MEDDOCS Open Access Publisher

Hematology and Oncology: Current Research

Open Access | Case Report

Steroid-Refractory Evans Syndrome Secondary to Chronic Lymphocytic Leukemia (CLL), Successfully Treated with Rituximab

Sindhusha Veeraballi[1]; Zaineb Khawar[1]; Brooke Kania[2]*; Leena Bondili[2]; Vinod Kumar[2]; Michael Maroules[2]

[1]St. Michael's Medical Center, 111 Central Ave, Newark, NJ 07102, USA.

[2]St. Joseph's University Medical Center, 703 Main St, Paterson, NJ 07503, USA.

***Corresponding Author(s): Brooke Kania**

St. Joseph's University Medical Center, 703 Main St, Paterson, NJ 07503, USA.

Email: kaniab22@gmail.com

Received: Feb 24, 2022

Accepted: Mar 11, 2022

Published Online: Mar 15, 2022

Journal: Hematology and Oncology: Current Research

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

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.

Keywords: Evans syndrome; Rituximab; Chronic lymphocytic leukemia.

Introduction

ES represents an autoimmune condition where patients can develop both AIHA and ITP and may lead to development of immune neutropenia [1-2]. ES was initially characterized in 1951 and encompasses 0.3-7% cases of AIHA and 2-2.7% cases of ITP [3]. ES has been associated with primary immunodeficiencies, rheumatologic diseases, and lymphoproliferative disorders including CLL [1]. ES secondary to CLL is a rare association and has been reported in approximately 5-15% of patients [4]. Here, we report a patient with steroid-refractory ES secondary to CLL, who was found to have a positive outcome following treatment with Rituximab.

Case presentation

A 76-year-old Russian male with a past medical history significant for CLL, who was not receiving chemotherapy for his disease, presented to the Emergency Department (ED) with generalized weakness, exertional dyspnea, and palpitations for 1-week duration. He denied having B Symptoms, evidence of bleeding, or skin changes. In the ED, the patient was hemodynamically stable. His complete blood count revealed anemia with severe macrocytosis, leukocytosis, and thrombocytopenia. Additionally, the patient's reticulocyte count was elevated, his Lactate Dehydrogenase (LDH) was elevated, and his haptoglobin level was low (**Table 1**). The patient's Coombs' test result-

Cite this article: Veeraballi S, Khawar Z, Kania K, Bondili L, Kumar V, et al. Steroid-Refractory Evans Syndrome Secondary to Chronic Lymphocytic Leukemia (CLL), Successfully Treated with Rituximab. Hematol Oncol Curr Res. 2022; 5(1): 1014.

ed positive for IgG and C3. His flow cytometry was consistent with CLL, clonal B-cell population comprising 80-85% of the total, ZAP 70, and CD38 positive. The patient received 2 units of packed red blood cells and was initiated on Prednisone 60 mg twice daily for AIHA secondary to CLL, which improved his hemoglobin from 5.1 to 8g/dL. Due to clinical improvement, the patient was discharged on a steroid taper as well as Chlorambucil 8mg oral once daily.

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

Following a few weeks after discharge, the patient was ultimately re-admitted secondary to similar complaints. Blood work on re-admission was significant for recurrent AIHA and thrombocytopenia, macrocytic anemia, with elevated LDH, low haptoglobin, and a positive Coombs' test (**Table 2**). He was diagnosed with steroid-resistant ES. Molecular studies were significant for a negative P53 mutation (favorable), unmutated IGHV status (unfavorable prognosis), ZAP 70 positive, CD 38 positive (unfavorable prognosis), and del of chromosome 13 at q14 (favorable). The patient received 4 doses of Intravenous Immunoglobulin (IVIG) and 3 cycles of Rituximab, which stabilized his platelet count and halted hemolysis within 3 weeks. The patient was also initiated on Ibrutinib for CLL complicated with steroid-refractory autoimmune cytopenia.

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

ES secondary to CLL has been a rarely documented association, approximately seen in 5-15% of CLL patients [4]. The median age of ES diagnosis in the setting of CLL is approximately 66 years old, and 60% of patients have been found to be male [1]. There has been no statistical difference in other demographic factors as it pertains to the occurrence of ES in CLL patients [1]. It is important to investigate for pathologies such as hemorrhagic anemia, complicated ITP, thrombotic microangiopathies, deficiencies of specific vitamins, paroxysmal nocturnal hemoglobinuria, or myelodysplasia when AIHA and ITP are found to occur simultaneously [1].

Specific mutations including ZAP-70 expression, Immunoglobulin Heavy Chain Variable region gene (IGHV) status, and TP53 have been linked as prognostic indicators of ES secondary to CLL [5]. An analysis of patients diagnosed with CLL complicated by Autoimmune Cytopenia (AIC), ZAP-70 expression was elevated in approximately 79% of the patients with ES when compared to their non-ES counterparts [5]. A relationship has been identified between ES and IGHV unmutated status, where approximately 86% of CLL patients with ES had an unmutated IGHV when compared to their CLL without AIC counterparts [5]. Additionally, ES has been correlated with del (17)(p13)/TP53 mutations [5]. Patients with CLL complicated by ES who present with the above prognostic mutations may experience poor overall survival.

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 [6]. 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 [6].

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 [6]. 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 [6]. 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 [6]. Patients with splenomegaly, medication resistance or failure, and recurrent relapses following adequate treatment meet the criteria indicating for splenectomy [6].

Splenectomy represents a promising second line treatment of both isolated ITP, isolated AIHA, and ES complicated by CLL [1]. Splenectomy results in response rates of 70-88%, with 40-66% of patients undergoing complete remission in those with isolated ITP or AIHA [1,2]. Data concerning splenectomy in ES are limited, but preliminary research shows a response rate of 78-85%, with long-term remission achieved in 42-62% of patients [1]. Splenectomy should be discouraged in patients with other underlying autoimmune disorders, and other medical treatments should be exhausted prior to this treatment option [1]. The treatment of patients with CLL complicated by ES should be individualized and take multiple factors into account [6].

Conclusion

ES can develop secondary to CLL, a complication of the disease that can be relatively difficult to treat. 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 [6]. 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 [6]. 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 [5]. The development and further investigation into ES and the conditions that are associated are required in order to advance patient care.

Declaration

Disclosure of interest: The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent: As this is a case report, consent was obtained for the purpose of this paper.

Author affiliation: All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at both St. Michael's Medical Center and St. Joseph's University Medical Center.

References

1. Audia S, Grienay N, Mounier M, Michel M, Bonnotte B. Evans' Syndrome: From Diagnosis to Treatment. J Clin Med. 2020; 9: 3851.

2. Jaime-Pérez JC, Aguilar-Calderón PE, Salazar-Cavazos L, Gómez-Almaguer D. Evans syndrome: Clinical perspectives, biological insights and treatment modalities. J Blood Med. 2018; 9: 171-184.

3. Al Hazmi A, Winters ME. Evans Syndrome. Clin Pract Cases Emerg Med. 2019; 3: 128-131.

4. Shaikh H, Mewawalla P. Evans Syndrome. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing. 2021: 30085557.

5. Carli G, Visco C, Falisi E, Perbellini O, Novella E, et al. Evans syndrome secondary to chronic lymphocytic leukaemia: presentation, treatment, and outcome. Ann Hematol. 2016; 95: 863-870.

6. Yevstakhevych YL, Vyhovska YI, Yevstakhevych IY, Vyhovska OY, Pelenyo NV, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: diagnosis and treatment. Exp Oncol. 2020; 42: 318-323.