

## Review Article

# The spectrum of Evans syndrome: a literature review

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### ABSTRACT

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 in the absence of any underlying cause. Evans syndrome is a rare disorder although the exact frequency is unknown. No sex predilection is known and Evans syndrome has been described in all ethnic groups and at all ages. Classification of ES includes primary, with this being an exclusion diagnosis with no underlying condition, and secondary in the presence of an underlying disease. Clinical features are associated with anemia and thrombocytopenia including pallor, weakness, fatigue, jaundice, petechiae, ecchymosis, gingivorrhagia and epistaxis. First, a detailed history must be taken from the patient to determine the risk factors for developing ES then a family history of immune disorders along with a thorough physical examination. The management of Evans syndrome remains a challenge. Steroids with and without IVIG are recommended as front-line therapy. Red blood cell/platelet transfusion is indicated only in severe symptomatic patients due to the risk of exacerbations. Splenectomy may also be considered a second-line treatment.

**Keywords:** Anemia, Autoimmune, Evans, Reticulocytes, Steroid

### 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 in the absence of any underlying cause.<sup>1,2</sup> ES is a rare condition because it is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset.<sup>3</sup> Few and mainly pediatric data on ES are available in the literature.<sup>4,5</sup> Therefore, the characteristics and outcome of adult's ES are poorly known. Only one study has estimated incidence and prevalence. In Denmark in 2016 the annual incidence was 1.8 per 1,000,000 person years, and the prevalence was 21.3 per 1,000,000 living persons.<sup>6</sup> Evans syndrome seems to be a disorder of immune regulation but the exact pathophysiology is unknown. Autoantibodies targeted at different antigenic determinants on red cells and platelets are assumed to

cause isolated episodes of hemolytic anemia and thrombocytopenia, respectively. Those causing red blood cell (RBC) destruction are directed against a base protein portion of the Rh blood group, while those that destroy platelets are frequently directed against platelet GPIIb/IIIa.<sup>7</sup> Although many cases are idiopathic in origin (Primary Evans syndrome), ES has been associated with a number of other conditions (Secondary Evans syndrome) in approximately one-half of the cases, including infections (eg, HCV, HIV), systemic lupus erythematosus, lymphoproliferative disorders, common variable immunodeficiency, and autoimmune lymphoproliferative syndrome, and may be seen following allogeneic hematopoietic cell transplantation.<sup>8-10</sup> Secondary Evans syndrome is associated with higher mortality rate than primary Evans syndrome, with a 5-year survival of 38%. Among patients with Evans syndrome, the prevailing causes of death is bleeding, infections, and hematological cancer.<sup>6</sup> While Evans

syndrome is not thought to be inherited in most cases and rarely occurs in more than one person in a family, there are a few cases in the medical literature describing "familial Evans syndrome." The majority of familial cases involve siblings that are found to have Evans syndrome. Some of these cases were additionally associated with other symptoms, such as heart defects as well as other disorders that are known to be inherited, such as hereditary spastic paraplegia.<sup>11-13</sup> Often, patients with ES have discordance between their clinical symptoms and the severity of their laboratory abnormalities. AIHA, ITP, and neutropenia can develop sequentially or can all be present at the time of diagnosis.<sup>14,15</sup> The typical course of ES is characterized by a heterogeneous chronic disease with clinical variability at onset, spontaneous remissions and exacerbations.<sup>1,16,17</sup> Patients who are experiencing an exacerbation often present to the emergency department (ED) for evaluation and management. To minimize morbidity and the risk of death, it is important for the emergency physician to identify patients with ES and institute urgent therapy.

## REVIEW OF LITERATURE

### Epidemiology

Evans syndrome is a rare disorder although the exact frequency is unknown. The largest reported series of pediatric ES included 164 cases of ITP and 15 of AIHA; only 7 (4.1%) children were diagnosed with the syndrome.<sup>17</sup> A review of adult patients with immunocytopenias from 1950 to 1958 included 399 cases of AIHA and 367 cases of thrombocytopenia; only six of these 766 patients had Evans syndrome.<sup>18</sup> In the adult series of Michel et al., which included 68 ES patients, no primitive immunodeficiency (PID) was reported and eight cases were associated with hematologic malignant conditions while in another study of pediatric series, 3/156 PIDs were identified and no cases of cancer occurred despite significant follow-up and an adequate survey.<sup>8,19</sup> No sex predilection is known and Evans syndrome has been described in all ethnic groups and at all ages. In four reported series of children with Evans syndrome, the median age at presentation ranged from 5.5 to 7.7 years (overall age range 0.2 to 26.6 years).<sup>5,7,20</sup>

### Pathophysiology

Several authors have proposed different disease pathways but all indicate the presence of immune dysregulation with antibodies against erythrocytes, platelets and/or granulocytes.<sup>21</sup> Following is the theoretical description of immunologic variations observed in this syndrome.

#### Decreased CD4/CD8 ratio

Abnormalities of immune regulation have been demonstrated in ES patients with a decreased level of helper T and increased cytotoxic T cells with a low

CD4:CD8 ratio compared with healthy controls. Excessive production of T cytotoxic lymphocytes or a diminished activity of T helper cells could avoid the production of immunoglobulins (Ig) M and G, as observed in common variable immunodeficiency (CVID) patients.<sup>21</sup> In another study increased constitutive production of interleukin-10 and interferon- $\gamma$  was found and it was postulated that it causes activation of auto-reactive, antibody-producing B cells.<sup>22</sup> These mechanisms could plausibly cause a disruption of T-cell homeostasis with an elevated concentration of interferon  $\gamma$  and subsequent activation of B-cells against erythrocytes and platelets.

#### Deficiency of CTLA-4 (CD152) and LRBA

CTLA-4 or CD152 is an inhibitory transmembrane receptor at the surface of regulatory T-cells that bind with a high affinity to CD80/CD86 molecules in antigen-presenting cells with subsequent endocytosis and downregulation contributing to immune homeostasis. This deficiency has been related to ES.<sup>23</sup> On the other hand, LRBA is an intracellular protein that binds to CTLA-4 cytoplasmic fraction in regulatory T-cells following its endocytosis, avoiding its degradation. Recently, additional gain of function mutation in STAT-3 (c.2147C>T; c.2144C>T) and KRAS (c.37G > T) have been found along with LRBA (c.2450 + 1C > T) and CTLA-4 (c.151C> T; c.109 + 1092\_568-512del; c.110-2A > G) proteins in the patients of ES.<sup>24</sup>

#### Deficiency of TPP2

A recent clinical trial revealed that tripeptidyl peptidase 2 (TPP2) is a molecule with an important role in aging, immunosenescence, autoimmunity and tumorigenesis. Serological analysis shows that the deficit of TPP2 is related to the presence of anti-nucleolar, anti-cytoplasmic, anti-nuclear antibodies and an increased level of age-associated B cells (ABCs), CD11, with a higher expression of major complex histocompatibility I molecules. This may indicate the presence of antigens on their surface, explaining the association between ABCs and autoimmune diseases like ES.<sup>25</sup>

All these currently proposed mechanisms are listed in Table 1.

### Classification

Classification of ES includes primary, with this being an exclusion diagnosis with no underlying condition, and secondary in the presence of an underlying disease.

#### Secondary ES

##### Autoimmune lymphoproliferative syndrome (ALPS)

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder characterized by a Fas gene mutation with an

alteration in T-cell apoptotic pathways causing lymphoproliferation manifested as hepatomegaly, splenomegaly, lymphadenopathies, an increased risk of Hodgkin lymphoma and immune cytopenia, mainly AIHA and ITP, with the presence of antibodies against erythrocytes and platelets. Some authors suggest ruling out this diagnosis in all pediatric patients with AIHA and ES.<sup>26</sup> Others consider ALPS as a cause of secondary ES, as reported in a center with a higher frequency of

concomitant ALPS and ES in 47%-50% of patients, confirmed by the presence of elevated double-negative T-cells.<sup>7,27</sup> The majority of patients with ALPS have mutations in the FAS gene, but mutations have also been found in other components of the pathway including Fas ligand, caspase 8 and caspase 10.<sup>28,29</sup> By contrast, patients with Evans syndrome, by definition do not have these mutations.

**Table 1: Principal mechanisms proposed to explain the pathogenesis of Evans syndrome.**

Studies	Design	Study population	Mechanism
Karakantza et al,	Retrospective cohort	01	Increased levels of Th1 cytokines, especially INF explains the presence of autoreactive B-cells against platelets and erythrocytes, confirmed by the lower levels of IFN after splenectomy.
Besnard et al,	Clinical trial	18	CTLA-4, LRBA, KRAS, STAT3 gain-of-function mutations are associated with ES secondary to a loss of T-cell homeostasis.
Stepensky et al,	Case report	02	TPP2 is an essential molecule for cell survival under stress; deficiency is associated with higher levels of autoantibodies, ABCs, perforins and MHC I, with a consequent immunosenescence; there is an increased risk for viral infections and development of autoimmunity.

*Systemic lupus erythematosus (SLE)*

Several studies have demonstrated the relationship between SLE and ES.<sup>8,30</sup> The prevalence of secondary ES in SLE has been reported in 1.7-2.7% of cases.<sup>31</sup> Hemorrhagic manifestations are frequently observed in this group, including petechiae, ecchymosis, epistaxis, gingivorraghia, gastrointestinal bleeding and hematuria.<sup>16,31</sup>

*Common variable Immunodeficiency Syndrome (CVID)*

Common variable immunodeficiency (CVID) comprises a large heterogeneous group of patients with primary antibody deficiency. The affected patients are characterized by increased susceptibility to infections and low levels of serum immunoglobulin. The concomitance of immunodeficiency and autoimmunity appears to be paradoxical and creates difficulties in the management of autoimmune complications affecting these patients.<sup>32</sup> CVID has also been considered as a cause of secondary ES.<sup>33</sup> A recent study documented the increased expression of Fas in patients with ES and CVID.<sup>34</sup>

*Chronic lymphocytic leukemia (CLL)*

CLL is a worldwide common cause of hematologic cancer in the elderly.

It is frequently associated with autoimmune cytopenias.<sup>35</sup> The frequency of ES in CLL is 2.9%.<sup>36</sup>

*Autoimmune hepatitis*

The relationship between ES and autoimmune hepatitis has been reported by few centers, with main clinical features including pallor, fatigue and splenomegaly.<sup>36</sup> The breakdown of all underlying causes of secondary ES is given in Table 2.

*Clinical features*

Patients may present with AIHA or ITP either separately or concomitantly. Neutropenia occurs in up to 55% of patients at presentation.<sup>1,5,17,20</sup> The development of the second cytopenia may occur months to years after the first immune cytopenia and may delay diagnosis.<sup>20</sup> Clinical features are associated with anemia and thrombocytopenia including pallor, weakness, fatigue, jaundice, petechiae (Figure 1), ecchymosis, gingivorraghia and epistaxis.<sup>16,24</sup> Due to the prolonged immunosuppressive therapy and/or the associated underlying immune deficit, there is a risk of 66.6% of patients developing respiratory tract infections.<sup>24</sup> Examination may reveal lymphadenopathy, hepatomegaly and/or splenomegaly. The lymphadenopathy and organomegaly may be chronic or intermittent and in some cases may only be apparent during episodes of acute exacerbation.<sup>5,7,17</sup>

*Differential diagnosis*

Evans syndrome is a diagnosis of exclusion and by definition other confounding disorders should not be

present.<sup>1</sup> Therefore, before diagnosing Evans syndrome other causes of acquired immune cytopenia should be excluded, as all require different management.<sup>7</sup> The differential diagnoses for ES include immune

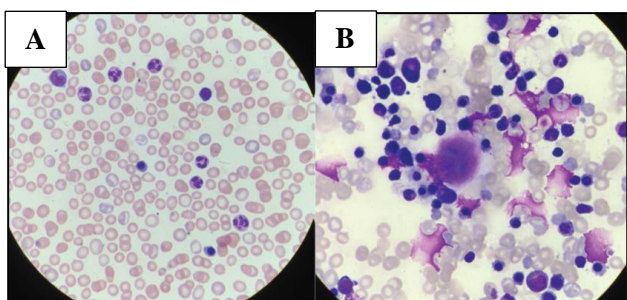
thrombocytopenic purpura, chronic cold agglutinin disease, hemolytic uremic syndrome, kasabach merritt syndrome, paroxysmal nocturnal hemoglobinuria, drug-induced hemolytic anemia and/or thrombocytopenia.<sup>37</sup>

**Table 2: Secondary cases of Evans syndrome, n=34.**

Secondary cases	n	
Autoimmune diseases	Systemic lupus erythematosus	7
	Incomplete lupus	3
	Primary antiphospholipid syndrome	2
	Sjögren syndrome	2
Immunodeficiencies	Common variable Immunodeficiency	4
	IgA deficiency	2
Lymphomas	B-cell non-Hodgkin malignant lymphoma	2
	Chronic lymphocytic leukemia	3
	T-cell non-Hodgkin lymphoma	1
Miscellaneous	Chronic myelomonocytic leukemia	1
	Unclassified lymphoproliferative disorder	3
	Monoclonal gammopathy of unknown significance	1
	Hepatitis C	1
	Congenital asplenia	1
	Idiopathic CD4 lymphocytopenia	1

**Diagnosis**

First, a detailed history must be taken from the patient to determine the risk factors for developing ES, such as infections, malignancies, autoimmune diseases, recent vaccinations, drugs or a family history of immune disorders along with a thorough physical examination checking for signs of anemia or thrombocytopenia.<sup>38</sup>



**Figure 2: (A) Peripheral blood smear reveals anemia and thrombocytopenia; increased reticulocyte count and occasional normoblasts are seen, (B) Bone marrow smears reveal erythroid hyperplasia.**

Laboratory investigations include a complete blood count with direct examination of peripheral blood; anemia, thrombocytopenia, reticulocytosis, poikilocytosis, and of bone marrow smear; erythroid hyperplasia.<sup>5,9</sup> (Figure 2) The direct antiglobulin test (DAT) is almost invariably positive (although often weakly so), even in the absence

of haemolytic anaemia, and may be positive for IgG and/or complement (C3).<sup>5,17,20</sup> The indirect antiglobulin test may also be positive.<sup>20</sup>

Assays for antiplatelet and antigranulocyte antibodies have shown varied results. Fagiolo (1976), in a report of 32 adult patients with AIHA, showed antiplatelet antibodies (PA-IgG) in 91% (demonstrated by thromboagglutination and indirect anti-globulin consumption tests) and leukocyte antibodies in 81% (demonstrated by a cytotoxicity test). Other antibodies must be considered to identify main autoimmune diseases associated with ES.

**Management**

The management of Evans syndrome remains a challenge. The syndrome is characterized by periods of remission and exacerbation and response to treatment varies even within the same individual. Most patients require treatment although occasional spontaneous remissions have been recorded: one patient of 42 patients with Evans syndrome in the national survey.<sup>20</sup> There are no clinical trials available for ES treatment and indications for starting therapy have not been established by evidence-based studies. It is reasonable to treat patients with clinically significant decreased platelet and hemoglobin levels; nevertheless, as observed in ITP, the decision to start therapy in non-symptomatic patients varies in each case depending on physician experience.<sup>3</sup> There is no therapeutic regimen established. Steroids with

and without IVIG are recommended as front-line therapy.<sup>3</sup> Red blood cell/platelet transfusion is indicated only in severe symptomatic patients due to the risk of exacerbations.<sup>3</sup>

#### First line treatments

**Steroids:** Prednisolone or prednisone at 1-2mg/kg/day must be administered in all cases, and in patients with severe clinical manifestations, an initial dose of 4-6 mg/kg/day within the first 72 hours is recommended.<sup>3</sup> The initial response rate documented for patients who receive steroids at 1-2 mg/kg/day is about 82%-83%.<sup>8</sup> A regimen including a prednisolone megadose of 30 mg/kg/day for 3 days, then 20 mg/kg/day for 4 days, followed by progressive tapering to 10, 5, 2, 1 mg/kg/week has been administered and most patients have shown complete response.<sup>3,17</sup>

#### Intravenous immunoglobulins

In some centers, it is recommended as a first-line treatment together with steroids, and in others as a complementary drug in severe thrombocytopenic patients.

**Table 3: Options for second and third-line therapy of Evans syndrome.**

Immunosuppressive agents	Ciclosporin Mycophenolate mofetil
Chemotherapy	Vincristine Cyclophosphamide
Therapeutic antibodies	Rituximab Alemtuzumab
Danazol	
Splenectomy	
Miscellaneous	Azathioprine Tacrolimus 6-Thioguanine Antilymphocyte globulin Plasmapheresis

#### Second and third line treatments

The range of options for second and third line therapy is shown in Table 3. These include immunosuppressive agents [cyclosporin, mycophenolate mofetil (MMF) and danazol], the monoclonal antibody rituximab and chemotherapy (vincristine). Splenectomy may also be considered a second-line treatment. Most of the data are anecdotal and inconclusive with interpretation difficult because of the concomitant use of corticosteroids and other modalities.<sup>20</sup>

## DISCUSSION

Author have reviewed the classification, clinical features, differentials, diagnostic features and management of

Evans syndrome with its possible pathophysiology. ES is more than a coincidental combination of immune cytopenias but rather a chronic state of profound dysregulation of the immune system that may be associated with or show other autoimmune or lymphoproliferative disorders as well as primary immunodeficiencies. It is very important to differentiate between primary and secondary ES because it may influence the management of the disease. More studies and clinical trials should be done to get more knowledge about the patho-physiology and course of the disease so that evidence based management can be possible.

Success rate of medical thoracoscopy were found comparable to other studies.<sup>7-10</sup>

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## REFERENCES

1. Evans RS, Takahashi K, DUANE RT, Payne R, Liu CK. Primary thrombocytopenic purpura and acquired hemolytic anemia: evidence for a common etiology. *AMA Arch Int Med.* 1951 Jan 1;87(1):48-65.
2. Evans RS, Duane RT. Acquired hemolytic anemia: I. The relation of erythrocyte antibody production to activity of the disease. II. Significance of thrombocytopenia and leukopenia. *Blood.* 1949 Nov;4(11):1196-213.
3. Norton A, Roberts I. Management of Evans syndrome. *Br J Haematol.* 2006 Jan;132(2):125-37.
4. Soo-chin NG. Evans syndrome: a report on 12 patients. *Clini Lab Haematol.* 1992 Sep;14(3):189-93.
5. Savaşan S, Warriier I, Ravindranath Y. The spectrum of Evans' syndrome. *Arch Dis Child.* 1997 Sep 1;77(3):245-8.
6. Hansen DL, Möller S, Andersen K, Gaist D, Frederiksen H. Evans syndrome in adults-incidence, prevalence, and survival in a nationwide cohort. *Am J Hematol.* 2019 Oct;94(10):1081-90.
7. Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). *Blood.* 2005 Mar 15;105(6):2443-8.
8. Michel M, Chanet V, Dechartres A, Morin AS, Piette JC, Cirasino L, et al. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. *Blood, J Am Soc Hematol.* 2009 Oct 8;114(15):3167-72.
9. Wright DE, Rosovsky RP, Platt MY. Case 36-2013: A 38-Year-Old Woman with Anemia and Thrombocytopenia. *N Engl J Med.* 2013 Nov 21;369(21):2032-43.
10. Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms,

- novel differential diagnoses, and treatment. *Blood*. 2014 Oct 9;124(15):2337-44.
11. Ahmed FE, AlBakrah MS. Neonatal familial Evans syndrome associated with joint hypermobility and mitral valve regurgitation in three siblings in a Saudi Arab family. *Ann Saudi Med.* 2009 May;29(3):227-30.
  12. Ahmed FE, Qureshi IM, Wooldridge MA, Pejaver RK. Hereditary spastic paraplegia and Evans's syndrome. *Acta Paediatrica.* 1996 Jul;85(7):879-81.
  13. McLeod AG, Pai M, Carter RF, Squire J, Barr RD. Familial Evans syndrome: a report of an affected sibship. *J Pediatr Hematol/Oncol.* 1999;21(3):244-7.
  14. Sarode R. Atypical presentations of thrombotic thrombocytopenic purpura: a review. *J Clin Apher: Official J Am Soc Apher.* 2009;24(1):47-52.
  15. Zhang C, Chen XH, Zhang X. Quick development and sudden death: Evans syndrome followed by thrombotic thrombocytopenic purpura. *Am J Emerg Med.* 2014 Sep 1;32(9):1156-e3.
  16. Dhingra KK, Jain D, Mandal S, Khurana N, Singh T, Gupta N. Evans syndrome: a study of six cases with review of literature. *Hematology.* 2008 Dec 1;13(6):356-60.
  17. Pui CH, Wilimas J, Wang W. Evans syndrome in childhood. *J Pediatr.* 1980 Nov 1;97(5):754-8.
  18. Silverstein MN, Heck FJ. Acquired hemolytic anemia and associated thrombocytopenic purpura: with special reference to Evans' syndrome. *In Proceedings of the staff meetings. Mayo Clinic.* 1962 Feb;37:122-8.
  19. Aladjidi N, Fernandes H, Leblanc T, Vareliette A, Rieux-Laucat F, Bertrand Y, et al. Evans syndrome in children: long-term outcome in a prospective French national observational cohort. *Frontier Pediatr.* 2015 Sep 29;3:79.
  20. Mathew P, Chen G, Wang W. Evans syndrome: results of a national survey. *J Pediatr Hematol/Oncol.* 1997;19(5):433-7.
  21. Wang W, Herrod H, Pui CH, Presbury G, Wilimas J. Immunoregulatory abnormalities in Evans syndrome. *Am J Hematol.* 1983 Dec;15(4):381-90.
  22. Karakantza M, Mouzaki A, Theodoropoulou M, Bussel JB, Maniatis A. Th1 and Th2 cytokines in a patient with Evans' syndrome and profound lymphopenia. *Br J Haematol.* 2000 Sep;110(4):968-70.
  23. Schmidt RE, Grimbacher B, Witte T. Autoimmunity and primary immunodeficiency: two sides of the same coin?. *Nature Rev Rheumatol.* 2018 Jan;14(1):7.
  24. Besnard C, Levy E, Aladjidi N, Stolzenberg MC, Magerus-Chatinet A, Alibeu O, et al. Pediatric-onset Evans syndrome: heterogeneous presentation and high frequency of monogenic disorders including LRBA and CTLA4 mutations. *Clin Immunol.* 2018 Mar 1;188:52-7.
  25. Stepensky P, Rensing-Ehl A, Gather R, Revel-Vilk S, Fischer U, Nabhani S, et al. Early-onset Evans syndrome, immunodeficiency, and premature immunosenescence associated with tripeptidyl-peptidase II deficiency. *Blood, J Am Soc Hematol.* 2015 Jan 29;125(5):753-61.
  26. Colino CG. Avances en el conocimiento y manejo del síndrome linfoproliferativo autoinmune. *In Anales de Pediatría* 2014 Feb 1;80(2);122-e1.
  27. Seif AE, Manno CS, Sheen C, Grupp SA, Teachey DT. Identifying autoimmune lymphoproliferative syndrome in children with Evans syndrome: a multi-institutional study. *Blood, J Am Soci Hematol.* 2010 Mar 18;115(11):2142-5.
  28. Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, et al. Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. *Cell.* 1999 Jul 9;98(1):47-58.
  29. Rieux-Laucat F, Le Deist F, Hivroz CE, Roberts IA, Debatin KM, Fischer A, et al. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. *Science.* 1995 Jun 2;268(5215):1347-9.
  30. Thakur N, Chandra J, Dhingra B, Singh V. Pediatric lupus: varied haematological picture and presentation. *Indian J Hematol Blood Transfusion.* 2015 Mar 1;31(1):68-70.
  31. Lube GE, Ferriani MP, Campos LM, Terreri MT, Bonfá E, Magalhães CS, et al. Evans Syndrome at Childhood-Onset Systemic Lupus Erythematosus Diagnosis: A Large Multicenter Study. *Pediatr Blood & Cancer.* 2016 Jul;63(7):1238-43.
  32. Azizi G, Abolhassani H, Asgardoost MH, Alinia T, Yazdani R, Mohammadi J, et al. Autoimmunity in common variable immunodeficiency: epidemiology, pathophysiology and management. *Expert Rev Clin Immunol.* 2017 Feb 1;13(2):101-15.
  33. Abraham RS, Podjasek JC. Autoimmune cytopenias in common variable immunodeficiency. *Frontiers Immunol.* 2012 Jul 24;3:189.
  34. Savaşan S, Warrior I, Buck S, Kaplan J, Ravindranath Y. Increased lymphocyte Fas expression and high incidence of common variable immunodeficiency disorder in childhood Evans' syndrome. *Clin Immunol.* 2007 Dec 1;125(3):224-9.
  35. O'Reilly A, Murphy J, Rawe S, Garvey M. Chronic lymphocytic leukemia: a review of front-line treatment options, with a focus on elderly CLL patients. *Clin Lymphoma Myeloma Leukemia.* 2018 Apr 1;18(4):249-56.
  36. Carli G, Visco C, Falisi E, Perbellini O, Novella E, Giaretta I, et al. Evans syndrome secondary to chronic lymphocytic leukaemia: presentation, treatment, and outcome. *Ann Hematol.* 2016 May 1;95(6):863-70.
  37. Ohkawara H, Furukawa M, Ikeda K, Shichishima-Nakamura A, Fukatsu M, Sano T, et al. Steroid-resistant autoimmune myelofibrosis in a patient with autoimmune hepatitis and Evans syndrome complicated with increased expression of TGF-β in

the bone marrow: a case report. *Inter J Hematol.* 2017 Nov 1;106(5):718-24.

38. Schneppenheim R, Budde U, Hassenpflug W, Obser T. Severe ADAMTS-13 deficiency in childhood. *Seminars Hematol.* 2004 Jan 1;41(1):83-9.

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