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Review article

Evans syndrome in the course of COVID-19 infection; essentials and approaches

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Abstract

Redundant studies proved coronavirus infection results from a defect in a suitable immune response that may exacerbate immune-inflammatory reactions like cytokine storm and autoimmunity. Evans syndrome (ES) is a rare chronic autoimmune disease that distinguishes it from autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). Reports have shown significant differences in immune cells and laboratory parameters in Evans syndrome/COVID-19 co-infected patients. Also, the contribution between autoimmune diseases and SARS-CoV-2 infection could result in immune response disequilibrium that considers a possible mechanism for ES development. Moreover, we will briefly explain the double-edged sword role of immunosuppressive drugs in Evans syndrome/COVID-19 co-infected patients. Generally, the pathophysiology of SARS-CoV-2 in hematologic autoimmune disorders progression, particularly ES, remains unclear, but some investigations explain the COVID-19 infection mechanism in the mentioned disorders development. The purpose of the current study is to look at the coronavirus effects on Evans syndrome aggravation, the immune cells and laboratory markers alterations in Evans syndrome/COVID-19 co-infected patients, the coronavirus effects on Evans syndrome patients during their pregnancy, and the Evans syndrome / COVID-19 co-infected patient management.

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1. Introduction:

In late 2019, a novel viremic disease emerged in China and rapidly spread worldwide [1, 2]. More investigation showed that the virus caused the pandemic disease evolved from the coronaviridae family and manifested flu-like clinical symptoms in suffering patients as well as fatigue, dry cough, sore throat, fever, and dyspnea [1, 2]. Due to the virus exhibiting a high tendency to target the human respiratory system, its name was altered to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Redundant studies proved SARS-CoV-2 infection results from a defect in a suitable immune response that may exacerbate immune-inflammatory reactions like cytokine storm and autoimmunity [1-4].

Notably Evans syndrome (ES) is a rare autoimmune status resulting from the existence of autoimmune cytopenia (involving at least two blood cell lines), autoimmune hemolytic anemia (AIHA), and immune thrombocytopenia (ITP). Based on accurate reports, it could include autoimmune neutropenia (AIN) which occurs either sporadically or concurrently in a few cases (approximately 15%) [1, 2, 4]. Although due to the intricate mechanism of ES, its etiology is not correctly understood. Investigations indicate that pathologic autoantibody generation against the blood cells may contribute to ES development. Therefore, it can be implied ES has a significant relationship with immune dysregulation [1-3, 5].

The syndrome was recognized for the first time by Robert Evans in 1951 when he explored the relationship between AIHA and ITP and observed patients suffering from AIHA and cytopenia simultaneously, while there was no report of any family history of hemolytic diseases [6]. The proposed hypothesis described that the neutropenia and thrombocytopenia with acquired hemolytic anemia in these patients were owing to the existence of an immune body with a wide-ranging response to the red cells or a released immune substance or portions more specific for platelet and white cell tissue [1, 6-8]. ES is one of the multifactorial and complicated immune-hematologic disorders. Therefore, due to the paucity of knowledge about the effect of COVID-19 on hematologic disorders and particularly ES, we were persuaded to review the coronavirus effects on Evans syndrome aggravation, the immune cells, and laboratory markers alterations in Evans syndrome/COVID-19 co-infected patients, the coronavirus effects on ES patients during their pregnancy and the Evans syndrome/COVID-19 co-infected patient management.

2. Epidemiology and Pathophysiology of Evans syndrome

Although ES is commonly considered a childhood disease, evidence showed it could affect adult individuals [6, 9]. Due to limited performed studies about the syndrome, the exact rate of ES incidence among children and adults is unclear. Therefore, the ES reported in incidences of ITP and AIHA separately [10], could better support some assumptions of ES incidence.

Clinical observations demonstrated that ES co-occurs in less than 5% of all patients with either ITP or AIHA at the diagnostic stage (**Table 1**) [10, 11].

Moreover, valid data recorded the occurrence of ES among ITP patients at about 1%, while the rate of ES incidence in AIHA patients is markedly higher than in ITP patients (approximately 6-7%) [9]. On the other side, the percentage of occurrence of this syndrome in AIHA patients is different; it has been reported between 37%-73% and is higher than in ITP patients [2, 6, 10, 12]. The average age of ES patients at the time of diagnosis is 52 years; similar to most other autoimmune diseases, it is more common in women, and the gender ratio is 3:2 in women to men. Although various mechanisms have been proposed that led to ES; nevertheless, the pathophysiology of ES is still ambiguous. Classical scientists believe that ES may be an "idiopathic condition" and could be an autoimmune condition in which B lymphocytes could attack its own cells that predominantly include red blood cells (RBCs), platelets, and white blood cells through auto-antibody (Ab) production. Based on recent studies, it is supposed that ES is caused by a defect in immune regulation [1, 7, 10, 12]. While the presented data indicate a number of different causes could lead to ES; the most common of which involve autoimmune lymphoproliferative syndrome (ALPS), common variable immunodeficiency (CVID), systemic autoimmune disease, most prominent systemic lupus autoimmune leuko-proliferative disease (RALD), and ALPS-related disorders [9, 10, 13-16]. The causes and mechanisms are summarized in **Table 2.**

Table 1: Clinical features of Evans syndrome in the presence of AIHA, ITP and, AIN.

Clinical symptoms in the presence of AIN	Clinical symptoms in the presence of ITP	Clinical symptoms in the presence of AIHA
Recurrent infections	Bleeding, purpura, and bruising or bleeding from minor injuries and death (in some cases)	Fatigue, jaundice, dizziness, shortness of breath, physical weakness, spleen enlargement, and ischemic complications such as acute coronary syndrome (over 60 years of age)

AIHA: Autoimmune hemolytic anemia, **ITP:** Immune thrombocytopenic purpura, **AIN:** Autoimmune neutropenia

Table 2: Main mechanisms in pathophysiology of Evans syndrome.

Mechanism	Cause
Mutation in apoptotic pathway related to FAS-FAS L ~)70%) Mutation in apoptotic pathway related to CAS10~) 2-3 (% Imbalance between T helper 1 & 2 populations	**ALPS**
Defective in B lymphocytes maturation Decreased regulatory T cells population Mutation in TACI encoding gene	**CVID**
Loss of central and peripheral tolerance in mature and immature B lymphocytes Loss of tolerance in T cells due to decreased number of regulatory T cells or lack of anergy in autoreactive T cells Presence of anti c-MPL autoantibody Presence of anti GPIIb/IIIa autoantibody Presence of anti-CD 40 autoantibody Defect in complement C4 compound	**SLE**
Somatic mutation in KRAS and/or NRAS gene	**RALD**
Increasing the number of DNT cells, impaired in apoptotic pathway related to FAS gene, augmentation of BCL2 anti-apoptotic protein and impairment of intrinsic apoptosis Disruption in FOXP3+ regulatory T cells function: a)Disruption in B lymphocyte maturation b)Disruption in T cells homeostasis through reduced T regs population Mutation in P110δ gene encoding Mutation in STAT1 & STAT3 genes MHC I molecule upregulation & presence of anti-nucleolar, anti-cytoplasmic, anti-nuclear antibodies	**ALPS-like syndromes:** **•CTLA-4 deficiency** **•LRBA deficiency** **•PI3KD syndrome** **•Gain-of-function mutations in STAT gene** **•TPP2 insufficiency**

ALPS: Autoimmune lymphoproliferative syndrome, **CVID:** Common variable immunodeficiency, **SLE:** Systemic lupus erythematosus, **CTLA-4:** Cytotoxic T-lymphocyte-associated protein 4, **TPP2:** Tripeptidyl Peptidase 2, **LRBA:** Lipopolysaccharide-responsive and beige-like anchor protein, **RALD:** RAS-associated autoimmune leuko-proliferative disease, **PI3KD:** Phosphatidylinositol 3-kinase catalytic delta

3. Diagnosis of Evans Syndrome

A thorough clinical history is a prerequisite to determining ES developing risk factors that include infections, malignancies, autoimmune diseases, recent vaccinations, drugs, or a family history of immune disorders; it could be approved with a comprehensive physical examination focused on signs of anemia or thrombocytopenia [8]. Notably, the primary mentioned ES is a "diagnosis of exclusion" [2]. Given that, there are tangible differences between primary and secondary ES in their treatment and responses. Therefore, exploration for ascertaining a baseline disease could be helpful to secondary ES diagnosis. Evaluation of laboratory features demands a complete blood count and direct examination of peripheral blood; anemia, thrombocytopenia, reticulocytosis, and poikilocytosis basically owing to the presence of spherocytes, elevated indirect bilirubin and lactate dehydrogenase and a positive direct anti-human globulin test (DAT) test verifying ongoing immune hemolysis are to be anticipated [7]. More investigations can detect antibodies produced against platelet (PA-IgG) markers. In 35% of the suspected individuals it was found that most of the antibodies were produced predominantly against IIb-IIIa. Anti-granulocyte antibodies can be detected in some patients, tests of the patient's platelets and serum for antibodies and DNA typing for human platelet alloantigen (HPA) can help approve a clinical diagnosis of ITP (Figure 1). Correctly interpreted platelet serologic test data, accompanied by a complete clinical history and other laboratory results, promises a more accurate diagnosis and suitable treatment [2, 7, 17]. Figure 2 is a Peripheral blood smear of an Evans syndrome patient.

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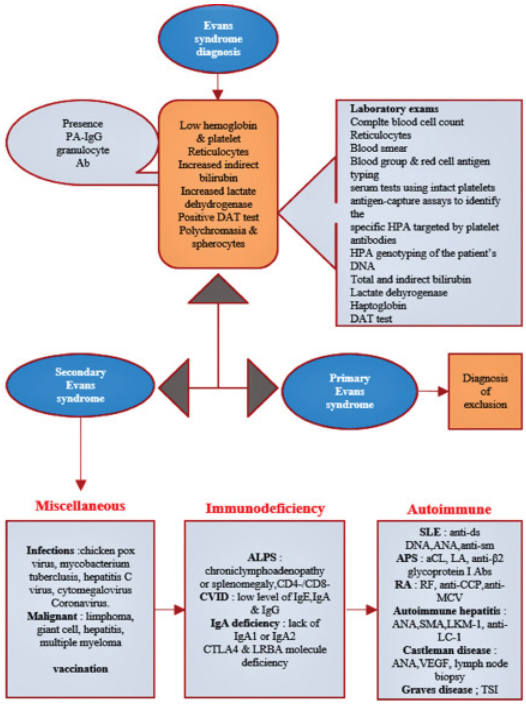

Figure 1: Evans syndrome diagnostic methods. **aCL,** anticardiolipin; **ANA**, antinuclear antibodies; **anti-CCP,** anti-cyclic citrullinated peptide; **anti-LC1**, anti-liver cytosol antibody; **anti-MCV**, anti-mutated citrullinated vimetin; **anti-Sm,** anti-Smith antibody; **APS,** antiphospholipid syndrome; **LA,** lupus anticoagulant; **LKM-1,** liver kidney microsomal type 1 antibodies; **PA-IgG**, platelet-associated IgG; **SMA,** smooth muscle antibody; **TSI,** thyroid stimulating immunoglobulin; **VEGF,** vascular endothelial growth factor; **HPA,** human platelet alloantigens.

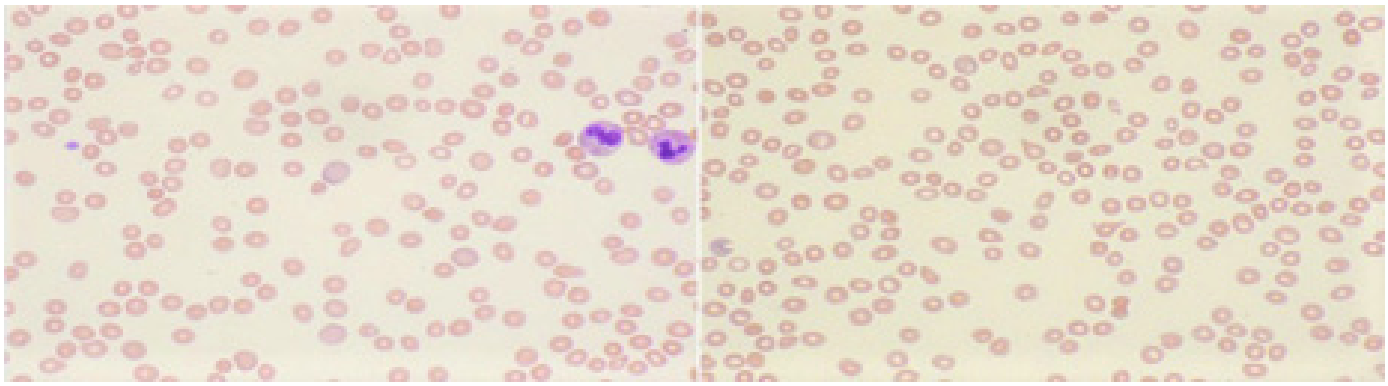

Figure 2: Peripheral blood smear of an Evans syndrome patient: Peripheral blood smear showing microcytic, slightly hypochromic anemia with anisocytosis and polychromasia, thrombocytopenia, and slight leukocytosis. Teardrop cells, reticulocytes, and small spherocytes are present. No overt schistocytes, fragmentation of red blood cells, overt dysplasia, or presence of blasts noted [8].

Effects of COVID-19 on hematologic autoimmune disorders

Although the pathophysiology of COVID-19 in hematologic autoimmune disorders progression including AIHA, ITP, TTP, APS, autoimmune neutropenia, and ES remains unclear, confined studies could explain the COVID-19 infection mechanism in the mentioned disorders' development. One of the proposed justifications is that viral infection may result in immunological tolerance failure through a wide range of mechanisms like molecular mimicry, bystander activation, epitope spreading, and autoreactive effector cells immortalization which create a connection between auto-inflammatory and autoimmune reactions that were previously observed in different types of viral infections [6, 9, 10]. Thereby, it is reasonable that COVID-19 infection is potentiated in commencing a dual pathway of immune response and subsequently leads to different types of autoimmunity [4, 7]. Moreover, thrombocytopenia has been detected in thirty percent of the patients with COVID-19 infection. The mechanism of this symptom during the infection appears vague. Nevertheless, several mechanisms could be considered: 1) cytokine storm may originate from the viral infection and may cause limited platelet production. 2) SARS-CoV-2 may directly induce autoimmune reaction against platelet or attack on bone marrow that leads to hematopoietic stem cell function disruption. 3) Endothelial injury during mechanical ventilation provokes platelet activation and accumulation in the lung to thrombosis, therefore resulting in platelet overconsumption. 4) Lung is considered as a location for converting matured megakaryoblast to platelet; it is possible that platelet fragmentation occurs while it passes within the pulmonary capillary [1, 4, 7, 9] .

Laboratory findings in Evans Syndrome/ COVID-19 co-infected patients

Case report studies show significant differences in immune cells and laboratory parameters in Evans syndrome/COVID-19 co-infected patients have been observed. The alterations have been expressed briefly in Table 3. Although the infected patients had a normal range lymphocyte count, an abnormal increase in their white blood cell count was observed that was probably due to elevated neutrophil count. Also, hemoglobin level and platelet count were decreased. In addition, haptoglobin, iron, and ferritin levels were diminished. In contrast, D-dimer, lactate dehydrogenase, and alkaline phosphatase levels grew up which may be due to an inflammatory response mediated by the virus infection which prepares a condition for ES progression. Furthermore, direct and indirect bilirubin levels were increased. Nonetheless, some parameters like Aspartate aminotransferase, Alanine aminotransferase, fibrinogen, and vitamin B12 remained in a normal range. Notably, serological tests including direct (IgG and C3d) and indirect Coombs test were extremely positive, while antinuclear antibody was negative [3, 6, 10].

Table 3: Evans syndrome/ COVID-19 co-infected patients Laboratory parameters.

Lab parameters	Patient value		
	Decrease	Normal	Increase
Haemoglobin (g/dL)	✓		
WBC count (cells/mm3)			✓
Lymphocyte count (cells/mm3)		✓	
D-dimer (ng/mL)			✓
LDH (U/L)			✓
AST (IU/L)		✓	
ALT (IU/L)		✓	
ALP (IU/L)			✓
Haptoglobin (mg/dL)	✓		
Total bilirubin (mg/dL)			✓
Indirect bilirubin (mg/dL)			✓
Fibrinogen (mg/dL)		✓	
Corrected reticulocyte ratio (%)			✓
Ferritin (ng/mL)ratio (%)	✓		
Iron (µg/dL)	✓		
Vitamin B12 (pg/mL)		✓	
Serological test			
Direct coombs (IgG & C3d)	4+		
Indirect coombs	3+		
Antinuclear Ab	Negative		

WBC, White blood cell; **LDH,** Lactate dehydrogenase; **ALT,** Alanine aminotransferase; **AST,** Aspartate aminotransferase; **ALP,** Alkaline phosphatase; **IgG,** Immunoglobulin G; **C3d,** Complement component 3d; **Ab,** Antibody.

Effects of corona virus on Evans syndrome patients during their pregnancy

ES diagnosis during the patient's gestation should be distinguished from pregnancy disorders. Several studies stated the patient did not suffer from pregnancy diseases [3]. Moreover, most of the clinical lab tests involving hemolysis, liver function test, blood pressure, and coagulation status on the patient's gestation were normal. While only platelet count was reduced profoundly and could result from pregnancy thrombocytopenia. However, the ES presenting in the patient is not detectable. As mentioned previously, vast cytokine response during the pregnancy may stimulate extreme immune response and lead to AIHA. Besides, an increasing population of ES patients deal with at least one other autoimmune disease like SLE. The combination of autoimmune diseases and SARS-CoV-2 infection could result in immune response disequilibrium that is considered a possible mechanism for ES development [3].

Management of Evans syndrome/COVID-19 co-infected patient

According to evidence-based studies, valid clinical trials for ES treatment have not been conducted. The priority is the treatment of patients who have considerable clinically reduced platelet and hemoglobin levels; however, as observed in ITP, physicians experience determining start therapy in non-symptomatic patients [1, 18-20]. The main objective consists of achieving a long-term complete response. No plausible therapeutic regimen has been documented. Steroids with and without intravenous immunoglobulin (IVIG) are considered first-line therapy. RBC or platelet transfusion is performed only in severe symptomatic patients as it could aggravate the patient clinical status. Generally, treatment lines in ES patients depend on their efficiency, long-term complete response, and safety, and are classified into first, second, and third treatment lines [1, 18-20]. However, no effective drug or treatment has been

determined for COVID-19 infection; nonetheless, immunosuppressive therapy such as corticosteroids, which is considered an important therapy for autoimmune diseases, especially ES, is not appropriate for Evans syndrome/ COVID-19 co-infected patients. Nevertheless, in infected patients suffering from lung injury, alternative immunosuppression administration could help in suppressing inflammatory response and managing the co-infected patient [3, 9, 12-15].

First-line treatment of ES does not differ from frontline ITP or AIHA management and combined therapy is not necessary. Controlling the acute symptoms of bleeding or anemia that routinely happen as a result of corticosteroids or IVIG injection in the case of ITP is crucial [12].

There are several "secondary" immunomodulatory treatment options including: azathioprine, cyclosporine, danazol, 6-thioguanine (6-TG), tacrolimus, vincristine, cyclophosphamide, splenectomy, alemtuzumab (anti-CD52 antibody), mycophenolate mofetil (MMF), rituximab (anti-CD20 antibody), meanwhile rapamycin (sirolimus), and thrombopoietin receptor agonists (TPO-RAs) Eltrombopag and romiplostim are cutting edge and novel therapies for ES management [1, 21, 22]. Treatment lines, mechanisms, complications, and treatment lines advantages have been shown in **Table 4.**

Table 4: Therapeutic methods used, effectiveness mechanism and side effects and their applications in the treatment of Evans syndrome/COVID-19 co-infected patient.

Treatment method	Treatment line	Mechanism	Complications	Considerations
Steroid drugs (prednisolone and prednisone)	First	Inhibition of macrophage ability to clear platelets and erythrocytes	Short-term effect, Patients become refractory to steroid treatments	Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient
Intravenous immunoglobulin (IVIG)	First	Blocking the FC¥ receptor at the surface of the macrophage	Mild side effects: fever, headache, fatigue, nausea, palpitations and muscle pain Acute complications: acute renal injury, arterial thromboembolism, noninfectious meningitis, hemolytic anemia and infection	Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient
Anti-CD20 antibody (Rituximab)	Second	B lymphocytes depleted from peripheral blood after transfusion	Risk of mild infusion reaction, decreased immunoglobulin level, infection after treatment in immunocompromised patients, vomiting, urticaria, facial swelling, pneumonia and temporary cytopenia up to 2 weeks after blood transfusion	Appropriate for patients with refractory ES. Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient

Treatment method	Treatment line	Mechanism	Complications	Considerations
Mycophenolate mofetil (MMF)	Second	Inosine monophosphate inhibition resulting in a decreased lymphocyte proliferation	Cytopenia (leukopenia, neutropenia and anemia), gastrointestinal problems (diarrhea, abdominal pain and increased liver transaminase), headache and lymphoma propagation	Lack of demand of prolonged use of steroids, suitable for steroid refractory patients or IVIG Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient
Cyclosporine	Second	was previously used instead of Rituximab	Surgical risk, High risk of sepsis or meningitis, Bleeding, Thromboembolic events	Not recommended for children under 6 years
Cyclophosphamide	Third	Anti - mitotic effect, immune regulator and suppression of progressive immune response	Secondary malignancy and infection	It is an effective treatment for the recovery of patients with ES, which can even improve patients without complementary therapy. Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient
Anti-CD52 antibody (Almetozumab)	Third	B & T lymphocytes depleted	Malignancy	Prescribe cautiously for Evans syndrome/ COVID-19 co-infected patient
Thrombopoietin Receptor Agonists (Romiplostim and Ultrombopag)	Third	Decreased platelet destruction and increased megakaryocyte proliferation and maturation	Thrombosis (due to both drugs), increased hepatic transaminase and cataract formation (due to the use of ultrombopag), and neutralizing antibody formation (due to the use of romiplostim).	Suitable for patients with steroid-resistant ES or IVIG, splenectomy, and rituximab

Conclusion

Although based on studies about ES, the development of antibodies against blood cells can play a role in ES progression; the mechanism of the immune-reaction and the pathophysiology of SARS-CoV-2 against ES is still not well understood. On one hand, several studies proved SARS-CoV-2 infection results from a defect in a suitable immune response that may exacerbate immune-inflammatory reactions as well as cytokine storm and autoimmunity. On the other hand, the viral infection may result in immunological tolerance failure through a wide range of mechanisms like molecular mimicry, bystander activation, epitope spreading, and autoreactive effector cells immortalization which create a connection between auto-inflammatory and

autoimmune reactions that were previously observed in different types of viral infections. SARS-CoV-2 infection can affect Evans syndrome in two ways, increasing inflammation and imbalances in the immune system which also affect the number of blood cells as well as laboratory parameters, meanwhile, it could be considered as a possible mechanism for the development of ES. The optimum treatment consists of achieving a long-term complete response. Generally, treatment lines in ES patients are dependent on their efficiency, prolonged complete response and safety. It is remarkable that, immunosuppressive drugs such as corticosteroids should not be prescribed for ES patients with SARS-CoV-2 infection but as patients with the COVID-19 infection manifest lung involvement, immunosuppression administration prescription could help to suppress inflammatory response and manage patients.

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Conflict of interest

All authors declare no conflict of interest.

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