A Rare Case of Steroid- Refractory Evans Syndrome Secondary to Chronic Lymphocytic Leukemia, Successfully Treated with Rituximab

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Abstract

Evans Syndrome (ES) is an autoimmune disorder where patients develop autoimmune hemolytic anemia (AIHA) as well as immune thrombocytopenia (ITP), with or without immune neutropenia. The previous use of corticosteroid treatment for ES secondary to CLL has shown to be a temporary solution, with most patients developing recurrent disease within 36 months. Therefore, the treatment of ES has been under investigation, where research has demonstrated chemotherapy with or without Rituximab having improved outcomes when compared to the previous standard of treatment (steroids alone versus steroids combined with intravenous immune globulin). Ibrutinib, a drug utilized to treat autoimmune dysfunction, works as an immunosuppressant by inhibiting Bruton's tyrosine kinase (BTK), and has been utilized to treat CLL. Here, we present a rare case of ES secondary to CLL successfully treated with Rituximab.

Case summary

A 76-year-old Russian male diagnosed with chronic lymphocytic leukemia (CLL), not on any chemotherapy, presented to the emergency department with generalized weakness, exertional dyspnea, palpitations for 1 week. He denied having any B Symptoms, bleeding from anywhere, and skin changes. He was hemodynamically stable. His complete blood count revealed hemoglobin of 5.1g/dl, MCV 148.5, WBC was 144.8 cells/microliter, Platelet count 255k, Reticulocyte count elevated at 26, elevated LDH 338 U/L, low Haptoglobin< 10 mg/dl. Coombs test positive for IgG, C3. He was given 2 units of packed red blood cells and was started on prednisone 60 mg BID, for Autoimmune hemolytic anemia secondary to CLL, which improved his hemoglobin to 8 g/dl. He was discharged on a tapering dose of steroids and Chlorambucil 8 mg PO once a day, which he was non-compliant with. The patient got readmitted to the hospital after a few weeks with similar complaints. Blood work showed recurrent autoimmune hemolytic anemia and thrombocytopenia, with hemoglobin of 6 g/dl and platelet count of 90K. He is diagnosed to have steroid-resistant Evans syndrome. The molecular study is negative for P53 mutation (favorable), IGHV status unmutated (unfavorable prognosis), ZAP 70, CD 38 positive (unfavorable prognosis), del of chromosome 13 at q14 (favorable). He was given 4 doses of IV immunoglobulins and 3 cycles of rituximab, which stabilized his platelet count and halted hemolysis. He was started on Ibrutinib for CLL complicated with steroid-refractory Evans syndrome.

Laboratory Studies

Table 1. Laboratory results for initial workup

Name of Test	Reading	Reference Range
Hemoglobin	5.1 g/dL	13.5 - 17.5 g/dL
Mean Corpuscular Volume (MCV)	148.5 fL	80 - 100 fL
White Blood Cell (WBC) Count	14,480 cells/µL	4,500-11,000 cells/µL
Platelet Count	255 K/mm^3	150 - 450 K/mm^3
Reticulocyte Count	26%	0.5 – 2%
Lactate Dehydrogenase (LDH)	338 unit/L	140 - 280 unit/L
Haptoglobin	<10 mg/dL	23 - 355 mg/dL

Table 2. Laboratory results during second admission

Name of Test	Reading	Reference Range
Platelet count	90 K/mm^3	150 - 450 K/mm^3
Hemoglobin	6 g/dL	13.5 - 17.5g/dL
Mean Corpuscular Volume (MCV)	135 fL	80 - 100 fL
Lactate dehydrogenase (LDH)	286 unit/L	140 - 280 unit/L
Haptoglobin	<10 mg/dL	23 - 355 mg/dL

Discussion

Evans syndrome(ES) is an autoimmune condition with simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), with or without immune neutropenia. ES is associated with primary immunodeficiencies, rheumatologic diseases, and lymphoproliferative disorders including chronic lymphocytic leukemia (CLL). Evans Syndrome secondary to CLL is a rare association and is seen in 5-15% of patients[1].

Due to the low prevalence of ES, current guidelines are inferred from the current management of isolated ITP and AIHA. Therefore, the first line therapy for ES has been corticosteroids [1]. The duration of treatment is determined by the severity of cytopenia, yet typically ranges approximately 3 - 4 weeks, with a subsequent one-week taper [1].

In life-threatening cases deemed more severe, Methylprednisolone can also be added to the regimen [1]. Up to 80% of patients are responsive to initial steroid treatment; however, approximately 20-33% of patients undergo remission within one year [1, 2]. This makes the use of corticosteroids as a first line treatment for ES, a short-term option that can be used in the acute setting [3]. Other methods of treatment include IVIG, and transfusion support [1]. In cases of steroid-refractory ES, second line treatments include Rituximab, splenectomy, immunosuppressants, stem cell transplantation, bone marrow stimulating agents, and anticoagulation [1]. When managing ES in conjunction with CLL, second line therapy with Rituximab has demonstrated a response rate of 75% following one-year in patients with isolated AIHA or ITP [1]. In one study, the initial response rate to Rituximab in patients with ES was 82%, which decreased to 64% following one year [1]. In a study that reported specifically on ES secondary to CLL, where patients were treated with corticosteroids, IVIG or chemotherapy, the initial response rate was higher when chemotherapy was used compared to the first line treatment group [1]. Data suggests that chemotherapy is effective in approximately 50% of CLL patients with ES; however, most patients concluded their remission within a 32-month span [3]. Rituximab as a monotherapy has also been investigated amongst patients with secondary ES with remission achieved in 60% of patients without relapse for a median time of 40 months [3]. Patients who are refractory to steroid treatment who received Rituximab in conjunction with chemotherapy were able to achieve long term remission (72% of patients) with a median remission period of 76 months [3]. Furthermore, for patients with ES secondary to CLL with lymphadenopathy, splenomegaly, or significant lymphocytosis, the use of chemotherapy in conjunction with Rituximab is an appropriate treatment [3]. Patients with splenomegaly, medication resistance or failure, and recurrent relapses following adequate treatment meet the criteria indicating for splenectomy [3].

Conclusion

It is key to detect and treat ES promptly and manage long-term remission to maximize patient outcomes. The previous use of corticosteroid treatment for ES secondary to CLL has shown to be beneficial in the acute setting. Therefore, the treatment of ES has been under investigation, where research shows chemotherapy with or without rituximab is associated with better patient outcomes than the previous standard of treatment. The investigation into biological markers of prognosis is key in determining treatment plans to maximize patient management. The prognosis of ES secondary to CLL can be determined by the presence of ZAP-70 expression, immunoglobulin heavy chain gene status, and TP53 deletions. The development and further investigation into ES and the conditions that are associated are required in order to advance patient care.

References

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