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Atypical Hemolytic Uremic Syndrome in a Patient with Acute Promyelocytic Leukemia: A Case Report

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Abstract

Introduction: Acute Promyelocytic Leukemia (APL) is highly associated with hemostasis alterations. The atypical hemolytic uremic syndrome (aHUS) is a rare type of Thrombotic Microangiopathy (TMA) due to an overactivation of the alternative complement pathway. **Case Presentation:** A 48-years-old woman was diagnosed with APL and achieved molecular remission after induction therapy. During the second consolidation cycle she presented with TMA. She began treatment with plasma exchange plus corticotherapy but due to aggravation of symptoms Eculizumab was initiated. Thrombotic thrombocytopenic purpura, infections and drug toxicity causes were ruled out. There was no evidence of relapse of the APL. Genetic studies of the hereditary anomalies of the alternative complement pathway were negative and the decision of stopping Eculizumab was made. During maintenance therapy for the APL she presented a severe relapse of the aHUS, requiring dialysis. She re-started treatment with Eculizumab with a progressive hematologic recovery and improvement of renal function. She completed APL treatment without relapse of the leukemia for the moment and continues to be treated with Eculizumab. **Conclusion:** This is the first published case of coexisting aHUS and APL successfully treated with Eculizumab.

Keywords

Atypical Hemolytic Uremic Syndrome, Acute Promyelocytic Leukemia

1. Introduction

The acute promyelocytic leukemia (APL) represent the 10% - 15% of the newly

diagnosed acute myeloid leukemia cases and results from a balanced translocation, t(15;17) (q22;q12-21), which leads to the fusion of the promyelocytic leukemia (PML) gene with the retinoic acid receptor alpha (RARα) gene [1]. It is well known that this type of leukemia is highly associated with hemostasis alterations at the time of diagnosis, specially hyperfibrinolysis, disseminated intravascular coagulation, and thrombocytopenia [2] and hemorrhagic death remains the main cause of induction failure [3] [4]. However, with current treatments, the overall survival of this type of leukemia is high (>90% at 3 years) [5] [6] compared to other types of acute leukemias. The most important step in preventing bleeding complications is the prompt treatment with all-trans retinoic acid (ATRA), with or without arsenic trioxide (ATO) together with supportive transfusions and repletion of coagulation factors [3].

Atypical hemolytic uremic syndrome (aHUS) is a rare and severe type of thrombotic microangiopathy (TMA) with a reported annual incidence ranging from 0.23 to 1.9 per million population. In 40% - 60% of the cases there is a genetic component that results in the overactivation of the alternative complement pathway [7]. These mutations are in the genes that encode complement regulatory proteins, Factor H, Factor I, membrane cofactor protein, complement 3 (C3), Factor B or thrombomodulin. In other patients the physiopathology is characterized by the presence of anti-FH antibodies resulting in activation of the complement system.

Clinically, it is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Kidneys are the most vulnerable organs affected which is mainly due to a dysfunction of endothelial cell exacerbated by anaphylatoxins (C3a and C5a) produced during complement activation and the formation of microthrombi in the kidney vasculature [8]. The diagnostic is made by excluding other causes of TMA, demonstrating preserved ADAMTS13 function and searching germline variants in complement genes or autoantibodies against complement regulatory proteins, which are present in 50% of the patients [9].

Treatment of aHUS is based on supportive care together with C5 inhibitors (Eculizumab or Ravulizumab) [9]. About 75% of patients achieve hematologic normalization and preservation of renal function with this treatment [8].

Although malignant hemopathies can be related to TMA syndromes, the APL is not specifically described as a triggering cause of HUS. Only 3 cases of coexistence of these two pathologies have been published and they were not treated with complement-blocking drugs.

The objective of this report is to present a rare case of coexisting APL and aHUS successfully treated with Eculizumab that can be useful to the reader as a recognition pattern to identify similar cases in their own practices.

2. Case Presentation

2.1. Diagnostic of Acute Promyelocytic Leukemia

We report the case of a 48-years-old French woman that consulted the emer-

gency service addressing asthenia, bone pain, generalized ecchymosis, fever and metrorrhagia.

She had a history of papillary carcinoma thyroid at 43 years old (treated by thyroidectomy and Iratherapy, under hormonal supplementation with thyroxine), cholecystectomy, and presence of cysts in ovaries. The family history was negative for hematological diseases.

In the laboratory workup at admission a deep pancytopenia was observed with 7 g/dL of hemoglobin, 15.000 platelets/mm^3, and 3.000 WBC/mm^3 with 73% circulating blasts and 370 neutrophils/mm^3. Renal and hepatic function were preserved. The coagulation laboratories showed no alteration.

Myelogram and molecular biology studies were performed in which acute promyelocytic leukemia PML-RARα positive was diagnosed.

Due to the presence of a white blood cell count lower than 10,000/mm^3 and an age under 60 years old, the patient belongs to the standard risk group for relapse.

The patient started induction chemotherapy treatment based on ATRA and Idarubicin together with transfusion support.

After the induction treatment the patients achieved hematological and molecular complete response with normalization of hemoglobin and platelet count. She received two consolidation cycles with ATO, anthracyclines and cytarabine.

During the first consolidation cycle she presented peri-catheter axillary thrombosis treated with low molecular weight heparin.

2.2. Development of Thrombotic Microangiopathy and Initial Treatment

The patient began maintenance treatment with ATO, 6-mercaptopurine and methotrexate. Four weeks later she presented with clinical deterioration, vomiting and jaundice. Blood examination showed 10.3 g/dL of hemoglobin, 36.000/mm^3 platelets, 5700 WBC/mm^3, renal impairment (creatinine 133 μmol/L) and alteration of hepatogram (ASAT 96 UI/l, ALAT 107 UI/l) with a undetectable dosage of methotrexate.

24 hours after she had aggravation of the anemia (Hemoglobin 6.9 g/dL) and thrombopenia (platelets 4.000/mm^3), increased analytical parameters of hemolysis (undetectable haptoglobin and 2.5% of schistocytes) and progressive deterioration of renal function (creatinine 276 μmol/l) with preserved diuresis, without alteration of general hemostasis tests. No neurological symptoms were detected.

Considering the presence of signs compatible with TMA, the patient was transferred to the Intensive Care Unit and a determination of ADAMTS-13 activity was performed. Drug-related toxicity causes of TMA were ruled out, including methotrexate dosage which was negative. The Shiga toxin test was negative as well as HIV serology. There was no evidence of relapse of her APL as the PML-RARα was negative. She did not present clinical signs of bleeding.

The patient continued with progression of anemia (Hemoglobin 5.6 g/dL) and thrombocytopenia (1.000 platelets/mm^3) and creatinine increase, so she started

emergency treatment with daily plasma exchange plus corticotherapy. There was no significant improvement with this therapy.

The result of the ADAMTS13 enzyme activity dosage was 83% and the CH50 dosage was 16% (reference range 70% - 100%). The diagnosis of aHUS was made as other causes of TMA were ruled out.

The patient was transferred to a high complexity hospital where she started treatment with Eculizumab showing a clear clinical and analytical improvement, with initial recovery of blood count and renal function.

Complement system blockade was confirmed by Eculizumab dosing.

Antibacterial prophylactic treatment was performed with Oraciline and immunizations against encapsulated germs were applied.

However, the genetic study of the hereditary anomalies of the alternative complement pathway were negative (Factor H, MCP/CD46, Factor I, Factor B, C3, DGKE, CFHR and thrombomodulin) and there were no evidence of anti-factor H antibodies. Five months after the first application of the drug, the decision to discontinue treatment with Eculizumab was made.

2.3. Recurrence of Atypical Hemolytic Uremic Syndrome

After 4 months from discontinuation of Eculizumab, the patient presented a relapse of TMA with a severe renal involvement requiring hemodialysis. When the humanized monoclonal antibody against complement C5 treatment was restarted, the patient showed a favorable evolution with progressive normalization of blood count and improvement of renal function (creatinine 91 μmol/l) achieving the suspension of dialytic support.

The patient developed arterial hypertension that was controlled with a low dose of angiotensin-converting enzyme inhibitor.

Considering that the patient presented a recurrence with very severe renal involvement that responded favorably to treatment, the decision to continue with the treatment every 15 days was taken.

Despite the high risk of infections that patients under treatment with eculizumab have, the patient presented only recurrent episodes of urinary infection by *Escherichia coli* treated with oral antibiotic therapy and hygienic and dietary measures.

2.4. Evolution and Follow-Up

The patient resumed maintenance therapy for her leukemia 6 months after the aHUS and she occasionally required red blood cell transfusion due to anemia secondary to the toxicity of such treatment, with no signs suggestive of hemolysis.

She has been in complete molecular response for 3 years since le diagnosis of the APL. After 2.5 years since the diagnosis of aHUS, the patient continues under Eculizumab, maintains a creatinine 91 μmol/l, clearance of 64 ml/min; hemoglobin >14 g/dL and platelets >200,000/mm^3.

The patient remains under C5 inhibition and clinical-analytical controls,

without complications requiring hospitalization in relation to her treatment and pathology and with good quality of life.

3. Discussion

TMA is frequently associated with the malignant hemopathies, the treatments used (chemotherapies, bone marrow transplantation), and the associated complications (infections). In this setting, the diagnosis of aHUS is much less straightforward for patients with these comorbid conditions, are more difficult to handle, and require multidisciplinary work.

The diagnosis of aHUS relies on the absence of associated disease, no criteria for Shiga Toxin-HUS, and not meeting the criteria for thrombotic thrombocytopenic purpura (serum ADAMTS 13 activity <10% excludes the diagnosis of aHUS) [10]. TMA with comorbidities (eg. pre-existing nephropathy, autoimmune diseases, malignancy, hemopoietic stem cell transplantation) can exclude an aHUS diagnosis [7]. In the case presented the patient had a history of malignancy, however, APL is a disease that does not belong to the group of pathologies with a clear causal relationship to cause TMA. Moreover, the patient was in complete molecular remission of her leukemia at the time of manifesting the aHUS. Therefore, we do not consider it to be a case of TMA secondary to this patient's APL.

Ruling out pharmacological causes of TMA requires multidisciplinary work together with the pharmacovigilance team. In the presented case, the causal relationship with methotrexate was ruled out since the methotrexate dosage was negative at the time of the development of aHUS. All other chemotherapies that the patient was receiving (Mercaptopurine and ATRA) do not appear to be associated in the literature with the occurrence of HUS.

Our review of the literature identifies 3 reported cases of coexistence of APL and suspected aHUS. Candoni *et al.* reported in 2004 a case of a 68-years-old woman with clinical findings compatible with aHUS during induction therapy in which the patients died 5 weeks after the diagnosis [11]. Breccia *et al.* presented a case of a 47-years-old man with APL and a retinoic acid syndrome mimicking the haemolytic uremic syndrome during induction therapy [12]. Polania-Rusiilo *et al.* published in 2013 the case of a 37-years-old man with a TMA at the time of diagnosis of APL who developed renal cortical necrosis [13]. These published cases did not report the performance of genetic studies or dosage of ADAMTS13 activity to rule out other causes of TMA. To the best of our knowledge, this is the first published case of the presentation in a patient with a PML under maintenance treatment successfully treated with Eculizumab.

Multicenter studies are required to assess whether there is a causal relationship between these two pathologies or whether this is a random isolated case.

The patient presented had a negative test for mutations that causes dysregulation of the complement alternative pathway, but these alterations are detected only in 40% - 60% of patients with aHUS [14] as presently available laboratory tests do not identify all patients with defective complement regulation.

Therapeutic terminal complement blockade at the level of C5 with Eculizumab changed the natural history of complement mediated HUS, reducing the percentage of mortality or acquired end-stage renal disease within 1 year of diagnosis from 50% to 15%. The clinical improvement is usually observed in the first weeks after C5 inhibition, achieving a complete or near complete response after 3 to 6 months of therapy [9].

The adult treatment protocol consists of four weekly 900 mg doses, followed by a maintenance 1200 mg doses every two weeks. There is no consensus on the duration of therapy [15]. The literature published support the practice of early Eculizumab initiation and a trial of cessation with regular monitoring when patients achieve clinical remission. In case of recurrence, restarting terminal complement inhibition is the most cost-effective treatment as it permits recovered renal function in virtually all patients [9] [15]. Our patient presented a relapse of aHUS after discontinuation of treatment and the response to the restart of treatment was satisfactory, allowing her to complete the treatment of her APL.

There is no previously published literature on the use of Eculizumab in patients with aHUS presenting simultaneously with APL. The question of whether this is a concomitant coincidental presentation or a causal relationship between the two pathologies cannot be answered. The presented case could serve as an example of therapeutic management for future similar cases, although controlled clinical trials are required to establish recommendations based on solid clinical evidence.

4. Conclusions

The importance of the presented case lies in the coexistence of two rare and severe hematologic pathologies (LPA and aHUS), with similar clinical presentations but with different molecular bases.

This is the first published case in which a successful treatment of aHUS with Eculizumab is performed in the context of a patient undergoing chemotherapy treatment for APL.

Studies are needed to evaluate the relationship between these two diseases in order to achieve a better understanding of their biology and to optimize the therapeutic management of complex cases such as the one presented.

Informed Consent

The patient's oral consent was obtained for the publication of this case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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