รายงานผู้ป่วย Evans Syndrome มีภาวะเม็ดเลือดต่ำเมื่อมีการติดเชื้อโควิด 19

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A Case Report of Worsening Pancytopenia in a Patient with Evans Syndrome During a COVID-19 Infection

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Abstract

In 2019, a coronavirus called SARS-CoV-2 was first discovered as a cause of adeadly pneumonia in China, before spreading worldwide leading to global COVID-19 pandemic. Major manifestations of the disease arefever and respiratory symptoms, with possible consequences of acute respiratory distress syndrome, thromboembolism, and multi-organ failure in severe cases. In addition to respiratory manifestations, hematologic complications have also been affecting patients with COVID-19 infections. This includes cytopenias, hemolysis and abnormal coagulation. Cases of newly diagnosed Evans syndrome have also been reported to occur both after and concomitantly with COVID-19 infections. In this case report, we present a case of Evans syndrome developing intopancytopenia during aCOVID-19 infection. A 48 year-old man with Evans syndrome was admitted due to acute fever and dark urine. He was positive for COVID-19 infection and his laboratory investigations showed pancytopenia withacute hemolysis. Remdesivir was given along with systemic glucocorticoid. This resulted in an overall improvement of cytopenias and his clinical status.

Keywords: Evans syndrome, COVID-19, Pancytopenia

บทคัดย่อ

ไวรัสโคโรนาสายพันธุ์ SARS-CoV-2 เป็นไวรัสที่ก่อให้เกิดโรคทางระบบหายใจโควิด 19 (COVID-19) มีรายงานก่อโรคปอดอักเสบครั้งแรกที่ประเทศจีนในปี พ.ศ. 2562 ก่อนจะเริ่มแพร่ระบาดไปทั่วโลกโรคโควิด 19 (COVID-19) มีอาการสำคัญคืออาการทางระบบทางเดินหายใจ ในรายที่มีอาการรุนแรงอาจมีภาวะหายใจล้มเหลว ลิ่มเลือดอุดตัน หรือมีภาวะอวัยวะอื่น ๆ ล้มเหลวตามมา นอกจากอาการทางระบบทางเดินหายใจแล้ว ผู้ป่วยโรคโควิด 19 อาจมีอาการทางระบบโลหิตร่วมด้วย เช่น ภาวะเม็ดเลือดต่ำ เม็ดเลือดแดงแตก หรือการแข็งตัวของเลือดผิดปกติ มีรายงานพบผู้ป่วยกลุ่มอาการอีแวนส์ (Evans syndrome) รายใหม่ หลังจากติดเชื้อโควิด 19 หลายราย รายงานผู้ป่วยฉบับนี้ได้นำเสนอผู้ป่วยกลุ่มอาการอีแวนส์ชายอายุ 48 ปีรายหนึ่งที่มีเม็ดเลือดต่ำลงขณะติดเชื้อโควิด 19 ผู้ป่วยมาด้วยอาการไข้ ปัสสาวะเข้ม ผลตรวจทางปฏิบัติการพบการติดเชื้อโควิด 19 ภาวะเม็ดเลือดแดงแตก

และมีเม็ดเลือดต่ำลง หลังได้รับการรักษาด้วยยาต้านไวรัสและสเตียรอยด์ อาการและผลเลือดของผู้ป่วยค่อยๆ ดีขึ้น

คำสำคัญ: เม็ดเลือดต่ำ, ผู้ป่วยกลุ่มอาการอีแวนส์, โควิด 19

Introduction

Evans syndrome is a condition characterized by autoimmune cytopenias; most commonly presenting with warm autoimmune hemolytic anemia and immune thrombocytopenia. More rarely, autoimmune neutropenia might also be exhibited in some cases. Infection has been described as one of the causes associated with Evans syndrome, and also an important triggering factor for relapse of the disease. This includes viral infections; such as Parvovirus B19, HBV, and HCV.[1] Since the emergence of the COVID-19 pandemic in 2019, several cases of Evans syndrome have been reported to develop both after and concomitantly with COVID-19 infections[2] ;implying the association of SARs-CoV-2 infection and immune cytopenia. In this report, a known case of Evans syndrome developing worsening cytopenias during a COVID-19 infection is illustrated.

Case report

A 48 year-old man, a known case of Evans syndrome, presented at our hospital with acute fever and cough. His latest medication included: azathioprine 50 mg/day, prednisolone 10 mg/d, folate and ferrous supplement. He reported as having darker urine during the past few days. He did not observe any abnormal, overt bleeding. His initial vital signs were a blood pressure of 94/52 mmHg, pulse rate of 84 bpm, respiratory rate of 30 /min, body temperature of 38.7°C, and oxygen saturation of 93%; without supplemental oxygen. Other physical examinations revealed that he was remarkably pale and icteric, without notable rash, lymphadenopathy, abdominal tenderness or hepatosplenomegaly. His septic work up came back with a positive antigen test kit result for COVID-19 infection and negative for other bacterial sources of infection: CXR was unremarkable. Hemoculture was reported with negative results. Other laboratory investigations showed a strikingly low hemoglobin level, with thrombocytopenia and leukopenia; hemoglobin level 3.8 g/dL, a platelet count of 100×10^3/µL and a white blood cell count of 3.26×10^3/µL, with an apparent drop from his baseline laboratory values: as shown in Table 1. He also had indirect hyperbilirubinemia and elevated aminotransferases. Direct antiglobulin testing was positive (4+). Additional laboratory tests and his baseline laboratory values are summarized in Table 1.

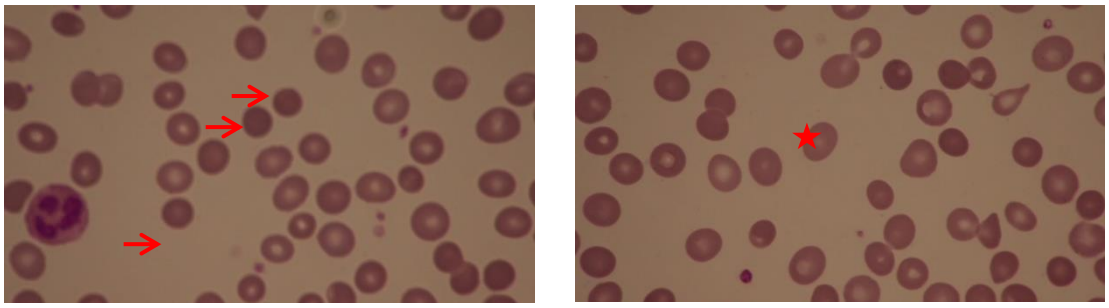
Hemolysis was suspected with anemia, jaundice, elevated transaminases and indirect hyperbilirubinemia. A review of his peripheral blood smear exhibited polychromasia and microspherocytes, as shown in Figure 1, indicating autoimmune hemolytic anemia. At this point, he was diagnosed with COVID-19 infection, with acute hemolysis and pancytopenia. Remdesivir was given for 5 days along with empiric antimicrobial therapy. Systemic glucocorticoid was prescribed as hydrocortisone 200 mg/day on the first day due to hypotension, and later on as dexamethasone 16 mg/day for immune cytopenia for 5 days, before switching to prednisolone 50 mg/day prior to discharge from hospital. A unit of packed red cells was given with a delay on day 2 of admission due to difficulty in cross matching. With given treatment, fever subsided. His hemoglobin level rose to 7.4 g/dL, his total bilirubin level decreased to 4.2 mg/dL, while his platelet count remained at approximately $72\text{-}75\times10^3$/µL and a white blood cell count around $2.70\text{-}4.61\times10^3$/µL; resulting in an overall improvement in the patient's clinical status. He was discharged with prednisolone 50 mg/day and azathioprine 50 mg/day was reinitiated.

A month later, a follow up laboratory investigation at the out-patient clinic revealed improving cytopenia, with a hemoglobin level of 9.3 g/dL, platelet count of 146×10^3/µL and white blood cell count of 2.38×10^3/µL.

Table 1 shows laboratory values during hospital course

Date	Hb (g/dL)	Hct (%)	MCV (fL)	WBC count (x10^3/uL)	Platelet count (x10^3/uL)	TB/DB (mg/dL)	AST/ALT/ALP (U/L)
baseline	9.1	28.6	107.5	5.54	190		
Day 1 of admission	3.8	11.4	108.6	3.26	100	9.4/1.9	148/33/51
Day 2 of admission	2.9	8.9	115	3.70	120		
Day 3 of admission	4	12.8	109	6.32	131		
Day 4 of admission	5	16.6	111	6.29	80		
Day 6 of admission	6.1	21.3	113	4.61	75	4.2/0.8	47/113/47
Day 8 of admission	7.4	25.6	111	2.70	72		

Figure 1 shows peripheral blood smear during the first days of admission (prior to blood transfusion)



→ indicates microspherocyte

★ indicates polychromasia

Discussion

Evans syndrome is an autoimmune disease featuring cytopenias, with anemia and thrombocytopenia with or without neutropenia occurring either simultaneously or sequentially.[3] Although rare, the estimated prevalence of this disease being 1-9 per million[4], it is not unexpected in patients with cytopenia. The median age of onset is 50 - 58.5 years and the sex ratio is just about 1 according to an observational multicenter study in 12 European tertiary centers[4] and a retrospective cohort study in Denmark[5]. Evans syndrome can be defined as primary or secondary. Associated conditions in secondary Evans syndrome include: lymphoproliferative disease, autoimmune disease, primary immunodeficiencies; especially in children, and viral infections.[3] Among Ebstein Barr virus, hepatitis C and cytomegalovirus, SARs-CoV-2 is also one of the

viral infections reported to be possibly related to secondary Evans syndrome.[3]

Infections have been implied to play a role in Evans syndrome; as both the contributing factor for disease development and the triggering factor for disease relapse.[1] With SARs-CoV-2 infection being introduced and having spread worldwide, cases of Evans syndrome occurring during and following COVID-19 infection have been increasingly reported.

Presently, there are several reviews on COVID-19 infection and Evans syndrome. While new cases of immune cytopenia, occurring after a COVID-19 infection, are being reported, cases of patients with preexisting Evans syndrome developing worsening cytopenia during the viral infection are also being documented. The first case report of newly diagnosed Evans syndrome after a COVID-19 infection was from early 2020. This described a 39 year-old man that developed immune thrombocytopenia and immune hemolytic anemia after the pandemic viral infection.[6] As for SARS-CoV-2 infections in known cases of Evans syndrome, such as our case report, a few cases have been described: as shown in Table 2. The onset of cytopenia was concomitant with COVID-19 infection in a case report in Italy[7], the same as in our patient, while in 2 other cases the onset was unknown[8, 9]. Cytopenia involved was anemia in all of the cases. One of the cases developed accompanying leukopenia[8] and another patient had associated thrombocytopenia[9]. However, in our case pancytopenia occurred. The extent of cytopenia appeared to have no correlation to the severity of COVID-19 pneumonia. Hemoglobin was the lowest in our patient (Hemoglobin level 2.9 g/dL) whom had mild desaturation without oxygen support. All the patients received systemic corticosteroids, with or without empirical antibiotics, with improved outcomes.

Several mechanisms for cytopenias in COVID-19 infections have been proposed. Lymphocyte apoptosis may be induced by cytokine storm, with elevated levels of interleukins and tumor necrosis factor alpha.[10] Cell lysis might also be a result from direct infection of ACE2 receptor expressed-lymphocytes.[10] As for thrombocytopenia, platelet aggregation in the lungs and microthrombi[1], increased hepatic clearance of platelets during a viral infection[8] and molecular mimicry, generation of anti-platelets antibodies; for example anti-GP IIb/IIIa, and anti GP-Ib/IX[8], may all play a part. Molecular mimicry mechanism causing anemia is also possible, with ankyrin 1, and the erythrocyte membrane protein, sharing similar identity with surface glycoprotein on SARS-CoV-2.[1] Various erythrocyte morphological abnormalities have been reported in patients with COVID-19 infection; including anisocytosis, spherocytosis, stomatocytes and polychromasia, and are suspected to be a result of oxidative stress in the inflammatory state.[11] These changes in erythrocyte structure, a consequence of viral infection and imbalance redox status, may lead to early lysis.[12] One or more of these mechanisms might explain pancytopenia in our patient.

Table 2 compares patients with Evans syndrome and COVID-19 infection in previous and current reports

Patient profile	***Our case report*** 48 year-old male Evans syndrome	78 year-old male relapsed/refractory Evans syndrome hypertension previous myocardial infarction with ventricular fibrillation, stroke (Barcellini et al[11])	77 year-old female Evans syndrome hypertension, mitral prolapse, lower limb venous insufficiency (Osti et al[12])	10.1155/2020/8862545 23 year-old female Evans syndrome diagnosed during peripartum period (Vadlamudi et al[13])
Baseline laboratory results	Hb 9.1 g/dL, platelet 190×10^3/μL	baseline lab not revealed	Hb 12g/dL, platelet 15x10^3/μL	At first diagnosis Hb 7.1 g/dL platelet< 10x10^3/μL
Previous medication for Evans syndrome	Azathioprine 50 mg/day, prednisolone 10 mg/d, folate and ferrous	steroids and intravenous immunoglobulin, cyclophosphamide, 2 cycles of rituximab experimental spleen tyrosine kinase inhibitor	prednisone 1 mg/kg/d	-
Onset of cytopenia	Concomitantly with COVID-19 infection	Onset relative to COVID-19 infection not mentioned	Concomitantly with COVID-19 infection	Peripartum period then worsening thrombocytopenia on postpartum day 9, 18 rtPCR for COVID-19 was positive on postpartum day 34 The onset of COVID-19 infection was unknown
Severity of cytopenia - Lowest Hemoglobin level (g/dL) - Lowest WBC count (×10^3/μL) - Lowest platelet count (×10^3/μL)	- 2.9 g/dL - 2.7×10^3/μL - 72×10^3/μL	- 7.3 g/dL - Lymphopenia nadir 0.85×10^3/μL - Platelet count not mentioned	- 5.7 g/dL - 15.8×10^3/μL - 286×10^3/μL	- 7.1 g/dL - 9.9×10^3/μL - < 10×10^3/μL

Severity of COVID-19 infection	On O_2 cannula	Desaturation to 80% low-flow oxygen support	Bilateral interstitial pneumonia required oxygen supplementation	Imaging revealed ground-glass opacities and an acute pulmonary embolism
Management	- Remdesivir 5 days - Empiric antimicrobial therapy - Hydrocortisone 200 mg/day on the first day dexamethasone 16 mg/day prednisolone 50 mg/day	- Steroids, HCQ, azithromycin, full-dose low molecular weight heparin, and empirical antibiotic therapy for superimposed bacterial infection. - Intravenous immunoglobulin and prednisone 1 mg/kg/day for 3 weeks	- Oral prednisone 1 mg/kg/d - intravenous immunoglobulin 0.4 g/kg/d for 5 consecutive days	Peripartum period oral dexamethasone 40 mg/day for 4 days oral prednisone 60 mg/day Postpartum day 9 second 4-day course of oral dexamethasone 40 mg/day Postpartum day 18 third 4- day course of dexamethasone 20 mg/day intravenous immunoglobulin 1 mg/kg for 2 days rituximab Postpartum day 34 high-intensity heparin infusion
Outcome	A month later hemoglobin level was 9.3 g/dL, platelet count was 146×10^3/μL and white blood cell count was 2.38×10^3/μL.	Autoimmune hemolytic anemia was in remission.	After 18 days of hospitalisation cold agglutinins were undetectable with hemoglobin level of 9 g/dL and platelet count of 211×10^3/μL.	Platelet count on readmission on postpartum day 34 was 131 $\times10^3$/μL and remained stable over 200×10^3/μL.

Management of Evans syndrome in the setting of active infection can be challenging, balancing the risk of cytopenias and worsening infection with immunosuppressives. Systemic corticosteroids, prednisolone 1 mg/kg/day, is considered first-line treatment for Evans syndrome.[13] While in COVID-19 infection, therole of glucocorticoid is only strongly recommended in severe and critically ill patients.[14] This is due to concernsof the potential risks for superimposed bacterial and fungal infection versus its benefits in thehyperinflammatory state of COVID-19 infections.

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As illustrated in this case report, COVID 19 might have its role in inducing pancytopenia in patients with Evans syndrome. Systemic corticosteroids

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