A strange case of Evans syndrome

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ABSTRACT

Evans syndrome is a rare autoimmune disease presenting hemolytic anemia, thrombocytopenia and/or neutropenia. It may be associated with other autoimmune or lymphoproliferative diseases. It can have an extremely serious disease course and, in rare cases, this can even be life-threatening. First-line treatment consists of steroids and/or immunoglobulin. Further therapy with rituximab, vincristine, cyclophosphamide and other immunosuppressive drugs can be considered in unresponsive patients. We report a case of Evans syndrome in a 54-year old woman admitted to the Emergency Department (ED) for asthenia. Etiopathogenic, clinical, therapeutic and evolutive aspects are discussed. In contrast to many cases described in the literature, our patient had a satisfactory response to corticoids. We also discuss how to make a specific diagnosis, even in a suburban ED with limited resources, in order to admit patients to the appropriate hospital department and allow the correct therapy to be started as early as possible.

Introduction

First reported in 1951, Evans syndrome is an autoimmune disease characterized by recurrent relapses of autoimmune hemolytic anemia (AIHA) and primary thrombocytopenic purpura (ITP).[1,2] It is a potentially life-threatening condition that may be associated with other underlying autoimmune or lymphoproliferative disorders.[1] It was observed that 91% of patients affected by Evans syndrome presented anti-platelet antibodies while approximately 81% exhibit anti-neutrophil antibodies, as shown by cyto-toxicity test.[3,4]

Patients may present AIHA or ITP either separately or together. Moreover, neutropenia occurs in up to 55% of cases at the moment of Evans syndrome diagnosis.[5] The development of the second cytopenia can occur from several months to many years after the first, and this may delay diagnosis.[3] Laboratory investigations should include a full blood count that will confirm the presence of cytopenias. A blood film should be examined to verify the presence of AIHA (polychromasia, spherocytes) and to exclude other underlying diagnoses (malignancies, microangiopathic hemolytic anemia, congenital hemolytic and thrombocytopenic conditions).[5,6] However, Evans syndrome diagnosis remains one of exclusion.

Case Report

A 54-year old Caucasian woman arrived at our ED for an asthenia of some months without other symptoms. There was no history of black feces, meno-metrorrhagia or use of drugs. Pharmacological and infective anamneses were negative. Upon her arrival in ED, the patient showed pale mucosa and cutis, she had weak tachycardia and had neither splenomegaly nor lymph-adenomegalies involving the explorable lymph node sites.

On collecting her medical history, the patient re-

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ported hospitalization in 1999 on a medical ward for a severe thrombocytopenia (platelets 5×10^9/L) during which no other alterations in the hematic profile were observed and a diagnosis of idiopathic thrombocytopenia was made. Moreover, no pharmacological treatment was started, but there was a spontaneous re-establishment of platelet values.

After examination in our ED, she then underwent some routine checks (the last had been in 2005) and no significant changes were observed. Serum chemistry tests show that the patient's initial level of hemoglobin and her mean corpuscular volume were 54 g/L and 105.5 fL, respectively (Table 1). The anisocytosis rate was 25.0% mean corpuscular hemoglobin concentration 700 g/L. Platelet count was 25×10^9/L whereas white blood cells were normal (7.6×10^9/L). Moreover, total and direct bilirubin levels were 44.30 µmol/L and 13.34 µmol/L, respectively, and the lactate dehydrogenase level was 763 U/L. Myoglobin was 1.20 nmol/L, ferritin was 249.42 pmol/L, polymerase chain reaction and vitamin C12 levels were normal, and hepatitis markers were negative. The direct and indirect Coombs test was positive and reactive warm autoantibodies for AIHA were immunoglobulin G (IgG). While in ED, transfusion of a concentrated sac of erythrocytes and steroid therapy (prednisone 1.5 mg/kg/die) were immediately started.

Suspecting Evans syndrome, the patient was moved to the hematology ward where she was treated with a polyvalent human immunoglobulin treatment (500 mg/kg/die). Haptoglobin type 2-2 level was 690.00 mg/L, corresponding to the lower limit of normal. The serum iron and ferritin levels were 8.95 µmol/L and 247.17 pmol/L, respectively. Autoimmunity examination showed: antinuclear antibody 8.2 U/mL, C3 0.68 g/L, and C4 0.7 g/L. TORCH screening was performed and this resulted positive for IgG anti-rubella and CMV and negative for anti-Epstein Barr virus antibodies. The peripheral smear excluded the presence of schistocytes. The Coombs test showed AHIA from IgG^+ C3d warm antibodies.

Our patient also had a normal renal function index and presented a slight proteinuria that regressed once she started therapy.

A bone marrow biopsy revealed a normo-cellular marrow and a markedly increased number of megakaryocytes with no dysplastic changes. In addition, there was slight erythroid hyperplasia and myeloid/erythroid (M/E) ratio was 1.4.

Total body computed tomography scan did not show any modifications in the pleuroparenchymal nor any ilo-mediastinal lymphadenopathies but slight hepatosplenomegaly was observed.

A diagnosis of Evans syndrome was finally made on the basis of a positive Coombs test, hemolytic anemia, and thrombocytopenia with reactive bone marrow changes.

Starting with the first treatment administration, there was an increase in the blood count cytometric values and the hemolysis index normalized (Figures 1 and 2).

Our patient is now being treated with small doses of corticosteroid (prednisone 10 mg/die) and, six months after diagnosis, maintains normal blood count values and appears to be asymptomatic.

Table 1. Patient's main serum chemistry values.

Laboratory data	Numerical value (SI units)	Female normal range values
Hb	54 g/L	120-160 g/L
MCV	105.5 fL	81-99 fL
MCHC	700 g/L	330-370 g/L
PLT	25×10^9/L	$130\text{-}400\times10^9$/L
WBC	7.6×10^9/L	$4.8\text{-}10.8\times10^9$/L
Myogl	1.20 nmol/L	0.0571-3.768 nmol/L
Iron	8.95 µmol/L	7.518-24.165 µmol/L
Ferritin	249.42 pmol/L	24.717-689.829 pmol/L
ANA	8.2 U/mL	<5 U/mL
C3	0.68 g/L	0.88-2.06 g/L
C4	0.7 g/L	0.13-0.75 g/L
LDH	763 U/L	50-150 U/L

Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; PLT, platelets; WBC, white blood cells; ANA, antinuclear antibody; LDH, lactate dehydrogenase.

Discussion

In Evans syndrome, there is evidence of supporting abnormalities in both cellular and humoral immunity (Table 2).[7] The exact frequency is unknown and there is no gender preference.[8] Kakaiya[9] reported that anti-RBC and anti-platelet antibodies differ and this has been confirmed by other studies. Moreover, they do not cross-react with each other.[5] It was suggested that the involvement of a hematopoietic bipotent cell in the development of antibodies directed against red blood cells and against platelets could be responsible for the making of both the erythroid and the megakaryocytic line.[10] This can be found in normal hematopoiesis in which the existence of bipotent cellular progenitors represented by a middle developmental stage in the course of the final specific-line placement is well known.[10]

The hypothesis whereby, in Evans syndrome, the bipotent progenitor M/E is damaged does not contradict with the observations that suggest the presence of two different antibodies that do not cross-react between erythrocytes and mature platelets.[5] The clinical observation that Evans syndrome does not respond well to therapy could suggest, at least in some cases, a different mechanism or else an additional one. Zuelzer[11] suggested that patients with ES have a generalized immune dysregulation characterized by lymphadenopathy and abnormal serum immunoglobulins.

Most studies carried out so far have involved small

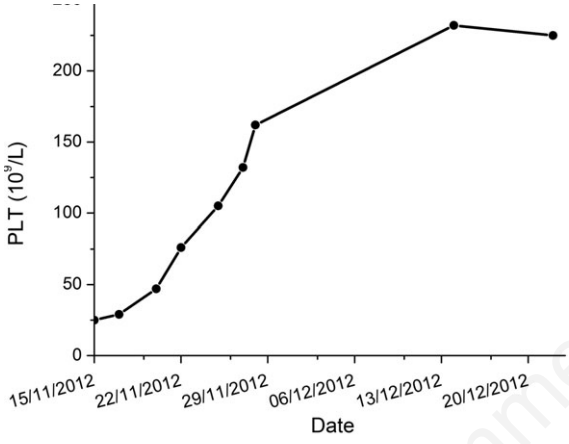

Figure 1. Response to prednisone in platelet (PLT) count.

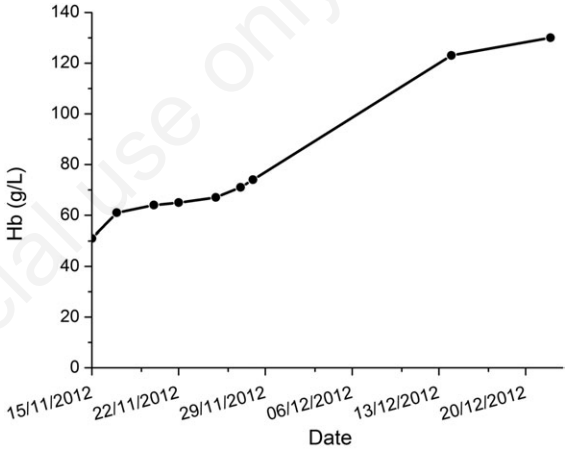

Figure 2. Response to prednisone in hemoglobin (Hb).

Table 2. Differential diagnosis of Evans syndrome compared with autoimmune lymphoproliferative syndrome.

Disease manifestation	Evans syndrome	Autoimmune lymphoproliferative syndrome
Autoimmune cytopenias	Required for diagnosis AIHA and ITP +/- neutropenia (simultaneous or sequential) Exacerbations and remissions	Not required for diagnosis Life-long risk (increases with age) Frequently seen exacerbations and remissions
Non-malignant lymphoproliferation	Not required for diagnosis Lymphadenopathy/hepatosplenomegaly in some cases	Required for diagnosis Lymphadenopathy and/or splenomegaly common 50% will have hepatomegaly
Defective lymphocyte apoptosis *in vitro*	Not seen	Required for diagnosis
≥1% $CD4^-/CD8^-$ (in peripheral blood and/or lymphoid tissue)	Not seen	Required for diagnosis
Molecular basis	Not known	76% have mutations in *FAS*, Fas-ligand, caspase 8 or caspase 10
Neoplastic risk	Not defined	Life-time incidence of 10% (especially lymphomas)
Serum immunoglobulins	Variable	Polyclonal hypergammaglobulinemia, increased IgG/IgA

AIHA, recurrent relapses of autoimmune hemolytic anemia; ITP, primary thrombocytopenic purpura; IgG/IgA, immunoglobulin G and A. *Adapted from Norton and Roberts, 2006.*[7]

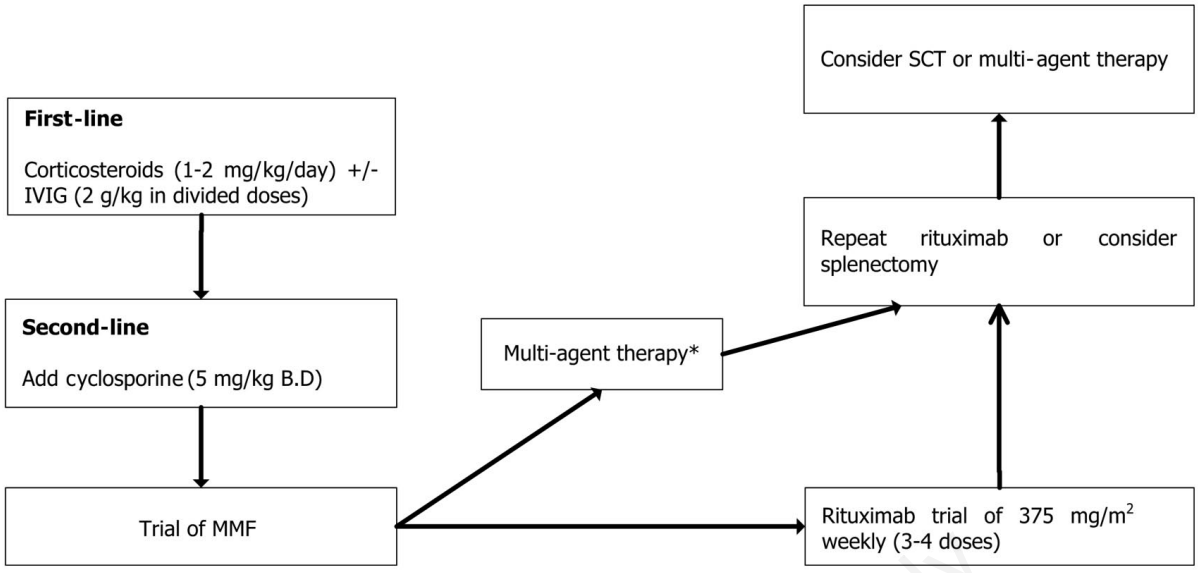

Figure 3. A sequential approach for therapeutic treatment. SCT, after stem cell transplantation; MMF, mycophenolate mofetil. *Steroids/IVIG/bincristine/danazol/cyclosporine. *Adapted from Norton and Roberts, 2006.*[7]

numbers of patients and the interpretation of their findings is made more difficult by the recent recognition that some cases of AIHA and ITP may be confused with secondary autoimmune cytopenias induced by autoimmune lymphoproliferative syndrome, also called Canale-Smith syndrome.[12] It is sometimes difficult to make a differential diagnosis between the two pathologies. The main differences reported in the international scientific literature are shown in Table 2. Patients with Evans syndrome generally require corticosteroids or intravenous immunoglobulins[13] in the acute setting. Blood and/or platelet transfusions may also be required to alleviate symptoms.

Evans syndrome typically appears with a chronic and relapsing clinical course after the first-line immunosuppressive therapies.[14] Michel[15] reported that immunosuppressive therapies could be discontinued in only 22 of 68 patients with Evans syndrome (32%), after a mean follow up of 4.8 years. AIHA patients responded well to steroids, but most of them remain steroid-dependent and many patients require a second-line treatment.[16] In consideration of this, it is very rare to maintain a remission of AIHA and ITP without immunosuppressive therapies.[17] Second-line treatment in ES has been developed over the last decade; however, despite novel treatment modalities, a standard therapy still needs to be established (Figure 3).

The B-cell targeted therapy using a mouse/human chimeric IgG1 anti-CD20 monoclonal antibody rituximab has been widely accepted as therapy for those cases refractory to more conventional treatments. The suppression of auto-reactive B cells may explain the positive response.[18] Chemotherapeutic agents, like vincristine or cyclophosphamide, have also sometimes been used with ambiguous results.[14] Micophenolate mofetil, a potent inhibitor of inosine monophosphate dehydrogenase, has been used in Evans syndrome treatment with good results.[19] Recently, Farruggia suggested the use of combination of mycophenolate mofetil and cyclosporin after conventional drugs.[20]

Conclusions

In an Emergency Department, careful surveillance of this rare disease, as well as knowledge of treatment protocols, together with prompt therapy based on a multidisciplinary approach are required to minimize complications and to improve patient outcome. The different therapeutic options discussed here must also be considered.

References

1. Friedmann AM, King KE, Shirey RS, et al. Fatal autoimmune hemolytic anemia in a child due to warm-reactive immunoglobulin M antibody. J Pediatr Hematol Oncol 1998;20:502-5.
2. Evans RS, Duane RT. Acquired hemolytic anemia; the relation of erythrocyte antibody production to activity of the disease; the significance of thrombocytopenia and leucopenia. Blood 1949;4:1196-213.
3. Guerreiro Hernández AM, Villaescusa Blanco R, Bencomo Hernández A, et al. Determinación de anticuerpos antinucleares en la anemia hemolítica autoinmune y la púrpura trombocitopénica autoinmune. Rev Cubana Hematol Inmunol Hemoter 2002;18:67-9.

4. Gianvecchio R, Percino T, Doralice M, Ellinger E. Púrpura trombocitopénica. Pediatría 2003;25;124-7.
5. Pegels JG, Helmerhorst FM, van Leeuwen EF. The Evans syndrome: characterization of the responsible autoantibodies. Br J Haematol 1982;51:445-50.
6. Savasan S, Warrier I, Ravindranath Y. The spectrum of Evans Syndrome. Arch Dis Child 1997;77:245-8.
7. Norton A, Roberts I. Management of Evans Syndrome. Br J Haematol 2006;132:125-37.
8. Pui CH, Wilimas J, Wang W. Evans syndrome in childhood. J Pediatr 1980;97:754-8.
9. Kakaiya RM, Sherman LA, Miller WV, Katz AJ, Nature of platelet antibody in Evans syndrome: a case report. Ann Clin Lab Sci 1981;11:511-5.
10. Hu M, Krause D, Greaves M, et al. Multilineage gene expression precedes commitment in the hematopoietic system. Genes Develop 1997;11:774-85.
11. Zuelzer WW, Mastrangelo R, Stulberg CS, et al. Autoimmune hemolytic anemia. Natural history and viral-immunologic interactions in childhood. Am J Med 1970; 49:80-93.
12. Teachey DT, Manno CS, Axsom KM, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 2005;105:2443-8.
13. Petz LD, Garratty G. Immune hemolytic anemias. New York: Churchill Livingstone; 2004.
14. Moyo VM, Smith D, Brodsky I, et al. High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. Blood 2002;100:704-6.
15. Michel M, Chanet V, Dechartres A, et al. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood 2009; 114:3167-72.
16. Lechner K, Jager U. How I treat autoimmune hemolytic anemia in adults. Blood 2010;116:1831-8.
17. Robak T, Robak P. Treatment options for autoimmune cytopenias. Transfus Med Hemother 2004;31:332-40.
18. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refrectory autoimmune hemolytic anemia in children. Blood 2003;101:3857-61.
19. Kotb R, Pinganaud C, Trichet C, et al. Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: a single center preliminary study. Eur J Haematol 2005;75:60-4.
20. Farruggia P, Macaluso A, Tropia S, et al. Effectiveness of cyclosporine and mycophenolate mofetil in a child with refractory evans syndrome. Pediatr Rep 2011; 3:e15.