Acquired factor V inhibitor in a patient receiving venous-venous extracorporeal membrane oxygenation for Legionella pneumonia

Anne KH Leung *, George WY Ng, KC Sin, SY Au, KY Lai, KL Lee, KI Law

CASE REPORT

We report a rare complication of factor V deficiency in a patient having Legionella pneumonia. This patient also had other complications like severe acute respiratory distress syndrome, acute kidney injury, and septic shock that required venous-venous extracorporeal membrane oxygenation support. This is the first reported case of acquired factor V deficiency in a patient receiving extracorporeal membrane oxygenation for Legionella pneumonia.

With the combined use of intravenous immunoglobulin, rituximab and plasma exchange, we achieved rapid clearance of the factor V inhibitor within 1 week so as to allow safe decannulation of extracorporeal membrane oxygenation.

Case report

This was the case of a 53-year-old lorry driver with a history of pulmonary tuberculosis and chronic smoking, who presented in December 2012 with fever, cough, and sputum. Chest X-ray (CXR) showed left lower zone consolidation; the patient was diagnosed to have community-acquired pneumonia which was treated with ceftriaxone and azithromycin. Two days later, both the renal and liver functions worsened with elevation of serum urea level to 23.2 mmol/L (reference range [RR], 8-8.1 mmol/L), creatinine level to 493 μmol/L (RR, 62-106 μmol/L), aspartate transaminase level to 300 IU/L (reference level [RL], <40 IU/L), and alanine transaminase level up to 94 IU/L (RL, <41 IU/L). There was severe rhabdomyolysis with increased serum creatine kinase levels to 11010 IU/L (RR, 39-308 IU/L). Urine tested positive for Legionella antigen. Antibiotic was changed to piperacillin-tazobactam and azithromycin. The patient developed respiratory failure the next day and was admitted to the intensive care unit (ICU) for ventilator support.

His condition gradually stabilised over the next 10 days and sputum culture showed growth of Legionella pneumophila serogroup 1.

By day 11 in the ICU, he developed secondary deterioration with rapid progression of pulmonary infiltrates on CXR, septic shock, and acute kidney injury. Sputum culture after ICU admission showed growth of Pseudomonas aeruginosa and Corynebacterium species. Antibiotic was changed to meropenem and levofloxacin. By day 12, his oxygenation could not be maintained with conventional ventilation and the Murray score was 3.5. The patient was referred for extracorporeal membrane oxygenation (ECMO) support.

As his condition was unstable for transfer to the ECMO centre, venous-venous ECMO (VV-ECMO) was initiated at the referring hospital by percutaneous placement of two ECMO cannulas (23F and 19F) into the femoral vein and right internal jugular vein, respectively. The ECMO circuitry consisted of the Quadrox-i hollow-fibre oxygenator and Cardiohelp centrifugal pump (Maquet Cardiopulmonary AG, Germany). The circuit flow was started at 3.2 to 2.8 L/min during the first ECMO day, and then subsequently increased to 4.0 to 5.0 L/min to achieve PaO2 of 8 to 10 kPa. The ventilator setting was then decreased to peak airway pressure of <25 cm H2O, positive end–expiratory pressure of 10 cm H2O and FiO2 of 0.4. Heparin was started according to protocol with bolus 70 unit/kg after cannulation, followed by continuous infusion at 10 unit/kg/h to achieve an activated clotting time (ACT) of 200 to 220 seconds.

Before initiation of VV-ECMO, the baseline international normalised ratio (INR) was 1.1 and activated partial thromboplastin time (APTT) was 33.7 seconds (RR, 28-34.6 seconds). A full blood count showed a haemoglobin concentration...
of 68 g/L, white cell count of 16 x 10⁹/L, and a platelet count of 169 x 10⁹/L. Continuous veno-venous haemofiltration (CVVH) was started for renal support. By day 4 of ECMO, INR started to prolong (1.61) and gradually increased to 2.32 and 3.36 over the next 2 days. Heparin was stopped, and vitamin K 10 mg and repeated fresh frozen plasma (FFP) transfusions ranging from 8 to 14 units per day were given. Throughout this period, the fibrinogen level remained normal at 4.44 g/L (RR, 2-4.5 g/L) and platelet count was greater than 100 x 10⁹/L. Liver function and ammonia level were normal. The coagulopathy could not be corrected by FFP. A haematologist was consulted and further tests were arranged. By day 8, the INR peaked at 4.06, and APTT increased to 115 seconds with slight prolongation of thrombin time (TT) to 15.3 seconds (TT control = 14.4 seconds). Coagulation factor assay showed factor V of 1% (RR, 50-200%) while factor VII, VIII, IX, X, XI and XII levels were within reference intervals. Factor V inhibitor assay showed levels increased up to 6 Bethesda units. The diagnosis of acquired factor V inhibitors was made.

In the presence of significantly high levels of factor V inhibitor and risk of spontaneous intracranial bleed, intravenous immunoglobulin (IVIG) at 60 g/day was given for 2 days. The patient’s INR decreased from 3.96 to 2.56 and APTT decreased from 105.4 to 55.3 seconds. The workup for immune markers including C3, C4, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic and perinuclear neutrophil antibodies, anti-extractable nuclear antigen, and anti-cardiolipin antibodies was negative. The tumour markers were negative as well. The patient received no surgical procedure. He had been put on four antibiotics after ECMO including azithromycin, meropenem, fluconazole, and linezolid. By day 4 of ECMO, fluconazole was replaced with anidulafungin for fungal cover.

Despite IVIG, the patient developed significant clinical bleeding with full-stream haematuria and bronchoscopy showed extensive blood clots in the left lower lobe. At the same time, his pulmonary mechanics and CXR started to improve after 10 days of ECMO support and he appeared ready to be weaned off from ECMO. It was decided to give him one dose of rituximab 700 mg on day 11 of ECMO. His INR decreased to 1.29 and APTT to 33.6 seconds over the next 2 days (Figs 1 and 2). The patient was successfully decannulated on day 13 of ECMO. The haematuria remained severe and...
required continuous bladder irrigation. Citrate CVVH was started for renal support. One session of plasma exchange was given after decannulation. The haematuria eventually stopped by day 16. Two days later, urinary output returned to normal and the patient was successfully extubated. By day 19, the patient was discharged back to the parent hospital with INR of 1.02, APTT of 30.4 seconds, and factor V assay of 173%. The patient was discharged 3 weeks later and his coagulation profile remained normal without further eradication therapy. At the time of discharge, the patient was able to walk with the help of a walking stick, could perform activities of daily living independently, and was dialysis-independent.

Discussion

Factor V deficiency: causes, clinical course, laboratory finding, treatment, and outcome

Factor V is a plasma cofactor that activates prothrombin to thrombin, thus, affecting the common final pathway of the coagulation cascade. About 20% of the circulating factor V is found within platelet α granules.1 The first reported case of congenital factor V deficiency was from Germany in 1955,2 and to date, about 200 reported cases have been reported.1 Congenital factor V deficiency is a rare autosomal recessive disease with a prevalence of 1 in 1,000,000.1 In acquired cases, it is related to the presence of factor V inhibitor.3 In one case series of 78 patients, the commonest cause was the use of antibiotics (42%), including β-lactam antibiotics, aminoglycosides, cephalosporins, tetracyclines, and quinolones. The next common cause was surgical procedure (31%) with exposure to bovine thrombin, which is a topical haemostatic agent widely used in cardiovascular or neurosurgical procedures.4 Infection, cancer, and autoimmune disease were present in 23%, 22%, and 13% of the cases, respectively. About 16 (21%) cases had no identifiable causes.3

The median age of presentation was 69 years, with a tendency for male predominance.3 Overall, 81% of cases had bleeding, and the mucous membranes of most frequently reported sites including gastro-intestinal tract, genito-urinary tract, and the airway were noted in up to 62% of cases.3 Cerebral haemorrhage occurred in only 8% of cases, but was associated with 50% mortality.3 Some cases were associated with thrombotic complications rather than haemorrhage.5

Laboratory findings included a prolonged prothrombin time and APTT that failed to be corrected by mixing studies. Thrombin time was usually normal unless there is presence of thrombin inhibitor. Bethesda assay is used to detect and quantify the presence of inhibitors. One Bethesda unit is defined as the amount that decreases factor V concentration by 50%.4,5 Bleeding correlated with factor V activity with median factor V activity being 1% in bleeders and 3% in non-bleeders.3

Treatment mainly consists of controlling bleeding and eradication of the autoantibody. Daily infusion of 15 to 20 mL/kg of FFP is usually

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**FIG 2. Detailed INR and APTT profiles of the patient from day 8 to day 12**

Abbreviations: APTT = activated partial thromboplastin time; ECMO = extracorporeal membrane oxygenation; INR = international normalised ratio; IVIG = intravenous immunoglobulin
sufficient.\textsuperscript{1} In refractory cases, recombinant factor VIIa, activated prothrombin complex concentrate, and platelet transfusion are therapeutic options.\textsuperscript{1,3,6} Plasmapheresis and immunoadsorption can rapidly reduce antibody titres. For immunosuppression, corticosteroids and cyclophosphamide have shown a success rate of 63%.\textsuperscript{3} Use of high-dose IVIG and anti-20 monoclonal antibody rituximab were associated with rapidly increasing factor V activity, although results were conflicting.\textsuperscript{1,6}

The alloantibody against factor V was polyclonal immunoglobulin G\textsuperscript{2} and it disappeared in the majority of cases (69%) either after eradication therapy (43/78 patients) or spontaneously (12/78 patients).\textsuperscript{3,7} For those patients who survived, factor V inhibitor persisted for a mean period of 5.1 months\textsuperscript{8} (range, <1 month to several years).\textsuperscript{6,7} For those related to bovine thrombin, the inhibitor emerged after a mean of 8.3 days of exposure and persisted for a shorter time of 2.3 months.\textsuperscript{8} Overall, 72% of patients with acquired factor V inhibitors suffered bleeding complications, with 17% of those being fatal.\textsuperscript{8} For those with acquired factor V deficiency with a known cause like bovine thrombin–induced factor V inhibitor, bleeding was less common (33%) and was associated with better prognosis and lower fatality (6%).\textsuperscript{8} The highest mortality was found in patients with autoimmune disorder (30%) or cancer (24%).\textsuperscript{8}

**Use of extracorporeal membrane oxygenation for Legionella pneumonia**

Use of ECMO has been reported locally for treating influenza H1N1 with good outcome.\textsuperscript{9} Use of ECMO in Legionella pneumonia with acute respiratory distress syndrome has been reported,\textsuperscript{10-12} with survival rate ranging from 67% to 84% in the UK series.\textsuperscript{10,11} Acute renal failure was a common complication of legionellosis with 53.7% requiring renal replacement therapy. The prognosis for this subgroup of patients was poor with only 33% (vs 70% in those without acute renal failure) surviving to decannulation and mortality increasing from 15% to 53%.\textsuperscript{10} Major bleeding complications reported in these series included intra-abdominal bleeding, cardiac tamponade, chest drain–related haemorrhage, and gastro-intestinal and intracranial bleeding.\textsuperscript{9-11}

This is the first reported case of acquired factor V inhibition in a patient put on VV-ECMO for Legionella pneumonia. Although our patient had acute renal failure and ECMO was instituted late in his course of illness (13 days after intubation), he responded favourably. The cause of the acquired factor V inhibition was uncertain. It may be related to the underlying infection, use of antibiotics, or be idiopathic in nature. The coagulopathy was not corrected by FFP transfusion and the patient had symptomatic bleeding with haematuria and pulmonary haemorrhage despite IVIG therapy. Although we could wait for the natural disappearance of the factor V inhibitor, it might prolong weaning from ECMO and increase the risk of fatal complications like intracranial bleeding. Yet, too early prescription of rituximab as in this patient might mask the effect of IVIG. Lastly, there was a remote possibility that the observed decrease in INR and APTT could be due to natural progression of the underlying disease rather than a treatment effect as only 15% of patients have spontaneous resolution of disease and the factor V inhibitors can persist in the body for months.\textsuperscript{1,3} In one case report, INR remained elevated for 10 days despite immunosuppressive therapy and returned to normal over the next 2 weeks.\textsuperscript{1} The need for ECMO decannulation and presence of active symptoms made correction of coagulopathy more imminent. The use of multimodal therapy including IVIG, rituximab, and plasma exchange in this patient successfully halted the progress of the factor V inhibitor and allowed safe decannulation within a period of 1 week.

**References**