Evans syndrome in a patient with COVID-19

Evans syndrome (ES) is a rare condition characterised by the combination of autoimmune haemolytic anaemia and immune thrombocytopenia (ITP). While the precise pathophysiology is not entirely understood, it is thought that dysregulation of the immune system is a primary contributor to the condition. ES has been observed in viral infections including hepatitis C, cytomegalovirus, varicella zoster and Epstein–Barr viruses.[1–4] Initial cases of coronavirus disease 2019 (COVID-19) were first described in early December 2019 and has now spread to a global pandemic. While knowledge about COVID-19 continues to evolve, clinicians have reported haematological complications associated with the virus. Presence of lymphopenia has been commonly reported in 35–40% of cases and appears to be associated with the development of acute respiratory distress syndrome.[5–7] Thrombocytopenia and coagulopathies, including disseminated intravascular coagulation, have also been reported in cases of COVID-19, which were associated with more severe disease.[8,9] Here, we present the first case, to our knowledge, of COVID-19-associated ES and discuss its unique management issues.

A 39-year-old man presented to the emergency department in late March 2020 with one day of haemoptysis and epistaxis in the setting of sore throat, productive cough, fevers, chills and dyspnoea lasting about 1 week. On evaluation, he was found to be febrile, tachycardic and tachypneic. Physical examination was notable for dried blood in the oropharynx and nares, as well as a blood blister in the mouth. He had no petechiae, ecchymoses or rash. Laboratory assessments demonstrated a leucocyte count of 11 000 cells/μl, haemoglobin of 156 g/l and platelet count of 3000 cells/μl. The neutrophil count was 8700 cells/μl, and lymphocyte count was 1700 cells/μl. Haemolysis laboratories were negative, and there were no schistocytes nor microspherocytes on peripheral blood smear. There was no infiltrate on chest X-ray. Rapid polymerase chain reaction assay for COVID-19 later returned a positive a result.

On admission, the patient developed worsening bleeding with haematemesis, melena and haematochezia, associated with a haemoglobin decrease to 64 g/l. Intravenous proton pump inhibitor therapy was initiated, as well as daily intravenous immunoglobulin (IVIG) therapy for presumed ITP secondary to COVID-19. Glucocorticoids were not administered, as organisations such as the Centers for Disease Control (CDC) and World Health Organization (WHO) recommended against the use of glucocorticoids in patients with COVID-19.[10,11] On day 5, the platelet count recovered to 52 cells/μl with resolution of bleeding. By day 6, platelets were 308 cells/μl, haemoglobin was stable at 76 g/l, and the patient was discharged.

Four days after discharge, the patient returned to the hospital with extreme weakness and fatigue, intermittent fever and cough without bleeding. Haemoglobin was 60 g/l with a normal platelet count. Laboratory assessments showed a reticulocyte count of 22%, lactate dehydrogenase (LDH) of 947 u/l, elevated fibrinogen, haptoglobin <20 g/l, and positive direct Coombs test (3+), concerning for new immune-mediated haemolytic anaemia. Peripheral blood smear was notable for microspherocytes, nucleated red blood cells, and reticulocytes (Fig 1). Coupled with his recent history of ITP, his clinical picture raised concern for ES *versus* immune haemolytic anaemia secondary to IVIG. Once again, corticosteroids were avoided in the setting of COVID-19 infection, and IVIG therapy was re-initiated. Meanwhile, the patient continued to have low-grade fevers with lower extremity weakness and hypoxaemia requiring 2 l of oxygen. After a second dose of IVIG, he developed a left popliteal deep venous thrombosis for which he was started on therapeutic heparin. His haemoglobin eventually stabilised at 70 g/l with a robust reticulocyte response. IVIG was discontinued with concern for its contribution to macrovascular thromboembolism. At 4 weeks after discharge, blood counts showed a haemoglobin level of 110 g/l and 505 platelets/μl.

The pathogenesis and management of ES in the setting of the inflammatory milieu of COVID-19 has not been previously described and represents a unique challenge in clinical management. The exact pathophysiology of ES is not fully elucidated, but studies suggest the intersection of autoimmunity and predisposing immune dysregulation is involved. Several proposed mechanisms of autoimmunity have been described, including activation of Bruton tyrosine kinase and overexpression of cytokines.[12,13] Evolving accounts of COVID-19 have reported a pro-inflammatory state with laboratory abnormalities such as elevated D-dimer, LDH, C-reactive protein and ferritin. Case series from China reported higher plasma levels of cytokines in critically ill patients.[14] Taken together, dysregulation of the immune system in COVID-19 infection could create favourable conditions for the development of ES.

The mainstay therapy for ES is typically immunosuppression, including corticosteroids. However, the routine use of corticosteroids in patients with COVID-19 is not recommended outside another indication such as shock or obstructive lung disease, according to established guidelines from the WHO, CDC and Infectious Disease Society of America [10,11,15]. The basis of this recommendation is founded on analysis from previous viral outbreaks. Retrospective data from the Middle East Respiratory Syndrome (MERS) outbreak have associated steroid therapy with increased mortality and delayed clearance of viral RNA.[10] Meta-analysis of steroid use in Severe Acute

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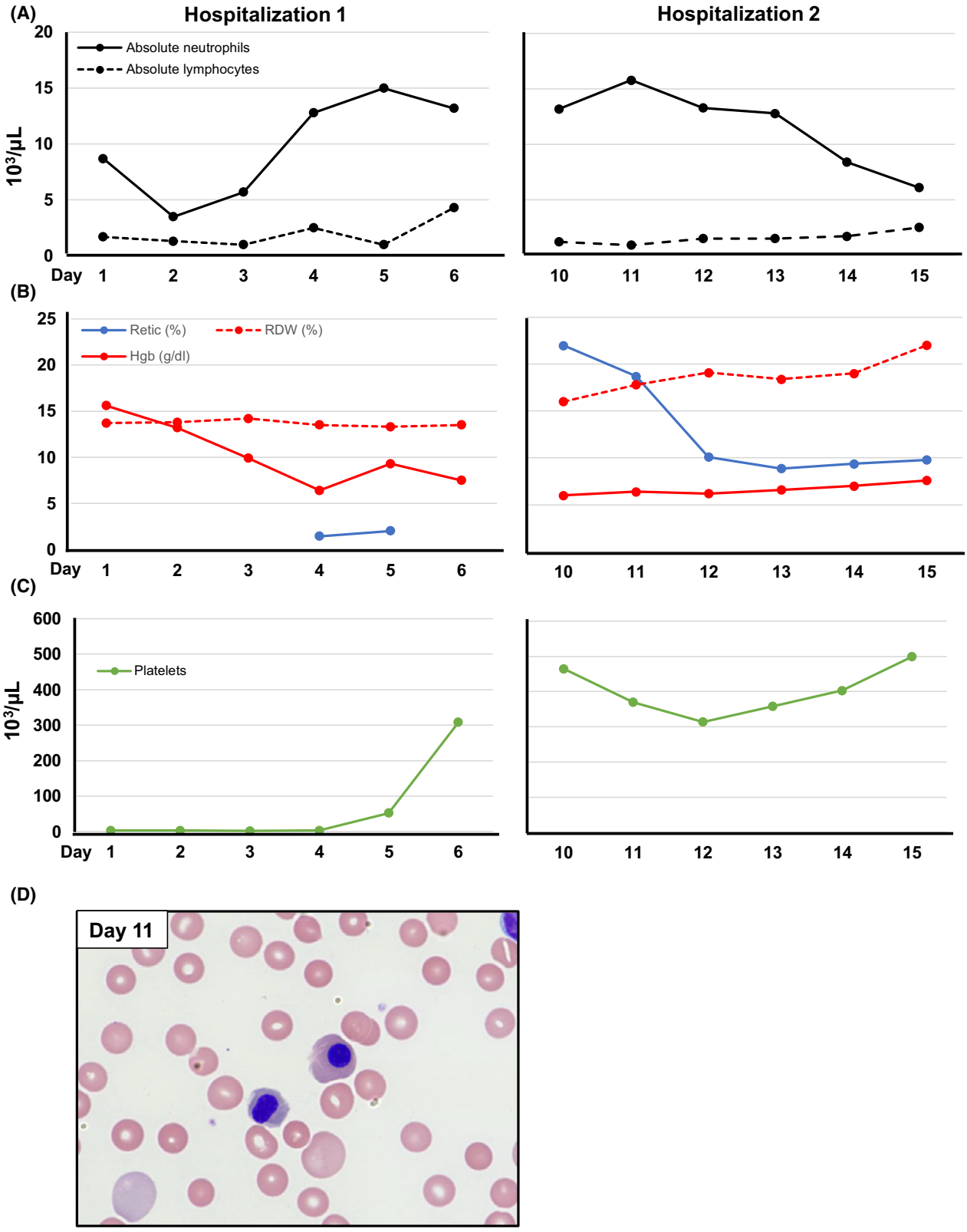

Fig 1. (A–C) Haematological cell line trends during the patient's clinical course. (D) Peripheral blood smear showing microspherocytes, nucleated red blood cells and reticulocytes. Hgb, haemoglobin; RDW, red cell distribution width; Retic, reticulocyte count.

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Respiratory Syndrome (SARS) has been associated with harm, and systematic review of corticosteroid use in patients with influenza was associated with increased mortality.[11] Thus, alternatives to corticosteroids were used to manage our patient with ES. IVIG, both diagnostic and therapeutic in this case, was used to treat our patient's thrombocytopenia. Thrombopoietin receptor agonists could also be considered in this scenario, as combination of these agents may be useful if platelet rebound is insufficient. It is difficult to know if autoimmune haemolytic anaemia in our patient is related to IVIG or underlying immune dysregulation from COVID-19. Nonetheless, treatment options are limited for patients with COVID-19 in this context, and further data are needed to guide the use of immunosuppression in patients with autoimmune complications of SARS coronavirus 2.

Based on the case above, we propose a framework for patients with COVID-19 with haematological dysfunction that addresses the acuity of bleeding, avoidance of immunosuppression, and support for both platelet and anaemia components of ES. Until more data emerge on the use of corticosteroids in setting of COVID-19, avoidance of corticosteroids should be considered in autoimmune haematological diseases in patients with COVID-19 in favour of alternative therapies.

Conflict of interest

The authors have no potential conflict of interest to disclose.

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COVID-19-associated immune thrombocytopenia

Thrombocytopenia is a risk factor for increased morbidity and mortality in patients infected with the new severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (COVID-19 infection).[1] Thrombocytopenia in COVID-19 patients may be caused by disseminated intravascular coagulation (DIC), sepsis or be drug-induced. Recently a single case

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