

## Case Report

# A case of recurrent and refractory Evans syndrome treated with rituximab, which led to severe fungal pneumonia

Meng Zhang<sup>1\*</sup>, Lei Zhang<sup>2\*</sup>, Wei Pan<sup>1</sup>, Xing-Yu Song<sup>1</sup>, Si-Jin Zhang<sup>1</sup>

<sup>1</sup>Department of Pediatrics, The Second Hospital of Jilin University, Changchun, China; <sup>2</sup>Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, China. \*Equal contributors.

Received May 24, 2018; Accepted August 3, 2018; Epub December 15, 2018; Published December 30, 2018

**Abstract:** A 13-year-old patient presented with features of autoimmune hemolytic anemia and immune thrombocytopenia and was diagnosed with Evans syndrome. During treatment, the thrombocytopenia relapsed three times and the last time it responded poorly to steroids, intravenous immunoglobulin, and cyclosporin A. Rituximab was then administered and the platelet count increased to the normal range. However, severe fungal pulmonary infection recurred about one month after the last dose of rituximab. The infection was finally eradicated with anti-infection and supporting therapies, but the platelet count decreased once more 15 months after rituximab. Rituximab is effective to this refractory Evans syndrome but its side effects should be monitored. Treatment of Evans syndrome needs further exploration and normalization.

**Keywords:** Evans syndrome, rituximab, pulmonary infection, intravenous immunoglobulin, steroids

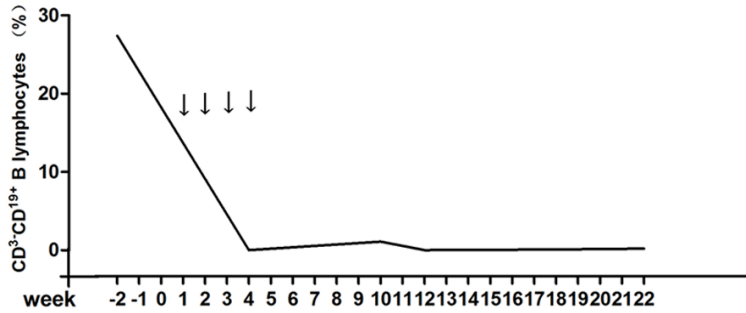
## Introduction

Evans syndrome (ES) is a rare disease first described by Robert S. Evans and his colleagues in 1951 and is characterized by autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) [1]. Immunosuppressive agents are the main therapies, and steroids are effective in most of the cases. Here we report a case of recurrent and refractory ES. The patient was treated with several immunosuppressive agents, but the effect on ITP was not satisfactory. After administration of rituximab, the platelet (PLT) count increased to the normal level. But severe fungal pulmonary infection occurred. The PLT count dropped again 15 months after the use of rituximab. However, treatment of ES requires further study and normalization.

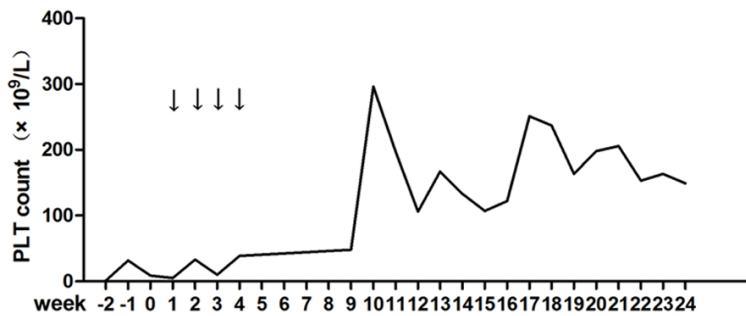
## Case report

A 13-year-old boy was referred to our department because of weakness, pallor, and petechiae for half a month on May 28, 2014. During the period, he occasionally had epistaxis,

hematemesis, and dark urine. On examination, the patient was severely pale with diffused petechiae on his skin and there was no palpable superficial lymph node or organomegaly. The complete blood count (CBC) revealed red blood cell (RBC) count  $1.01 \times 10^{12}/L$ , hemoglobin (HGB) 52 g/L, and PLT count  $4.0 \times 10^9/L$ . His total bilirubin was 95.30  $\mu\text{mol}/L$  (normal range: 2~20  $\mu\text{mol}/L$ ) with mainly indirect bilirubin. Indirect and direct antiglobulin tests were both positive. Immunoglobulin levels were normal. The CD55 and CD59 antigens on the surface of RBC and white blood cell (WBC) were normal and paroxysmal nocturnal hemoglobinuria was excluded. Connective tissue diseases were excluded since all anti-nuclear antibodies were negative. Bone marrow aspiration revealed active myeloid hyperplasia. Erythroid hyperplasia was active, mainly in the middle and late phase, and odd-numbers of nuclear erythrocytes were visible. The volume of mature RBCs was different. There were 431 megakaryocytes on the whole smear but platelets were rare, indicating megakaryocytosis and the dysmaturity of megakaryocytes. Depending on all the



**Figure 1.** CD<sup>3</sup>-CD<sup>19</sup><sup>+</sup> B lymphocytes of the patient before, during, and after rituximab. The treatment consisted of four weekly infusions (arrows).



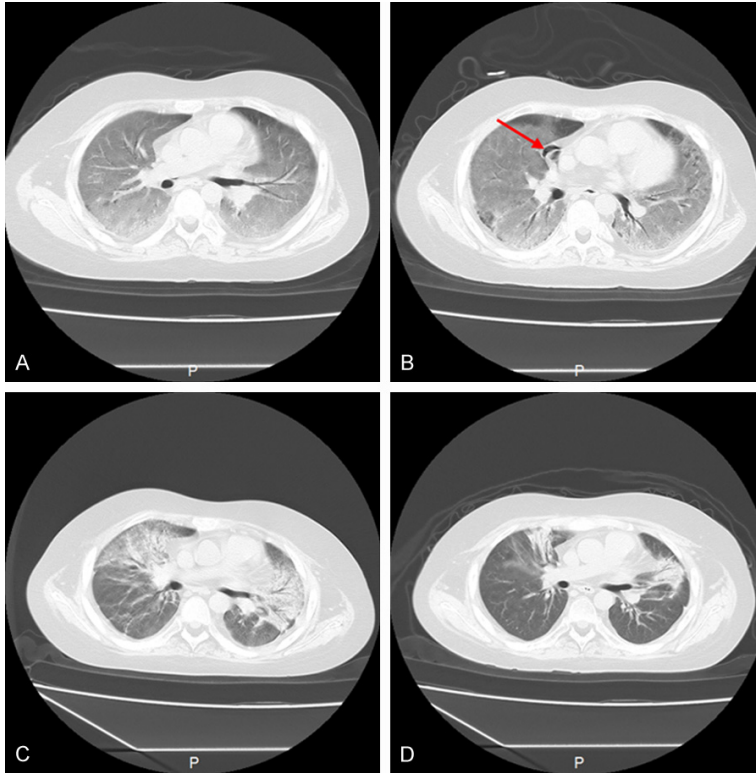
**Figure 2.** Patient's PLT count before, during and after rituximab. The treatment consisted of four weekly infusions (arrows).

evidence above, the patient was diagnosed with ES and was treated with blood transfusion (when necessary), methylprednisolone (2 mg/kg/d for 21 d, weight 41 kg), and intravenous immunoglobulin (IVIg, 400 mg/kg/d for 3 d). Pallor and petechiae disappeared in one week. He was discharged on June 17, 2014 with normal HGB, RBC, and PLT count. Four months later when oral prednisone was reduced to 5 mg/d, his PLT count dropped to 47×10<sup>9</sup>/L. Methylprednisolone (1 mg/kg/d for 7 d, weight 60 kg) was administrated and PLT count increased to 183.0×10<sup>9</sup>/L. However, a half a year later when oral prednisone was reduced to 2.5 mg/d, his PLT count dropped again to 13×10<sup>9</sup>/L. Treated with prednisone (20 mg/d) for a week, his PLT count returned to normal. During the whole course, the RBC count and HGB didn't change significantly, however, both indirect and direct antiglobulin test kept positive.

On the 21<sup>th</sup> month (Feb. 23, 2016) after his diagnosis with ES when the oral methylprednisolone was reduced to 24 mg/d from 40 mg/d (weight 60 kg), ES relapsed for the third

time. PLT count dropped to 31×10<sup>9</sup>/L, but this time full-dose methylprednisolone (1 mg/kg/d for 15 d) didn't increase PLT count at all. Then IVIG (400 mg/kg/d for 5 d) and cyclosporinA (75 mg/d for 7 d) were also tried but didn't work well. The PLT count fluctuated between 5×10<sup>9</sup>/L and 33×10<sup>9</sup>/L. At the point when he was off corticosteroids for 2 months and off cyclosporin A for 6 weeks and after informed written consent was obtained, he received rituximab (Mabthera® Hoffmann-La Roche, Grenzach-Wyhlen, Germany) at the dose of 375 mg/m<sup>2</sup>/week for four consecutive weeks (the last dose was on June 1, 2016) combined with oral methylprednisolone (20 mg/d). After 4 courses, the CD<sup>3</sup>-CD<sup>19</sup><sup>+</sup> B lymphocytes dropped to 0.0% from 27.4% (Figure 1). At the same time, the indirect and direct anti-

globulin test turned negative. In five weeks his PLT count increased to normal level (Figure 2). However, one month after the last dose of rituximab, the patient got a fever and persistent cough. Auscultation of the lungs was normal. WBC count was 11.5×10<sup>9</sup>/L with mainly granulocytes, while HGB, RBC, and PLT count were within the normal range. C-reactive protein was 26.5 mg/L (normal range: <10 mg/L) and 1,3-Beta-D-Glucan assay was strong positive. Procalcitonin was normal. Chest computed tomography (CT) scan showed glass opacities in both lung fields indicating severe infection (Figure 3A) and pneumomediastinum (Figure 3B). According to the evidence above, fungus was deduced the most possible pathogen and he was diagnosed with fungal pneumonia. Then the patient received systematically anti-fungus treatment, successively with voriconazole (4 mg/kg/time, 2/d, for 58 d, weight 60 kg), micafungin (150 mg/d for 7 d) and fluconazole (150 mg/d for 20 d). At the same time, antibiotics were administrated to eliminate the possible complicated pathogenic bacteria. IVIG was also applied to improve the immune function at a dose of 400 mg/kg/d for 9 d. The whole course



**Figure 3.** Chest CT of the patient before, during and after anti-infection treatment. A. At the time of diagnosis of fungal pneumonia. B. Two weeks later, arrow indicates the pneumomediastinum. C. Seven weeks later. D. Four months later, before he was discharged.

lasted 4 months. Finally, the symptoms disappeared and lung CT improved greatly (**Figure 3C, 3D**) and he was discharged on Nov. 6, 2016.

Eight months later, the patient's CD<sup>3</sup>CD<sup>19+</sup> B lymphocytes increased to normal level, while the CBC was normal (the details were absent because the patient had the test in the local hospital). Two months later (15 months after the administration of rituximab), the indirect and direct antiglobulin test turned positive and the PLT count dropped to 80×10<sup>9</sup>/L with HGB and RBC count within the normal range. From then on, the patient kept taking oral methylprednisolone (unknown dose) and the PLT count stays normal for the following two months. He was lost to follow-up since November 2017.

### Discussion

ES is an immune-mediated disease characterized by the combination of AIHA and ITP [2]. In nearly half of the cases, it is associated with

systemic autoimmune disease, such as systemic lupus erythematosus or lymphoproliferative disease [3]. ES tends to run a chronic course and is characterized by frequent exacerbations and remissions [4]. The main clinical manifestations include pallor, fatigue, dyspnea, and fever. Physical examination often reveals hepatomegaly, splenomegaly, jaundice, petechiae, bruising, and mucocutaneous bleeding. HGB, RBC, and PLT count are usually decreased and direct and indirect antiglobulin test are positive. In addition to these, indirect bilirubin may increase as well with this disease. Bone marrow can be normo/hyper-cellular [5, 6]. Our patient had the features of AIHA and ITP and got a certain diagnosis of ES.

The first-line treatment for ES includes steroids and IVIG. The dose of methylprednisolone is 1~2 mg/kg/d, and most of the patients have a

good response. IVIG can be used at the dose of 400 mg/kg/d for 4-5 days and it is always applied together with steroids. If the first-line treatment can't achieve remission or the disease relapses, the second-line therapy is required which includes immunosuppressive agents, rituximab, splenectomy, etc. Immunosuppressive agents include cyclosporin A, mycophenolate mofetil, or danazol, and the choice should be made depending on clinical criteria. Rituximab is a monoclonal antibody against CD20 molecule which targets and deletes B lymphocytes. It is usually used at the dose of 375 mg/m<sup>2</sup>/week for 4 courses for ES and about 75% ES respond to it [2, 4, 7]. Splenectomy is an option of second-line treatment because of the good response and short-term efficacy. In recent years, hemopoietic stem cell transplantation has also been used to treat ES in relapsing or drug-resistant cases [2, 4, 8, 9].

In the first more than one year, the patient responded well to steroids and IVIG, but was

steroid-dependent. For the relapse of the third time, several therapies didn't show a significant effect. He was diagnosed with recurrent and refractory ES. Rituximab (375 mg/m<sup>2</sup>/week for 4 weeks) reduced B lymphocytes to 0.0% and the indirect and direct antiglobulin test turned negative and the PLT count increased to the normal range. This effect lasted for more than 1 year. This showed the effectiveness of rituximab for recurrent and refractory ES.

Side effects of rituximab include noninfectious toxicity and infectious complications [10]. Non-infectious toxicity includes neutropenia and agranulocytosis. The pathogens of the infection include virus, bacteria, fungus, and pneumocystis carinii with virus being the most common one [11]. The prolonged and complete depletion of B lymphocytes contributed to the risk of infections, just as what happened in this patient. So a balance should be gained among the risks of B lymphocyte depletion, the potential infection, and the benefits of this treatment. If possible a lower dose may be a better choice. One hundred mg/dose/week rituximab for 4 weeks is enough to keep 4 out of 7 ITP patients in remission [12]. In addition, when rituximab is used in neuromyelitis optica, a type of neurological autoimmune disease, CD<sup>3</sup>-CD<sup>19</sup><sup>+</sup> B lymphocytes were monitored after the first three weekly doses. Whenever it reached 1% of the total lymphocyte population, rituximab (100 mg) was reinfused. This dosage was sufficient to deplete B cells and maintain low B-cell counts. This keeps the patients a comparatively long remission [13]. Therefore, we propose that a low-dose and a proper interval of rituximab might also be a reasonable choice for ES. More clinical trials and evidence are necessary to find an optional usage of rituximab in ES.

Management of Evans syndrome remains a challenge. Rituximab is effective for some recurrent and refractory ES cases but the side effects should be monitored at the same time. The treatment of ES waits to be further explored and normalized.

### Acknowledgements

This work was supported by Norman Bethune Program of Jilin University: 2015216 and grant from Jilin Provincial Science and Technology

Department, China: 20180414049GH to Lei Zhang.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Si-Jin Zhang, Department of Pediatrics, The Second Hospital of Jilin University, Changchun 130000, China. Tel: 86-431-88796302; E-mail: cczhangsijin@163.com

### References

- [1] Evans RS, Takahashi K, Duane RT, Payne R, Liu C. Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology. *AMA Arch Intern Med* 1951; 87: 48-65.
- [2] Miano M. How i manage evans syndrome and ALHA cases in children. *Br J Haematol* 2016; 172: 524-534.
- [3] Price V. Auto-immune lymphoproliferative disorder and other secondary immune thrombocytopenias in childhood. *Pediatr Blood Cancer* 2013; 60: S12-14.
- [4] Norton A, Roberts I. Management of Evans syndrome. *Br J Haematol* 2006; 132: 125-137.
- [5] Pui CH, Wilimas J, Wang W. Evans syndrome in childhood. *J Pediatr* 1980; 97: 754-758.
- [6] Mathew P, Chen G, Wang W. Evans syndrome: results of a national survey. *J Pediatr Hematol Oncol* 1997; 19: 433-437.
- [7] Ducassou S, Leverger G, Fernandes H, Chambost H, Bertrand Y, Armari-Alla C, Nelken B, Monpoux F, Guitton C, Leblanc T, Fisher A, Lejars O, Jeziorski E, Fouissac F, Lutz P, Pasquet M, Pellier I, Piguët C, Vic P, Bayart S, Marie-Cardine A, Michel M, Perel Y, Aladjidi N. Benefits of rituximab as a second-line treatment for autoimmune haemolytic anaemia in children: a prospective French cohort study. *Br J Haematol* 2017; 177: 751-758.
- [8] Benesch M, Urban C, Platzbecker U, Passweg J. Stem cell transplantation for patients with Evans syndrome. *Expert Rev Clin Immunol* 2009; 5: 341-348.
- [9] Porcaro F, Valenzise M, Candela G, Chiera F, Corica D, Pitrolo E, Santucci S, Romeo M, Nigro S, Zirilli G. Evans syndrome: a case report. *Pediatr Med Chir* 2014; 36: 91.
- [10] Mantadakis E, Danilatou V, Stiakaki E, Kalanti M. Rituximab for refractory Evans syndrome and other immune-mediated hematologic diseases. *Am J Hematol* 2004; 77: 303-310.
- [11] Cooper N, Bussel JB. The long-term impact of rituximab for childhood immune thrombocytopenia. *Curr Rheumatol Rep* 2010; 12: 94-100.

## A case of ES

- [12] Provan D, Butler T, Evangelista ML, Amadori S, Newland AC, Stasi R. Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults. *Haematologica* 2007; 92: 1695-1698.
- [13] Yang CS, Yang L, Li T, Zhang DQ, Jin WN, Li MS, Su N, Zhangning N, Liu Q, Shao ZH, Yu C, Shi FD. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. *Neurology* 2013; 81: 710-713.