HSPC The Open Access Publisher

ACR ARCHIVES OF CASE REPORTS
ISSN 2637-3793

Case Report

Treatment of autoimmune hemolytic anemia with erythropoietin: A case report

Juan P Ovalle[1], Estefanía M Orozco[2], Laura C Pedraza[3], María C Barrera[4], Renato A Guzmán[5]* and Dormar D Barrios M[6]

[1]Family Medicine Resident, Medicine Faculty, Fundación Universitaria Juan N. Corpas, Bogotá DC, Colombia

[2]Critical Medicine and Intensive Care Resident, Hospital San José, Fundación Universitaria de Ciencias de la Salud, Bogotá DC, Colombia

[3]Intern in Investigation, Medicine Faculty, Fundación Universitaria Juan N. Corpas, Bogotá DC, Colombia

[4]Therapeutic Alternatives and Vegetal Pharmacology, Medicine Faculty, Fundación Universitaria Juan N. Corpas, Bogotá DC, Colombia

[5]Internal Medicine Physician, Specialist in Immunology and Rheumatology, Instituto de Enfermedades Autoinmunes Renato Guzmán, Bogotá DC, Colombia

[6]Critical Medicine and Intensive Care Physician, Colombian Association of Critical Medicine and Intensive Care, Latin American Brain Injury Consortium, Certificate Reviewer of Revista Colombiana de Cardiologia, Bogotá DC, Colombia

More Information

***Address for Correspondence:** Renato A Guzmán, Internal Medicine Physician, Specialist in Immunology and Rheumatology, Instituto de Enfermedades Autoinmunes Renato Guzmán, Bogotá DC, Colombia,
Email: renatoguzman@cable.net.co

Submitted: 01 November 2019
Approved: 19 November 2019
Published: 20 November 2019

How to cite this article: Ovalle JP, Orozco EM, Pedraza LC, Barrera MC, Guzmán RA, et al. Treatment of autoimmune hemolytic anemia with erythropoietin: A case report. Arch Case Rep. 2019; 3: 043-046.

DOI: dx.doi.org/10.29328/journal.acr.1001022

Keywords: Autoimmune hemolytic anemia; Hematology; Erythropoietin

Abstract

In this article, we describe the case of a fifty-year-old patient with autoimmune hemolytic anemia (AIHA) with constitutional symptoms, jaundice, unquantified fever and progressive dyspnea. The patient had history of smoking and Hepatitis A and following a physical exam she was found in a regular condition, icteric but with no other further signs. Her laboratory tests revealed hemolytic anemia with a hemoglobin of 8.5 g/dL, an increase of total and indirect bilirubin, an elevated ferritin, a decreased transferrin and haptoglobin and a positive result for direct Coomb's test. Considering this, an immune profile was ordered finding a negative result of ANAs and ENAs and a decrease of complement C3 and C4. The patient was diagnosed with AIHA and as an initial step a corticosteroid treatment was administrated however the patient showed no clinical nor chemical improvement. At her third day of hospitalization, she was unstable hemodynamically requiring transfer to Intensive Care Unit (ICU) to optimize management. After 24 hours on ICU, due to persistence of deterioration of the patient, it was decided to manage with erythropoietin (EPO). In the following days, the patient showed a rise in her hemoglobin and an overall improvement made possible the transfer to hospitalization service. The AIHA is an uncommon disease and is not the first option that comes to mind with these symptoms, currently there are not controlled studies to the treatment due to its complexity and the heterogeneity of the results. We strongly support the use of EPO in refractory cases of this pathology.

Introduction

The AIHA is a rare disease, with an incidence of 1-3/100.000 patients per year. It is defined as the destruction of red cells due to a production of autoantibodies with or without complement activation, leading to agglutination or lysis of these cells when reacting with antigens [1,2]. AIHA can be classified in 4 types, depending of autoantibodies: warm antibodies (act at 37°C) is the most common, cold antibodies (act at less than 37°C), mixed (presence of both warm and cold antibodies) and drug induced, to highlight penicillin and cephalosporins [3].

For its diagnosis, its necessary evidence of hemolysis and anemia. Clinically, hemolysis can be expressed as jaundice at the expense of indirect bilirubin and choluria. However, only 60% of patients exhibit those signs. Taking into account that is a rare disease, is important to first rule out other causes of hemolysis [3]. In relation with anemia, is characterized by pallor, adynamia, dyspnea, palpitations, dizziness, as well as hepatomegaly, splenomegaly and lymphadenopathies [4]. In laboratory tests, there is a hemolytic anemia with variable levels of hemoglobin and hematocrit; mean corpuscular volume (MCV), reticulocytes count and lactate dehydrogenase increased; haptoglobin is decreased with mild leukocytosis and some time, neutropenia. In blood smear, there are variations of red cells shape, like spherocytosis in warm AIHA. If anemia appears simultaneously with thrombocytopenia, Evans Syndrome must be assessed. Direct antiglobulin test

(DAT), also known as direct Coomb's, is essential for the diagnosis of AIHA [3–5].

Likewise, the treatment begins once the diagnostic is confirmed with DAT and the first line for treatment in cases of warm AIHA are 1.5 mg per kilogram corticosteroids per day until the patient reaches a stable level of hemoglobin, so then the dose can be tapered for 3 to 6 months. Previous to corticosteroids administration, albendazole should be given to prevent infections caused by worms because the patient is going to be immunosuppressed [6]. However, a relapse may happen once the patient discontinues corticosteroids, therefore second line treatments such as splenectomy, immunomodulators as azathioprine or cyclophosphamide, biologic agents as rituximab can be considered [5]. Regarding cold AIHA, is important to maintain the patient at >37°C (>98.6°F) considering the benign process of the disease, but in particular cases can be necessary to treat with rituximab or cyclophosphamide. In the case of drug- induced AIHA, stopping the drug should be enough and the patient should show an improvement [3,4].

When there is severe hemolysis, reticulocytosis can be insufficient, making EPO an alternative treatment in refractory cases [7,8]. EPO is a hormone secreted by the kidney and stimulates proliferation and differentiation of stem cells in bone marrow [9]. The treatment of AIHA with this hormone has been documented in cases of cold AIHA but it has not been evaluated systematically [10,11].

Currently, the diagnosis, treatment and prognosis of AIHA are a challenge in medical practice. Based on evidence this illness is rare, lacks of standardized therapies and trigger factors are diverse [12]. In the following pages, we shared a case report of AIHA in which EPO improves clinical condition and outcomes in the patient.

Case Presentation

A 50-year-old female patient from Bogotá, Colombia, consulted for a 4-month history of constitutional symptoms, episodes of unquantified fever, jaundice and dyspnea. She worked as a nursing assistant and she had history of smoking and Hepatitis A. At physical examination on admission, vital signs were normal but laboratory tests report hemoglobin (Hb) of 8.5 g/dL so the patient is admitted immediately in the emergency room of a third level hospital. There, blood tests exposed hematocrit (Ht) 25%, ferritin (F) 223.1 ng/mL, transferrin (Tf) 160 mg/dL, total bilirubin 1.6 mg/dL at expense of indirect (0.82 mg/dL); c-reactive protein, urinalysis, urea nitrogen, creatinine, calcium, potassium, glucose, transaminases and alkaline phosphatase in normal range, HIV and Hepatitis C negative; hepatobiliary ultrasound with and unspecific hypoechoic image adjacent to pancreas. After these results, it was considered a diagnosis of hemolytic anemia of apparent autoimmune etiology and for that reason, the patient was referred to the hematology service. As a first line treatment, corticosteroids was given and prophylaxis dose of albendazole was administered.

Recognizing the need for immediate treatment, the patient was transferred to a nearby hospital to be assessed by the hematologist. At the admission, the patient was in regular condition, alert, afebrile, hydrated, with vital signs of: blood pressure 120/80 mmHg, respiratory rate 18 breaths/minute, cardiac rate 78 beats/minute, with 2 L of oxygen by nasal cannula to saturation of 92%; icteric skin and mucous membranes, painful hepatomegaly; but the rest of the physical examination was normal. The patient was hospitalized by the hematology service and began treatment with prednisolone 60mg daily, albendazole 400 mg and ampicillin sulbactam 1 g 4 times per day (the latter was given thinking in obstructive biliary syndrome as differential diagnosis). Also, laboratory tests were ordered: complete blood count, urea nitrogen, creatinine, ANAs, ENAs, complement C3 and C4, VDRL serology, bilirubin, transaminases, DAT, lactate dehydrogenase, haptoglobin, clotting time, blood smear, hepatitis B surface antigen and anti-hepatitis C virus antibody. Later the same day, laboratory tests exposed leukocytes 6.100U/L, neutrophils 78.6%, lymphocytes 8.7%, monocytes 9.7%, red cells count 1.500.000 per mm^3, Ht 17.8%, Hb 5.8 g/dL, MCV 119 fl, mean corpuscular hemoglobin 38.7 pg, RDW 14.7%. Taking into account that the Hb was noticeably lower than normal (12-15 g/dL) transfusion of red blood cells was not considered in the context of autoimmunity, because this is an option only in case of hemodynamic instability. Additionally, the same laboratory results showed elevations in lactate dehydrogenase (787 Ul/L) and total bilirubin of 1.68 mg/dL, DAT positive 4 +, and clotting time of PT of 16.1, INR of 1.32 and PTT of 18.7.

After the administration of the first line treatment, corticosteroids, the patient did not have an improvement in symptoms nor in laboratory tests, therefore as an alternative the dose of prednisolone was increased to 75 mg daily with 2 additional doses of deworming. The treating service considered a bone marrow aspiration to study lymphoproliferative disorders. However, it was not applied because the hospital did not have the supplies to perform it.

Next day, the patient persisted icteric and pale, at physical examination were found a systolic murmur grade II/IV at tricuspid and mitral focus and a grade I edema in lower limbs; taking this into account a new complete blood count and reticulocytes count was ordered. Twenty-four hours after, the patient was feeling faint and diaphoretic, her vital signs showed hypotension (80/39 and 70/44 mmHg), hypovolemic shock secondary to active hemolysis was identified (considering the Hb of 4.9 g/dL of the patient). For those reasons, the patient was transferred to ICU and hydric reanimation was started, also blood and urine cultures were ordered. The patient started to respond favorably to reanimation but she persisted pale, icteric with hypochromic conjunctives and Hb of 5.7 g/

dL, with incompatibility for transfusion given by the risk of increase hemolysis, generated a threatening condition to the patient's life. Consequently, the treating group decided to wait 24 hours to define another treatment with immunoglobulin if Hb kept going down. Meanwhile, the patient started to receive an intravenous methylprednisolone 1g daily for 3 days and fluconazole 200 mg twice per day to treat the yeast found in the urine. In table 1, laboratory tests during hospital stay are summarized.

In the following hours, the patient did not show improvement so the treatment with immunoglobulin G 1 g per kilogram for 2 days is ordered. However, since it was not available in the hospital, the treating group prescribed an EPO therapy of 2.000 U to be administered intravenously twice per day for 4 days taking into account refractoriness to corticosteroid. At the second day of EPO therapy, the patient is less icteric, hemodynamically stable and reached a Hb 6 g/dL, being possible to transfer her to Internal Medicine Ward. At the third day of EPO therapy, simultaneously, the patient started oral prednisone 1mg per kilogram daily along with azathioprine 50 mg twice per day.

Finally, after ten days of hospitalization, she was hemodynamically stable with an increased Hb level, so she was discharged from the hospital with a prescription of azathioprine 50 mg twice per day, prednisone 75 mg daily for 1 month and follow up check-ups of the hematology and internal medicine services (Table 1).

Discussion

Nowadays, the terminology AIHA is still unclear because it can be used to refer to a variety of pathologies, for example when its associated it with positive antithyroglobuline antibody [13]. AIHA is an uncommon disease, so the diagnosis is usually made after ruling out other causes of hemolytic anemia like microangiopathy, spherocytosis, Sickle cell disease and connective tissue diseases, specially, systemic lupus erythematosus [3].

In the case exposed above, the patient had warm antibodies AIHA, due to unquantified fever, positive DAT and laboratory tests matching with hemolytic anemia. As a first line treatment [14], the patient was treated without improvement and because of hemodynamic instability she was transferred to the ICU where a red cells transfusion was made [8,15]. It can be hypothesized that the unresponsiveness to the treatment was due to very low Hb values [16], and for that reason, as a second option, EPO and azathioprine were added to the treatment with impressive clinical and paraclinical improvement and without any show of adverse reactions. It's important to have in mind that response to treatment can be diverse [14], in this case was almost instantly but in some cases can even take months.

Consideringtheabovesituation,weascribetheimprovement of the patient to EPO therapy more than to corticosteroids, taking in mind that on day 3, methylprednisolone pulses started and on day 5, they were finished, having achieve Hb of 4.9 g/dL. Compared with EPO therapy, with which the patient improved her levels of Hb to 5.6 g/dL, and considering that response to this medication can be slower than corticosteroid, we suggest that EPO administration permitted that the patient was discharged with Hb of 6.3 g/dL.

Currently, the treatment options are diverse and the combination of low doses of rituximab plus high doses of dexamethasone have been proposed in refractory cases [5,16]. There are some cases of AIHA treated with EPO [8,10,11,17], especially when there is reticulocytopenia [18,19], with positive results, that support its use in this case. Based on this case, we strongly support the administration of EPO therapy in refractory AIHA.

Despite the benefits of EPO, there are some concerns about it: the price of the treatment, the cardiovascular risk associated and the effects in macrophages, which would increase the risk of Salmonella infections. Unlike the previous situation, other cases related with hemolytic anemia, like atypical hemolytic uremic syndrome, EPO therapy has been used without a positive results [20].

As an overall result, this case had some limitations: first,

Table 1: Patient's laboratory tests during hospital stay.

Laboratory test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Leukocytes U/L	6,100	4,400	8,300	8,000	6,200	6,200	4,300	4,200	5,300	5,500
Neutrophils U/L	4,800	3,600	7,800	7,200	5,700	5,600	3,700	3,800	4,600	4,600
Lymphocytes U/L	500	400	200	400	300	200	300	2.00	300	300
Red cell count mm³*	1,500	1,370	1,520	1,510	1,360	1,480	1,530	1,450	1,630	1,710
Hto %	17.8	16.1	17.6	17.3	15.5	17	17.3	16.7	18.6	19.4
Hb g/dL	5.8	5	5.7	5.5	4.9	5.2	5.6	5.1	6	6.3
MCV** fl	119	118	116	115	114	115	113	115	114	114
MCH pg	38.7	36.4	37.5	36.4	30.6	35.1	36.6	35.2	36.8	36.8
RDW %	14.7	16.3	14.7	15	16.1	15.9	15.5	16.7	15.4	15.6
Others	Transferrin 182.8 Haptoglobin <8 Ferritin 224.9 ng/dl	Factor C3 72 mg/dl Factor C4 11.8 ANAs and ENAs negative								
Important events			Start of methyl prednisolone	Start of EPO	Completion of methyl prednisolone		Completion of EPO			

there was not a measure of baseline erythropoietin level during the hospitalization, and second, after the hospital discharge of the patient it is unknown its evolution.

References

1. Anemia, Hemolytic, Autoimmune. MeSH. 2019.
   PubMed: https://www.ncbi.nlm.nih.gov/mesh/68000744
2. Kalfa TA. Warm antibody autoimmune hemolytic anemia. Hematol Am Soc Hematol Educ Program. 2016; 2016: 690–697.
   PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142448/
3. Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. Autoimmun Rev. 2014; 13: 560–564.
   PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24418298
4. Liebman HA, Weitz IC. Autoimmune Hemolytic Anemia. Med Clin North Am. 2017; 101: 351–359.
   PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28189175
5. Jaime-Pérez JC, Aguilar-Calderón P, Salazar-Cavazos L, Gómez-De León A, Gómez-Almaguer D. Treatment of autoimmune hemolytic anemia: real world data from a reference center in Mexico. Blood Res. 2019; 54: 131–136.
   PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31309092
6. Henriquez-Camacho C, Gotuzzo E, Echevarria J, White AC Jr, Terashima A, Samalvides F, et al. Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection. Cochrane Database Syst Rev. 2016; 2016: CD007745–CD007745.
   PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26778150
7. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. Blood. 2017; 129: 2971–2979.
   PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28360039
8. Salama A. Treatment Options for Primary Autoimmune Hemolytic Anemia: A Short Comprehensive Review. Transfus Med Hemotherapy Off Organ Dtsch Ges Transfusionsmedizin Immunhamatologie. 2015; 42: 294–301.
   PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678315/
9. Erythropoietin. MeSH. 2019.
   PubMed: https://www.ncbi.nlm.nih.gov/mesh/68004921
10. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Rev. 2012; 26: 107–115.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22330255
11. Berentsen S, Randen U, Tjønnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015; 29: 455–471.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26043385
12. Zeerleder S. Autoimmune haemolytic anaemia - a practical guide to cope with a diagnostic and therapeutic challenge. Neth J Med. 2011; 69: 177–184.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21527804
13. Hill QA, Hill A, Berentsen S. Defining autoimmune hemolytic anemia: a systematic review of the terminology used for diagnosis and treatment. Blood Adv. 2019; 3: 1897–1906.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31235526
14. Naik R. Warm autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015; 29: 445–453.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26043384
15. Brodsky RA. Warm Autoimmune Hemolytic Anemia. N Engl J Med. 2019; 381: 647–654.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/31412178
16. Barcellini W, Fattizzo B, Zaninoni A, Radice T, Nichele I, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood. 2014; 124: 2930–2936.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25232059
17. Arbach O, Funck R, Seibt F, Salama A. Erythropoietin May Improve Anemia in Patients with Autoimmune Hemolytic Anemia Associated with Reticulocytopenia. Transfus Med Hemotherapy Off Organ Dtsch Ges Transfusionsmedizin Immunhamatologie. 2012; 39: 221–223.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22851939
18. Nairz M, Sonnweber T, Schroll A, Theurl I, Weiss G. The pleiotropic effects of erythropoietin in infection and inflammation. Microbes Infect. 2012; 14: 238–246.
    PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278592/
19. Haley K. Congenital Hemolytic Anemia. Med Clin North Am. 2017; 101: 361–374.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28189176
20. Balestracci A, Martin SM, Toledo I, Alvarado C, Wainsztein RE. Early erythropoietin in post-diarrheal hemolytic uremic syndrome: a case-control study. Pediatr Nephrol Berl Ger. 2015; 30: 339–344.
    PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25138373