Case Report

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Veno-venous extra-corporeal membrane oxygenation in a COVID-19 patient with cold-agglutinin haemolytic anaemia: A case report

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Abstract

Overview: The use of extra-corporeal membrane oxygenation (ECMO) therapy to treat severe COVID-19 patients with acute respiratory failure is increasing worldwide. We reported herein the use of veno-venous ECMO in a patient with cold agglutinin haemolytic anaemia (CAHA) who suffered from severe COVID-19 infection.

Description: A 64-year-old man presented to the emergency department (ED) with incremental complaints of dyspnoea and cough since one week. His history consisted of CAHA, which responded well to corticosteroid treatment. Because of severe hypoxemia, urgent intubation and mechanical ventilation were necessary. Despite deep sedation, muscle paralysis and prone ventilation, P/F ratio remained low. Though his history of CAHA, he still was considered for VV-ECMO. As lab results pointed to recurrence of CAHA, corticosteroids and rituximab were started. The VV-ECMO run was short and rather uncomplicated. Although, despite treatment, CAHA persisted and caused important complications of intestinal ischemia, which needed multiple surgical interventions. Finally, the patient suffered from progressive liver failure, thought to be secondary to ischemic cholangitis. One month after admission, therapy was stopped and patient passed away.

Conclusion: Our case report shows that CAHA is no contraindication for VV-ECMO, even when both titre and thermal amplitude are high. Although, the aetiology of CAHA and its response to therapy will determine the final outcome of those patients.

Keywords

Venovenous, extra-corporeal membrane oxygenation, cold agglutinins, case report, haemolytic anaemia, COVID-19

Introduction

In 2020, our healthcare system was overwhelmed by patients suffering from severe respiratory failure due to Sars-CoV-2, a new variant of the coronavirus, that causes COVID-19 infection. In some patients, the lung was severely affected and mechanical ventilation was insufficient to provide sufficient gas exchange. Additional support by an artificial lung, VV-ECMO, in selected cases was necessary. As mortality numbers of those patients, following the first wave of pandemic, were acceptable (37.1%) and comparable with that of other ARDS-patients, VV-ECMO was more frequently applied.[1] We present, following approval of the ethical committee of our hospital (EC-2022-216), the challenging case of a patient with previous history of

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auto-immune haemolytic anaemia with cold agglutinins (CAHA) in whom ECMO was proposed because of severe COVID-19.

Case presentation

A 64-year-old man presented to the emergency department (ED) with incremental complaints of dyspnoea and cough since one week; oxygen saturation was 54% (PaO_2 of 41 mmHg on 15 L/min oxygen mask therapy with $PaCO_2$ of 25.2 mmHg) on admission. The patient history consisted of CAHA with cold agglutinins, active at 4°C and room temperature. The first symptoms were reported 10 years earlier. An underlying small monoclonal B-cell population with chronic lymphocytic leukaemia (CLL)-phenotype was identified as the causative factor. On current admission, the patient was treated with low-dose corticosteroids (methylprednisolone 2 mg/day) as maintenance treatment, after high dose corticosteroids and rituximab for CAHA recurrence triggered by an infection, two years earlier. Further he was known with diabetes mellitus, type 2, treated with metformin and gliclazide, with good metabolic control (HbA1c at admission 4.6% (NR 4.0-6.0).

Blood analysis showed metabolic acidosis (pH 7.20, Lactate 17.8 mmol/L and bicarbonate of 9.7 mmol/L), anaemia (Hb 7.2 g/dL), in association with elevated lactate dehydrogenase (2225 IU/L – normal values, NR < 250 IU/L), total bilirubin (3.4 mg/dL – NR <1.0 mg/dL) and potassium (>7 mmol/L – NR 3.5-5.0 mmol/L), with normal kidney function and undetectable low haptoglobin (<0.10 g/L- NR 0.3-2.00 g/L). Creatinine kinase level was only mildly elevated (213 U/L- NR 0-190). Seen the previous history of CAHA, those lab values were highly suspicious for active haemolysis in this patient. A COVID-19-test (polymerase chain reaction (PCR)) was positive and Mycoplasma PCR-test negative. High procalcitonin levels (0.96 μg/L [NR <0.25 μg/L]) and CRP (128.8 mg/L [NR <5.0 mg/L] prompted the initiation of intravenous piperacillin-tazobactam. Clinical examination showed acrocyanosis at both hands and feet. Core temperature was 36.7°C. Transthoracic echocardiography showed no structural cardiac problem. A CT-scan excluded pulmonary and systemic embolism and signs of intestinal ischemia.

Seen the profound hypoxemia, the patient was urgently intubated at the ED. Despite protective mechanical ventilation (inspiratory pressure of 30 mmHg, a positive end-expiratory pressure (PEEP) of 8 mmHg, tidal volume (TV) of 200 ml, and respiratory rate of 32 /min), muscular paralysis and prone ventilation initiated at the Intensive Care Unit (ICU), PaO_2/FiO_2 ratio persistently remained below 100.

As the patient was only 64 years old, living at home in a satisfactory condition, with previous good responses to treatment of his CAHA, reversible cause of respiratory failure, short term mechanical ventilation (only one hour) and availability of sufficient resources, we considered the patient for ECMO-therapy (Ecmolife®, Eurosets, Fem-jug, 25Fr-19Fr). Anticoagulation was performed with heparin (target activated partial thromboplastin time (APTT) 50-70). Continuous veno-venous hemofiltration (CVVH) was associated by a left-sided jugular catheter because of severe metabolic acidosis with hyperkalaemia, and possible component of metformin-associated-lactate acidosis (MALA). After start of ECMO, PaO_2 increased to 54 mmHg. The ECMO ran at an average bloodflow of 3.6 L/min. Gasflow was incrementally increased during the first hours of ECMO, to avoid too fast correction of hypercapnia. Afterwards, it remained stable at an average flow of 5 L/min to maintain normocapnia. pH normalised. Ventilator settings were set at rest settings (PEEP 10, Pinsp 20, RR 8/min, FiO2 30%). Precautions were taken to avoid cooling down of the patient and aggravating CAHA (coverage of the patient with a heat blanket (Bair Huger®, 3M), warming of infusion fluids and transfusion products in a blood warming system (Sahara III®, Sarstedt, Germany) and use of the heater-device on the ECMO (Ecmolife Heater-cooler®, Eurosets) and CVVH (Thermax(Baxter®)) circuit). Body temperature remained stable around 37°C. Following warming up of the patient, acrocyanosis almost totally disappeared. At day 4, a sweep-off of gasflow was performed. With a slight increase in FiO_2 (40%) on the ventilator and increase in driving pressure to 13 cmH_2O, the patient could be weaned from VV-ECMO. As the patient was already severely anaemic at initiation of ECMO, administration of 7 units of packed red blood cells were necessary during the total ECMO run to keep the haemoglobin level above 7 g/dL. Further no major complications occurred. Haemolysis was monitored on a daily basis, by following LDH, bilirubin and ALT.

A direct antiglobulin test, performed on admission, confirmed the presence of CAHA, with high cold agglutinins titres (>1/2048), reactive at 4°C, but also at room temperature and 37°C. Flow cytometry showed monoclonal B-cells and a small population of monoclonal plasma cells. Based on the phenotype ($CD10^-$, $CD23^-$, CD79b+, FMC7+, CD5 partly +, strong $CD22^+$ and weak $CD43^+$, MYD88 -) and imaging (splenomegaly without nodal involvement), we concluded to cold-agglutinin disease (CAD) associated

lymphoproliferative disease (LPD). High dose corticosteroids (methylprednisolone 120 mg/d) and 4 weekly administrations of rituximab 375 mg/m^2 were administered. Lactate levels normalised and markers for haemolysis abated during the first days of treatment. The patient was weaned from mechanical ventilation on day 13.

However high titres of agglutinins and haemolysis persisted (Figure 1). Plasma-exchange (PEX) was started. PEX was performed daily for 4 days with warmed circuits and fluids. Unfortunately, the patient did not respond to PEX, and cold agglutinin titres remained remarkably high. We started treatment with intravenous immunoglobulins (IVIg) and planned to add bortezomib to the treatment. However, the hospital stay was complicated with candidemia, persistent kidney failure with need for CVVH, and intestinal ischemia for which multiple surgical interventions were performed. Despite all our efforts, the patient developed progressive liver failure with tentative diagnosis of ischemic cholangitis. One month after admission, therapy was stopped and the patient passed away.

Discussion

CAHA accounts for 25% of the auto-immune haemolytic anaemias (AIHAs). CAD is a form of CAHA caused by a clonal B-cell lymphoproliferative disorder.[2] CAHA is characterized by complement-mediated intravascular haemolysis due to cold agglutinins, which are autoantibodies (mostly IgM) that are activated at 4°C and in some patients at higher temperatures too.[3] This explains why agglutination can occur in acral areas of the body in those patients even when the central temperature is rather preserved. Cases of COVID-19 infection triggering auto-immune haemolytic anaemia (AIHA) or CAD have been reported.[4–6] The degree of haemolysis is mainly determined by the antibody titre (amount of antibodies)

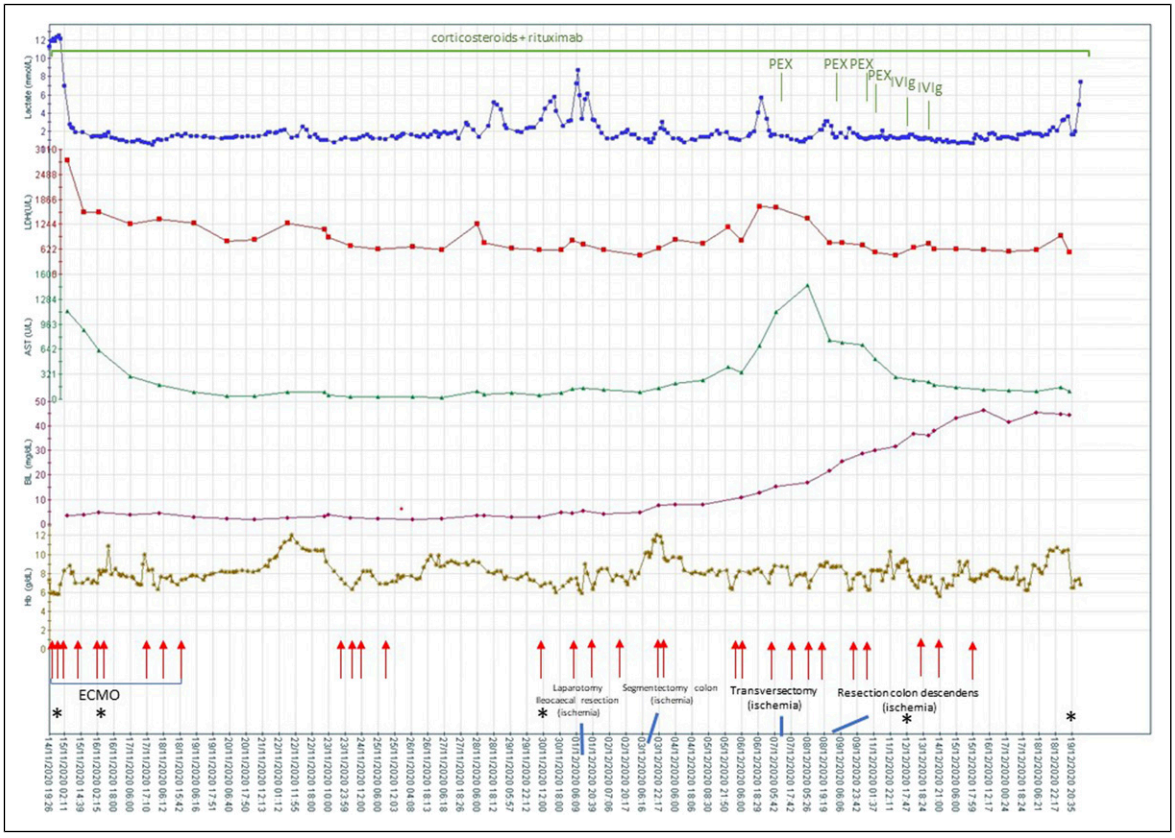

Figure 1. Evolution of haemolytic parameters during hospitalisation, treatment strategies and surgical interventions. LDH= lactate dehydrogenase; ALT= alanine aminotranferase; BIL= bilirubin, Hb= hemoglobin, PEX= Plasma Exchange, IVIg= Intravenous immunoglobulin, ↑= administration of RBC-packed cell, * undetectable haptoglobin level <0.10 g/L. After start of ECMO and CVVH, rapid decline in lactate, LDH and AST. Although further stagnation and frequently relapse of haemolysis pointed by LDH, slight increase in AST, unmeasurable haptoglobin and need for transfusion. Finally progressive increase in bilirubin, with tentative diagnosis of ischemic cholangitis.

and thermal amplitude (i.e., the highest temperature at which antibody-antigen binding occurs).

Principal management consists of avoiding further activation, by maintaining normothermia, and preventing further production of agglutinins by targeting the causal B-cell line (i.e. rituximab, bendamustine) and lowering circulating levels of cold agglutinins by applying plasmapheresis and immunoglobulins. However, as our patient already suffered from numerous infectious complications, a treatment with bendamustine seemed undesirable. Corticosteroids should be considered in CAHA patients with antibodies with a higher thermal amplitude and/or with an underlying disease for which corticosteroids are part of the treatment strategy, as was the case in our patient.

Experience in the management of patients with CAHA who need extra-corporal organ support is limited to cardiac surgery patients. Retrospective data, although marked by enormous heterogeneity in types of patients, time of diagnosis and pre- and per-operative management, show that cardiopulmonary bypass (CPB) can be performed without major complications in those patients. Avoidance of systemic hypothermia and cold cardioplegia are the key issues to be addressed[7,8]

Extrapolation of these data to ECMO patients might be dangerous as ECMO and CPB are two separate techniques, applied in different patient populations (cardiac surgery vs ARDS, optimized elective procedures vs severely sick patients, no infection vs multiple infections) with different treatment regiments (short-term - hours vs. long term – days or weeks; high-anticoagulation vs low anti-coagulation levels).[9] Two cases describe successful ECMO-runs in patient with CA, although the titre in one of these cases was very low.[10,11] As a titre above 1/512 is considered as significant and exceeds in many patients 1/2048,[12] it is questionable if in that patient with a titre of 1/256 this is of clinical importance. In our case, although ECMO-run itself was rather uncomplicated, cold agglutinin production continued following the weaning of ECMO. As most severe complications occurred more than one week after weaning of ECMO, it is difficult to find out if the ECMO-run itself contributed to the disease progression and final outcome in this patient.

Conclusions

This case-report describes a short ECMO run in a patient with previous history of CAHA, suffering from severe COVID-19 infection. It seems that CAHA is no contraindication for VV-ECMO, even when both titre and thermal amplitude are high. Avoidance of cooling down of the patient with further activation of cold agglutinins is of utmost importance. Use of heater-devices on patient body surface, circuits and fluids is essential to facilitate this. Although VV-ECMO is feasible in CAHA patients, the aetiology of the CAHA and response to the therapy will eventually determine the final outcome of those patients.

Declaration of Conflicting Interests

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