early in the management of MAS. In refractory right heart failure, VA-ECMO can be considered as a bridge to recovery. More clinical studies are needed to investigate its potential use in such a scenario.

Declaration of competing interest

None of the authors associated with this manuscript have any conflict of interest.

References

[1] F. Minoia, S. Davì, A. Horne, et al., Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients, Arthritis Rheum. 66 (11) (2014) 3160–3169.

[2] A. Ravelli, F. Minoia, S. Davì, et al., Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative, Arthritis Rheumatol 2016 68 (3) (2016) 566–576.

[3] G.S. Schulert, A.A. Grom, Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies, Annu. Rev. Med. 66 (2015) 145–159.

[4] J.I. Henter, A. Horne, M. Aricó, et al., HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis, Pediatr. Blood Canc. 48 (2) (2007) 124–131.

[5] E. Soon, A.M. Holmes, C.M. Treacy, et al., Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension, Circulation 122 (9) (2010) 920–927.

[6] P. Mehta, R.Q. Cron, J. Hartwell, et al., Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome, The Lancet Rheumatology 2 (6) (2020) e358–e367.

[7] M. Campos, E. Schiopu, Pulmonary arterial hypertension in adult-onset still's disease: rapid response to anakinra, Case Rep Rheumatol 2012 (2012) 537613.

[8] K. Cashen, R.L. Chu, J. Klein, P.T. Rycus, J.M. Costello, Extracorporeal membrane oxygenation outcomes in children with hemophagocytic lymphohistiocytosis, Perfusion 32 (2) (2017) 151–156.

[9] V.A. Saites, R. Hadler, J.T. Gutsche, K. Laudanski, Extracorporeal membrane oxygenation for hemophagocytic lymphohistiocytosis, Am J Case Rep 17 (2016) 686–689.