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Evans syndrome in an asymptomatic patient with COVID-19: Case report and review of the literature

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Dear Editor

COVID-19 infection is a fast-spreading and alarming global public health issue [1]. The clinical features of coronavirus infection vary widely, from asymptomatic infection to severe pneumonia with acute respiratory failure and even death [2-3]. Clinical experience and the emerging literature suggest that several organs and systems can all be affected by COVID-19 infection, with a different degree of severity [4-6]. It's therefore mandatory to be aware of the possibility that COVID-19 infection can occur and evolve with different non-specific symptoms. Among these, hematological manifestations, though rare, may play a predominant role [7] due to the rapid onset of symptoms and complications. In particular, Evans syndrome (ES) is a rare condition characterised by the combination of autoimmune haemolytic anaemia and immune thrombocytopenia. While the precise pathophysiology of this condition is not entirely understood, it is thought that dysregulation of the immune system can primary contribute to its development. ES can occur during different viral infections including hepatitis C, cytomegalovirus, varicella zoster and Epstein–Barr viruses. ES has been rarely described in patients with COVID-19 infection and, in most of these cases, COVID-19 was substantially asymptomatic [8]. In this paper, we describe a case of Evans syndrome occurring few days after COVID-19 diagnosis; we also reviewed the literature, focusing on the therapeutic approaches for ES in COVID-19 infected patients.

A 64-year-old woman with a previous history of cryptogenic hepatitis and pulmonary fibrosis was admitted to the emergency department with a 10 days history of fatigue, persistent hypothension and tachycardia. She had a recent diagnosis of mild symptomatic COVID-19 infection, with a nasopharyngeal swab RT-PCR for SARS-CoV2 that became negative two weeks before the admission. She had mild fever and cough at the time of COVID-19 diagnosis, not requiring hospitalization. When she presented at emergency, she had no fever, cough or dyspnea and chest x-ray was normal. On clinical examination jaundice was found, in absence of other abnormalities. Blood tests showed severe anaemia (haemoglobin: 5.3 g/dL; mean corpuscular volume: 128 pl; mean corpuscular haemoglobin: 41.7 pg; mean corpuscular haemoglobin concentration: 32.5%), mild thrombocytopenia (platelets 140.000/mm^3), normal leukocytes, increase of lactate dehydrogenase 727 U/L (normal range, 135–214 U/L) and of total and direct bilirubin (3.09 mg/dL and 0.92 mg/dL, respectively). No schistocytes were found at the peripheral smear. Direct Coombs test was positive (IgG and C3), suggesting immune-haemolytic anaemia, therefore methylprednisolon 1 mg/kg/daily was started. Tests for auto-immune conditions and other viral diseases were negative. A total body computed tomography was normal. Platelet count rapid declined (at day 3rd platelets were 68.000/mm^3, at day ^{4th} 37.000/mm^3); as a consequence, intravenous immunoglobulin (IVIG) 1 gr/kg for two consecutive days were added to steroid and diagnosis of ES was done. In the following days, a progressive increase of platelet count was observed, with a substantial normalization after 1 month (Figure 1). Steroid treatment dosage was progressively reduced and definitively stopped after 6 months with a subsequent maintenance of a normal platelet count after 12 months of follow-up (Figure 1).

At the moment, the pathogenesis and the management of ES in COVID-19 infected individuals have been rarely described; the combination of autoimmunity phenomena induced by COVID-19 infection and predisposing immune dysregulation may both play a role in the occurrence of this haematological complication. Several mechanisms of autoimmunity have been proposed for ES, including activation of Bruton's tyrosine kinase and over-expression of cytokines [9,10]. Further, the pro-inflammatory state induced by COVID-19 infection and the abnormal production of cytokine in this individuals may create favourable conditions for the development of ES.

The treatment of ES is usually immune-suppression with corticosteroid. However, in this specific scenario, IVIG can be effective, as demonstrated in other reports [11,12]. In the report by Georgy, *et al.* [8]. IVIG were not used due to lack of feasibility and only steroid was done; further, their patient had also an intra-cerebral haemorrhage and died few days after diagnosis, whilst in the other reports the clinical conditions associated to ES were less severe and recovered, at least in the short time. Finally, our patient was followed-up for a long period after ES, with no evidence of recurrence and with persistent maintenance of normal platelet count.

In conclusion, our case report highlights the need of a careful evaluation of COVID-19 infected individuals about hematologic dysfunction, addressing the risk of bleeding and eventually support them with both platelet and other blood components. According to the few reports currently available in the literature, the combination of steroid and IVIG could be considered the optimal therapeutic strategy of ES in COVID-19 infected patients.

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