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ABSTRACT

Evans syndrome is a rare condition characterized by simultaneous or sequential development of autoimmune hemolytic anemia and immune thrombocytopenia (and/or immune neutropenia). Coronavirus disease 2019 (COVID-19) may cause various hematologic conditions, such as coagulation abnormalities (e.g., bleeding or thrombosis) or cell count alterations (e.g., lymphopenia and neutrophilia). COVID-19 may also induce Evans syndrome via immune mechanisms. Here, we describe the case of a patient developing Evans syndrome shortly after COVID-19 infection. Immune thrombocytopenia and warm-type autoimmune hemolytic anemia developed simultaneously, and intravenous immunoglobulin and methylprednisolone were initially administered. Additionally, we intend to review all COVID-19-induced Evans syndrome cases currently present in the literature and emphasize the differences as well as the similarities regarding patient characteristics, relationship to COVID-19 infection, and treatment approach. Since autoimmune cytopenias are frequent in COVID-19 patients, clinicians should pay particular attention to profound and abrupt-onset cytopenias. In these circumstances, hemolysis markers such as lactate dehydrogenase, haptoglobin, Coombs tests, etc. should be investigated, and the possibility of Evans syndrome should always be considered to ensure prompt and appropriate treatment. These factors are essential to ensure hematologic recovery and prevent complications such as thrombosis.

1. Introduction

Evans syndrome (ES) is an autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), and/or immune neutropenia [1]. ES is a rare condition diagnosed in only 0.8%–3.7% of all patients with either ITP or AIHA. ES may be associated with diseases or conditions such as systemic lupus erythematosus, lymphoproliferative disorders, primary immunodeficiencies, and viral infections (e.g., hepatitis C, cytomegalovirus, varicella-zoster, and Epstein-Barr viruses). Although the exact pathogenesis of ES is currently unknown, immune disorders may be responsible. In some cases, patients may have a genetic predisposition [1,2]. Coronavirus disease 2019 (COVID-19) is known to have hematologic effects such as thrombocytopenia and coagulation abnormalities in varying degrees, including disseminated intravascular coagulation, lymphopenia, neutrophilia, and tendency toward thrombosis [3]. COVID-19 may be a risk factor for autoimmunity given its potential to trigger relapses in patients previously known to have autoimmune cytopenias [4,5]. ES induced by infection may pose a diagnostic and therapeutic dilemma for the clinician. Infections such as COVID-19 also have a prognostic significance due to increased risk of morbidity and mortality in patients with autoimmune cytopenias [6]. In addition, COVID-19-related thrombosis risk, caused by thrombomodulation, endothelial activation, and anti-phospholipid antibodies, is amplified by ongoing hemolysis and increased fractions of young platelets in ES [5,7]. Here, we aim to present a patient as well as the cases of five other patients who developed ES due to COVID-19, as documented in the literature [8–12].

2. Case report

A 63-year-old female patient with no known comorbidities was evaluated after presenting cough and high fever over a period of several days. The rapid polymerase chain reaction (PCR) test for COVID-19 was positive and found to be the British variant. In the computerized tomography (CT), bilateral lung infiltrates compatible with COVID-19 were detected (Fig. 1). Favipiravir treatment was initiated. After seven days, her weakness increased and petechiae were detected in the legs.
upon physical examination. Blood count analysis showed hemoglobin: 6.5 g/dL, platelet: 2000/mm$^3$, leukocyte: 13,120/mm$^3$ and lymphocyte: 1,140/mm$^3$. Her lactate dehydrogenase (LDH) level was 426 U/L (125–243 U/L) and the absolute reticulocyte count was 316,000/microL. Her lactate dehydrogenase (LDH) level was 426 U/L (125–243 U/L) and the absolute reticulocyte count was 316,000/microL (range: 20,000–200,000/microL; AIHA with adequate reticulocytosis). Direct antiglobulin test (DAT) with monospecific anti-sera was +4 in terms of both anti-immunoglobulin (Ig) G and anti-complement -3. Autoantibody specificity tests were not performed, and the patient was classified as warm (IgG $^+$). Our case (case 1) revealed a normal DAT +4 in terms of both anti-immunoglobulin (Ig) G and anti-complement -3. Autoantibody specificity tests were not performed, and the patient was classified as warm (IgG $^+$). Our case (case 1) revealed a normal DAT +4 in terms of both anti-immunoglobulin (Ig) G and anti-complement -3. Autoantibody specificity tests were not performed, and the patient was classified as warm (IgG $^+$). Our case (case 1) revealed a normal DAT $^+$.
(ANA) and antiphospholipid antibody (APA) positivities. The patient was likely to have lupus-like syndrome, and steroids and hydroxychloroquine were beneficial during treatment [11]. In the case report of Georgy et al. (Case 6), IVIG was not feasible, only dexamethasone could be used, and the patient died of intracranial hemorrhage [12].

4. Discussion

Infections, including COVID-19, may have a role in inducing new-developing autoimmune cytopenias or triggering relapses. Barcellini et al. reported a patient with a pre-existing diagnosis of ES who relapsed due to COVID-19 [4]. Molecular mimicry, spreading of hidden epitopes, and neo-antigen formation are possible pathogenetic explanations [7,13]. The mechanism of immune-mediated anemia is facilitated by a SARS–COV-2 surface glycoprotein spike that resembles ankyrin-1 (an erythrocyte membrane protein) and creates molecular mimicry [14]. In contrast, thrombocytopenia develops due to increased platelet aggregation in the pulmonary circulation with microthrombi formation and consumption [15]. Additionally, in ITP, Anti-GP IIb/IIIa, GP-Ib/IX, or GP-V antibodies and increased hepatic clearance of platelets can be responsible [4]. The diagnosis of ES can be challenging given that the COVID-19 state alone can cause cytopenias due to sepsis. In addition, the infection itself may be responsible for misleading autoimmunity tests [16]. It is suggested that the autoimmune etiology should be considered as a possibility when thrombocyte or hemoglobin count falls abruptly and profoundly and after the elimination of other causes [5].

Age is an important host risk factor for COVID-19 [3]. It is noteworthy that patients with ES are relatively young, and the subject of the present case study is older than the others. Although the female sex seems to be dominant in general, the female/male ratio in cases reported due to COVID-19 is 1/1 [1]. ES can present in immunocompromised patient groups (such as common variable immune deficiency and IgA deficiency). In addition, hepatitis B, C, and human immunodeficiency virus status are important to evaluation [1]. In our patient, there was no immune deficiency; however, in other patients, immune status was not reported except in case 5. Regarding potential effects of drugs, we could not find any precedent in the literature indicating that favipiravir could cause ES.

There are currently no prospective or controlled randomized studies concerning the treatment of patients with both ES and COVID-19. Most of the immunosuppressant drugs (e.g., steroids) used for autoimmune cytopenias also have immunomodulatory activity that can alleviate inflammation and improve prognoses in COVID-19. Therefore, available evidence suggests that the use of immunomodulatory/immunosuppressant drugs for autoimmune cytopenias is not detrimental to the course of COVID-19 [4,5]. First-line drugs that can be used in treatment are steroids and IVIG. High-dose IVIG is a safe and reasonable approach for patients with COVID-19-induced ES, especially with a high risk of bleeding [7,17]. Alternative options are recombinant erythropoietin which may be safer for patients with inadequate reticulocytosis and rituximab. Plasma exchange may be a resource in the acute setting, although it is not always feasible for elderly patients, particularly those with congestive heart failure [7]. Mycophenolate mofetil, cyclosporine, vincristine, azathioprine, sirolimus, and thrombopoietin receptor agonists can be considered second-line treatment options in ES independent of COVID-19 infection [18]. Thrombosis is a potential negative outcome in COVID-19-induced ES, as ongoing hemolysis and increased young platelet fraction in ITP further increase the risk of thrombosis due to COVID-19-induced thromboinflammation and endothelial activation [7]. Thromboprophylaxis with heparin is strongly recommended in all ambulatory or hospitalized COVID-19-infected patients [19]. Since the addition of ES further increases risk, particular attention should be given to thromboprophylaxis for as long as the platelet count allows [7].

5. Conclusion

Infections including COVID-19 may induce autoimmune cytopenias and relapse of preexisting autoimmune conditions. COVID-19-induced ES is a rare but challenging condition for clinicians that may present diagnostic, prognostic, and therapeutic dilemmas. Therefore, particular attention should be paid to ensure hematologic recovery and prevent complications such as thrombosis.

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Consent to participate

Informed consent form approving participation was obtained from the patient.

Consent for publication

Informed consent form approving publication was obtained from the patient.

Author contributions


The manuscript has been read and approved by all the authors, the requirements for authorship in this document have been met, and each author believes that the manuscript represents honest work.

CRediT authorship contribution statement

Atakan Turgutkaya: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - review & editing. Ali Zahit Bolaman: Conceptualization, Data curation, Resources, Supervision, Validation. İrfan Yavaşoğlu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - original draft.

Declaration of Competing Interest

None.

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