

Evans Syndrome: A case report

Sindrome di Evans: descrizione di un caso clinico

F. Porcaro,¹ M. Valenzise,¹ G. Candela,¹ F. Chiera,¹ D. Corica,¹ E. Pitrolo,¹ S. Santucci,¹ M. Romeo,¹ S. Nigro,¹ G. Zirilli¹

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Abstract

We describe a case of a 14-years old caucasian female affected by autoimmune hemolytic anemia and thrombocytopenia successfully treated with intravenous immunoglobulin and steroids. Nevertheless, neutropenia occurred during follow-up period. Positivity of direct antiglobulin test and sieric anti-neutrophil antibodies suggested the diagnosis of Evans syndrome trilineage.

Riassunto

Descriviamo il caso di una ragazza di 14 anni affetta da anemia emolitica e trombocitopenia autoimmuni sottoposta a terapia endovenosa con immunoglobuline e steroidi con beneficio. Le indagini di laboratorio eseguite durante il follow-up mettevano in evidenza una neutropenia. La positività del test di Coombs e degli anticorpi anti-neutrofili permetteva di porre diagnosi di Sindrome di Evans trilineage.

Introduction

Evans syndrome is an uncommon condition defined by the contemporary or sequentially association of immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA), with a positive direct Coombs test. There is no preferential distribution of Evans syndrome by age, gender, or ethnic group. Its chronic course

is characterized by recurrent relapses and remissions. First-line therapy includes corticosteroids and intravenous immunoglobulin with good clinical response, although relapse is frequent. Immunosuppressive drugs and splenectomy may be considered when first-line treatment has failed. We report a case of a 14-years-old female caucasian patient affected by Evans syndrome associated to immune neutropenia.

Case Report

A 13-years old caucasian female was admitted to our department for petechiae and bruising on the skin in absence of organomegaly. A complete blood count revealed severe thrombocytopenia (platelet counts <10.000/mmc). Idiopathic thrombocytopenic purpura (ITP) was suspected and intravenous immunoglobulin was given at a dosage of 0,8 g/Kg/die with good clinical response. During the following weeks she referred to another hospital where bone marrow aspiration was performed before starting high dose steroid therapy, in order to exclude lymphoproliferative disease. Bone marrow examination showed dysmorphic megakaryocytes with normal representation of erythroid cells. In this way, an underlying lymphoproliferative disorder was excluded and patient received a high dosage of intravenous methylprednisolone (30 mg/Kg/die for three consecutive days) and then oral prednisone (2 mg/Kg/die). Clinical and laboratoristic remission were observed after therapy and follow-up program was required. Nevertheless, platelet count decreased during the tapering of the prednisone and patient was referred again to our centre. One month after complete suspension of steroid therapy, cutaneous petechial hemorrhages and mucosal bleeding occurred. Peripheral blood count was performed and low platelet count was discovered (PLT 10.000/mmc). Intravenous immunoglobulins (0.8 g/Kg/die) were administered and the patient showed good improvement after treatment, with resolution of symptoms and normalization of platelet count. Nevertheless, autoimmune hemolytic anemia (Hb 10.7 g%), leucopenia (WBC 2.400/mmc) and neu-

¹ Department of Pediatrics, University of Messina, Messina, Italy.

tropenia (N 1.000/mmc) appeared during the follow-up period. The direct Coombs test and anti-neutrophil antibodies were positive with normal evaluation of the remaining immune response. On the basis of clinical manifestations and laboratory findings that confirmed autoimmune hemolytic anemia, neutropenia and thrombocytopenia, the diagnosis of Evans syndrome trilineage was made. Pancytopenia and low hemoglobin levels (6.1 g %) were revealed during follow-up. A second bone marrow examination was performed in order to exclude malignancies. The patient was treated successfully with intravenous immunoglobulin (1 g/Kg/die) and methylprednisolone (30 mg/Kg/die for three consecutive days); then oral prednisone therapy at starting dose of 2 mg/kg/day was continued. A complete blood count obtained 2 weeks later showed an increasing hemoglobin levels (Hb 8,5 g%), a normalization of neutrophil (N 4.094/mmc) and platelet count (PLT 257.000 mmc) with persistent positivity of direct antiglobulin test.

Discussion

Evans Syndrome was first described in 1951 by Robert Evans. The diagnosis is infrequent and requires a high index of suspicion with exclusion of other disorders characterized by autoimmune hemolytic anemia and thrombocytopenia. The etiology is unknown and immune dysregulation may be involved in the pathogenesis of the disease. Constitutive production of IL-10 and INF γ may lead to activation of autoreactive, antibody-producing B cells¹, although these abnormalities of immune response are seen in other autoimmune disorders. Recent reports underline that immunization may represent a trigger for the development of disease in susceptible individuals².

The appearance of the second cytopenia may occur months to years after the first immune cytopenia and may delay diagnosis³. Neutropenia occurs in up to 55% of patients at presentation³⁻⁴.

Clinical phenotype includes symptoms of hemolysis (fever, pallor, jaundice, lethargy) and thrombocytopenia (petechiae, bruising and mucocutaneous bleeding). Physical examination may reveal lymphadenopathy, hepatomegaly and/or splenomegaly. These signs may be chronic or intermittent and in same case may occur during acute exacerbations⁵.

The diagnosis of haemolytic anaemia requires direct Coombs positivity, although this investigation may be positive even in the absence of haemolytic anaemia. The indirect Coombs test may also be positive in a small percentage of patients.

Antiplatelet and antigranulocyte antibodies research is controversial because a negative result does not exclude the diagnosis. A complete medical history, an appropriate physical examination, a complete blood count and a peripheral smear are diagnostic. However, other causes of acquired immune cytopenia should be excluded (SLE, IgA deficiency, CVID, HIV, ALPS, TTP, HUS, Kasabach-Merritt syndrome, Castelman's disease and inherited ADAMTS-13 deficiency).

Bone marrow examination is an essential investigation for the diagnosis of Evans syndrome. It is necessary to exclude infiltrative process in patients with pancytopenia, especially before starting steroid therapy.

Clinical presentation, hemoglobin levels and platelet count guide the therapeutic decisions.

First-line therapy is represented by corticosteroids and/or intravenous immunoglobulin. Some studies recommend prednisolone at a daily dose of 1-4 mg/Kg³. Good clinical and laboratoristic response may be also obtained with intravenous methylprednisolone (30 mg/kg/die for 3 days, then 20 mg/kg/die for 4 days, subsequently 10, 5, 2, 1 mg/kg/die, 1 week each)⁶.

Norton et al. propose intravenous immunoglobulin (2 g/Kg in divided doses) for patients for whom steroids are ineffective or who require unacceptably high doses to remain in remission⁷. Blood and/or platelet transfusions may also be need to ameliorate symptoms in severe cases, even though their use is not routinely recommended.

Immunosuppressive agents such as ciclosporin (5 mg/Kg twice daily on alternate days), mycophenolate mofetil, vincristine (1,5 mg/m²/week i.v. for three week), danazol (200 mg/die), may be considered after failure of first-line therapy.

Successful use of rituximab (monoclonal anti-CD20 antibody) has also been shown for Evans syndrome resistant to first-line therapy and other second-line treatments. The dose of rituximab is 375 mg/m²/dose/week for four weeks, together with steroids.

Despite the relative lack of experience of rituximab used in childhood, it may be preferable to splenectomy whose effects on blood cells count are transient and often associated with frequent exacerbations in the months immediately after the surgery³.

Each treatment of second line therapy is burdened by short and long time side effects. For these reasons, therapeutic options should be individualized, basing on patient's age, natural history and severity of the disease.

Third-line therapy provides oral administration of cyclophosphamide (1-2 mg/Kg/die for 2 – 3 months)⁸ or intravenous administration of monoclonal anti-CD52 antibodies (10 mg/die for 10 days)⁹. Autologous and allogenic transplant stem cells may be performed only in a limited number of patients affected by Evans syndrome, after failure of pharmacological treatment¹⁰.

Conclusions

On the basis of our experience we suggest that: 1) autoimmune thrombocytopenia could represent the first clinical presentation of Evans syndrome; 2) the simultaneous involvement of erythroid and myeloid lines may occur after 6 months of the diagnosis of idiopathic thrombocytopenic purpura (ITP); 3) autoimmune hemolytic anemia, thrombocytopenia and neutropenia in association with positive direct Coombs test and sieric anti-neutrophil antibodies confirm the diagnosis of Evans syndrome trilineage. Bone marrow examination before starting steroid therapy permit to exclude mali-

gnancies and confirm the original diagnostic suspect. According to international literature, immunoglobulin infusion and high dosage of methylprednisolone represent the first line therapy, with following steroid maintenance therapy. In our case report, we observed a good long-term clinical response despite the delay of diagnosis due to late-onset of second cytopenia.

ABBREVIATIONS.

- ITP idiopathic thrombocytopenic purpura
- AIHA autoimmune haemolytic anaemia
- SLE systemic lupus erythematosus
- CVID common variable immunodeficiency
- HIV human immunodeficiency virus
- ALPS autoimmune lymphoproliferative syndrome
- TTP thrombotic thrombocytopenic purpura
- HUS haemolytic uraemic syndrome
- ADAMTS-13 ADAM metalloproteinase with thrombospondin type 1 motif, 13

References

- ¹ Karakantza M, Moukaki A, Theodoropoulou M, Bussel JB, Maniatis A. Th 1 and Th2 cytokines in a patient with Evans' syndrome and profound lymphopenia. *British Journal of Haematology* 2000; 110, 968–970.
- ² Chen RT, Pless R, De Stefano F. Epidemiology of autoimmune reactions induced by vaccination. *Journal of Autoimmunity* 2001; 16, 309–318.
- ³ Mathew P, Chen G, Wang W. Evans Syndrome: results of a national survey. *Journal of Pediatric Hematology/Oncology* 1997; 19, 433–437.
- ⁴ Evans RS, Takahashi K, Duane RT. Primary thrombocytopenic purpura and acquired hemolytic anemia. *Archives of Internal Medicine* 1951; 87, 48–65.
- ⁵ 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; 105, 2443–2448.
- ⁶ Özsoylo F. Megadose methylprednisolone for Evans syndrome. *Pediatric Hematology and Oncology* 2000; 17, 727–728.
- ⁷ Norton A, Roberts I. Management of Evans syndrome. *British Journal of Haematology* 2005; 132, 125–137.
- ⁸ Gombakis N, Trahana M, Athanassiou M, Kanakoudi-Tsakalidou F. Evans syndrome: successful management with multiagent treatment including intermediate-dose intravenous cyclophosphamide. *Journal of Pediatric Hematology/Oncology* 1999; 21, 248–249.
- ⁹ Willis F, Marsh JCW, Bevan DH, Killick SB, Lucas G, Griffiths R et al. The effect of treatment with Campath-1H in patients with autoimmune cytopenias. *British Journal of Haematology* 2001; 114, 891–898.
- ¹⁰ Passweg J, Rabusin M, Musso M, Beguin Y, Cesaro S, Ehninger G et al. for the Autoimmune Working Party of the EBMT. Haematopoietic stem cell transplantation for refractory autoimmune cytopenias. *British Journal of Haematology* 2004; 125, 749–755.