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COVID-19 and Mycoplasma Pneumoniae Co-infection Triggering Evans Syndrome; A Case Report

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Abstract

Background: Evan's syndrome (ES) is a rare autoimmune disease characterized by the coexistence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). The syndrome presents significant clinical challenges due to its diverse and often severe manifestations. The pathology is not well understood, but reports suggest that it may be triggered by infections, autoimmune diseases, hematological malignancies, and primary immunodeficiencies.

Case presentation: We present a case of ES in an 8-year-old child following Coronavirus Disease 2019 (COVID-19) and *Mycoplasma pneumoniae* infection. Initially, he presented with respiratory distress and symptomatic anemia. Several days later, he developed thrombocytopenia along with symptoms of myocarditis. Therefore, he was diagnosed with ES triggered by infection. Since the initial episode, he has experienced recurrent episodes of AIHA and ITP necessitating oral courses of corticosteroids.

Conclusion: Clinical reports and cohort studies of ES in the pediatric population are crucial to further understand this rare disease and guide management options.

Key Words: Autoimmune cytopenia, Evan syndrome, Hemolytic anemia, hematology, Immune thrombocytopenia.

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1- INTRODUCTION

Evan's Syndrome (ES) is a rare autoimmune disease characterized by the coexistence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) with a positive direct anti-human globulin test (1). The dual presentation, either simultaneous or sequential AIHA and ITP, results in diverse and often severe manifestations.

Patients with ES typically present with symptoms of anemia and thrombocytopenia such as fatigue, pallor, ecchymoses, epistaxis, gingivorrhagia, and petechiae (2,3,4). ES affects individuals of all ages and ethnic groups with no specific sex preference noted (5,6). The incidence of ES is considerably rare compared to isolated AIHA or ITP, with an estimated rate of 1.8 per million person-years (7). The incidence of AIHA is estimated at 1 per 80,000, while ITP occurs in approximately 5.5 per 100,000 individuals (4).

ES may occur primarily without a known cause or secondary due to hematological malignancies, autoimmune diseases, and primary immunodeficiencies (1,7). This suggests immune dysregulation as a key mechanism of the syndrome, although the precise pathophysiology remains poorly understood (8). There are a few published reports linking ES with Cytomegalovirus, Hepatitis C, Varicella Zoster, and Epstein-Barr viruses (7). Recently, it has been increasingly reported as a potential complication of Coronavirus Disease 2019 (COVID-19) (9,10,11). The virus is believed to act as a trigger provoking an exaggerated immune response, resulting in hemolysis and thrombocytopenia (12).

2- CASE PRESENTATION

2-1. Initial Presentation

We report on an 8-year-old who developed Evans Syndrome after a co-infection of COVID-19 and *Mycoplasma pneumoniae*. He initially presented with a short history of fever, respiratory distress, and lethargy. He had underlying well-controlled bronchial asthma without any interval symptoms. There was no history of anemia and no family history suggestive of hemoglobinopathies or hemolytic diseases. His developmental milestones were appropriate for his age, and his vaccinations were in accordance with to Malaysia's national immunization program. He had no prior history of blood transfusion.

Upon admission, examination revealed pallor, tachycardia, a displaced apex beat and a pansystolic murmur grade 3.6 heard all over the precordium. There were no facial dysmorphisms, hepatosplenomegaly, lymphadenopathy, or jaundice on examination. His height and weight were in the 50th percentile on the growth chart. He had mild respiratory distress with the use of accessory muscles, and lung auscultation revealed crepitations bilaterally without any wheezing.

2-2. Investigations and Diagnosis

Initial laboratory findings revealed severe anemia with a markedly raised red cell distribution width, leukopenia, and borderline thrombocytopenia. There was a presence of nucleated red blood cells and an elevated reticulocyte percentage (11.78%, normal<5%). A peripheral blood film showed severe normocytic anemia with marked polychromasia and the presence of spherocytes, microspherocytes, occasional nucleated red blood cells and schistocytes as shown in Figure 1. There was also true thrombocytopenia with no evidence of platelet clumps, and an average platelet count of 15 per high power field. An impression of autoimmune hemolytic anemia with true thrombocytopenia was given.

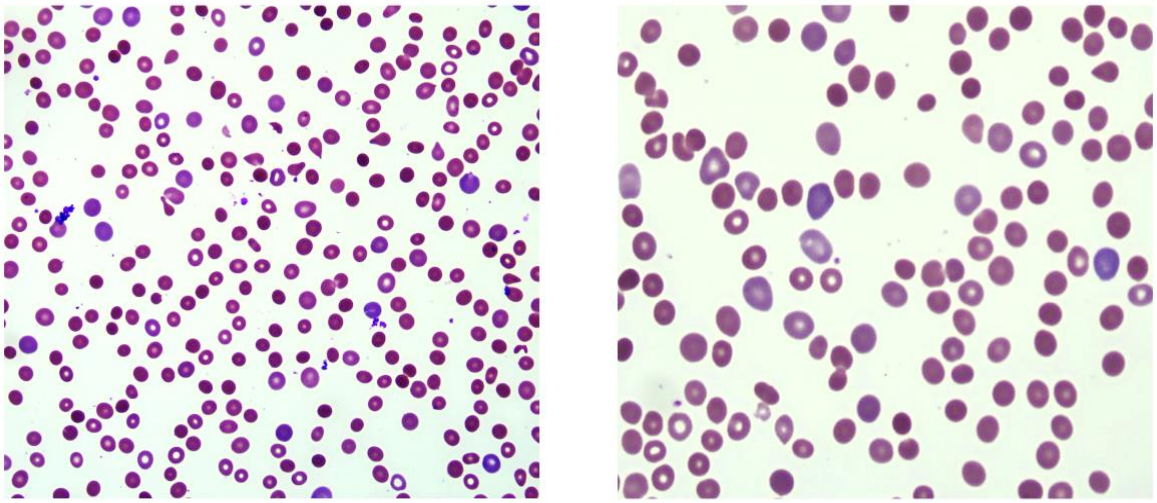

Figure-1: Patient's peripheral blood film.

Liver function tests indicated elevated total bilirubin and increased alkaline phosphatase and aspartate transaminase. Urine analysis showed no hemoglobinuria. Direct coombs test was positive. Haptoglobin levels were not available in our center during this time. His lactate dehydrogenase level was 892u/L (143-290 U/L). Iron studies were normal, besides an elevated ferritin level. These results are summarized in Tables 1 and 2. His complement levels were normal, and autoimmune markers including rheumatoid factor, antinuclear antibodies (ANA), and anti-double-stranded DNA antibodies were negative. These results are displayed in Table 3.

Table-1. Hematological related investigation.

Component	Unit	Results/Day of Admission					
		Day 1	Day 3	Day 4	Day 5	Day 8	Day 9
Hemoglobin	g/dL	3.8	8.1	12.4	12.9	10.2	13.2
Hematocrit	%	11.7	26.7	38.2	40.5	31.7	40.1
MCV	fL	106.4	100.4	97.2	97.1	96.1	92.4
MCH	pg	34.5	30.5	31.6	30.9	30.9	30.2
RDW	%	23.3	28.6	26.3	25.8	20.0	20.0
White cell count	K/uL	3.8	6.6	6.8	7.2	4.8	5.5
Platelet count	K/uL	149	161	142	135	222	226
nRBC	%	6.9	6.2	4.0	1.3	0.2	0.0
Retics	%		11.78	13.15			
Direct coombs test	+/-	++++					

Table-2. Inflammatory markers and liver function test.

Component	Unit	Results/Day of admission		
		Day 1	Day 4	Day 9
T. Bilirubin	umol/L	55.37	49.64	18.75
ALP	U/L	153	125	102
AST	U/L	78	72	32
ALT	U/L	18	15	27
CRP	mg/L	13.07	11.08	

Table-3. Autoimmune and infectious disease workup.

Component	unit	Results/ Day of admission		
		Day 1	Day 2	Day 3
Ab screen 1 AHG	+/-	+++		+++
Ab screen 2 AHG	+/-	+++		+++
Ab screen 3 AHG	+/-	+++		+++
C3	g/L			0.94
C4	g/L			0.14
IgG	+/-		++++	
C3d	+/-		+++	
ParvoVirus IgM	+/-	-		
ParvoVirus IgG	+/-	-		
HIV Ab	R/NR	Non Reactive		
EBV genome	R/NR	Not Detected		
HBs Ag	R/NR	Non Reactive		
HCV Ab	R/NR	Non Reactive		

A chest radiograph performed on the day of admission showed heterogeneous opacities bilaterally. His COVID-19 rapid antigen test was positive upon admission. An electrocardiogram showed sinus bradycardia with a prolonged QTc interval. An echocardiogram showed globular hypokinesia with an ejection fraction of 38% and poor left ventricular function. A full blood count during this episode also showed thrombocytopenia, in addition to persistent anemia. His mycoplasma serology was positive with an antibody titre of 1 in 640. All other viral and bacterial serology tests were negative. He was referred to the pediatric cardiology team and diagnosed with myocarditis secondary to COVID-19 and *Mycoplasma pneumoniae* co-infection.

Subsequently, due to the concomitant AIHA and thrombocytopenia with a positive Direct Antiglobulin Test (DAT), showing both C3D and IgG positive, the patient was diagnosed with mixed autoimmune hemolytic anemia known as Evan Syndrome. The diagnosis of ES was established based on the simultaneous presence of AIHA and ITP.

AIHA was confirmed by severe anemia, reticulocytosis, elevated lactate dehydrogenase, hyperbilirubinemia, and a positive direct antiglobulin (Coombs) test for both IgG and C3d. ITP was identified by persistent thrombocytopenia in the absence of platelet clumping or other secondary causes. Combining the hematological, immunological, infectious, and imaging investigations, the diagnosis was concluded to be ES triggered by COVID-19 and *Mycoplasma pneumoniae* co-infection.

2-3. Clinical Treatment and Hospital Stay

He required nasal prong oxygen supplementation for one day and was diagnosed with COVID-19 pneumonia with concomitant anemia. On day 4 of admission, he complained of chest pain associated with bradycardia, down to 60 beats per minute. He remained hemodynamically stable during these episodes. There was no increase in respiratory distress during this episode, and he maintained normal oxygen saturation levels on room air.

Consequently, he completed an intravenous infusion of immunoglobulin with a dose of 2g per kilogram for myocarditis and was started on oral corticosteroid therapy, with an initial dose of 2 mg/kg/day. The corticosteroid therapy was gradually tapered off prior to discharge. He was discharged in good

health ten days later with normal full blood count parameters.

2-4. Clinical Progress after Discharge

However, since this initial presentation, he has had three episodes of relapses presenting with symptoms of acute anemia and thrombocytopenia requiring corticosteroid therapy. He is currently still on a maintenance dose of corticosteroid therapy and is under regular surveillance by the pediatric hematology oncology service. Surveillance during follow-up revealed normal thyroid function tests, no evidence of autoimmune rashes and normal immunoglobulin levels.

3- DISCUSSION

We report a case of pediatric ES triggered by COVID-19 and *Mycoplasma pneumoniae* infection, which is extremely rare (13). The exact pathophysiology of ES is unknown, but it is postulated that it occurs due to immune dysregulation and the production of autoantibodies against red blood cells and platelets (14). It has a chronic and relapsing-remitting course, requiring immunosuppression therapy, as seen in this patient.

Although the pathophysiology of ES remains unclear, recent evidence suggests that infections, including viral and bacterial pathogens, may play a role in triggering immune dysregulation. There are several case reports showing the development of ES in patients with COVID-19 infection in adults (9,10,11,12, 15). While the association between COVID-19 and ES is emerging, to date, we were unable to find any case reports of pediatric ES triggered by COVID-19 infection. Due to the rarity of the presentation, it is unknown whether the *Mycoplasma pneumoniae* co-infection aggravated the immune response and triggered the manifestation of ES in this patient.

3-1. Clinical Manifestations

The progression of ES can vary, and patients may present with different hematological manifestations at different stages of the disease. This patient presented with AIHA first then subsequently developed immune thrombocytopenia. In a French national observational cohort by Aladjidi et. al. in 2015, 25% of their patients presented with AIHA initially (2). Despite this, subsequent small case series by Rivalta et. al. and Pincez et. al. showed a variable presentation of the cytopenia, namely simultaneous AIHA and ITP and ITP preceding AIHA (16, 17).

3-2. Literature Review

Table 4 exhibits a comparison between five reported cases of ES in adults with COVID-19 infection. The hemoglobin levels in the five patients ranged from 2.4 g/dL to 8.9 g/dL, indicating varying severity of anemia. Three cases received packed red blood cell transfusions, (9,11,12,15). Corticosteroids were the main treatment in all cases, with IVIG used in three patients (10,11, 12) and plasmapheresis performed in only one patient (10).

3-3. Management

Given the limited reports of pediatric ES associated with COVID-19, understanding its clinical course and presentation is crucial. The variability in hematological manifestations further complicates early diagnosis and management, which is critical, as ES carries significant risks and requires timely and appropriate management. Patients with ES have a significantly higher risk of severe bleeding tendencies and may require various immunosuppressive therapies which are associated with side effects and pose a considerable burden on patients and their families (2).

The primary treatment for ES involves immunosuppressive therapy, with corticosteroids and intravenous

immunoglobulin as first-line options, supplemented by supportive care (1, 2, 3). For refractory cases, advanced interventions like rituximab or splenectomy may be necessary (5,18). With such a high risk of complications, treatment strategies must be carefully considered to balance disease control with the potential adverse effects of immunosuppressive therapies. Additionally, the presence of co-infections such as *Mycoplasma pneumoniae* in this case raises additional concerns regarding immune activation and disease severity.

Table-4. Comparison of ES cases in adults with COVID-19.

Author (reference)	Age (years)/ Sex	Hb (g/dL)	Bone marrow erythroid series	Pharmacotherapy	Co-morbids
Demir et. al. [10]	22/M	3.9	Dysplasia (20% of erythroblasts)	Plasmapheresis, IVIG, corticosteroids, PRBC transfusion	None
Li et. al. (11)	39/M	6.4	Not reported	IVIG (no corticosteroids due to COVID-19)	None
Mohammadien et. al. (9)	54/M	5.4	Not reported	Favipiravir, dexamethasone, prednisone, PRBC transfusion	None
Namala et. al. (12)	30/F	2.4	Hyperplasia	IVIG, corticosteroids, thrombopoietin analogue, PRBC transfusion	Diabetes Mellitus
Zarza et. al. (15)	30/F	8.9	Hyperplasia with dysplastic changes	Methylprednisolone, prednisone, hydroxychloroquine, azithromycin, ceftriaxone, enoxaparin	Antiphospholipid syndrome, suspected SLE

4- CONCLUSION

As the understanding of ES continues to evolve, it is essential for clinicians to remain vigilant for potential triggers, especially in the context of emerging infectious diseases like COVID-19. Further research is required to understand the underlying pathophysiology, refine treatment strategies, and improve outcomes in these patients.

5- FUNDING

This study did not receive any funding.

6- CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

7- DATA AVAILABILITY STATEMENT

The database that led to this article is available upon request from the corresponding author.

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