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# Prophylactic Eculizumab Use in Kidney Transplantation: A Review of the Literature and Report of a Case with Atypical Hemolytic Uremic Syndrome

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**Background:** Atypical hemolytic uremic syndrome (aHUS) is a very rare disease, which presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Progression to end-stage renal disease (ESRD) from acute kidney injury is observed in 60% of aHUS cases. The prognosis of aHUS patients who undergo kidney transplantation (Ktx) is generally poor, but these patients should be treated prophylactically with eculizumab to prevent recurrence after transplantation.

**Case Report:** An 18-year-old man was referred to our center with a history of rapid progression to ESRD with unknown etiology. He had anemia, thrombocytopenia, high levels of LDH, and indirect bilirubin and creatinine on initial laboratory results. Our diagnosis was aHUS due to initial results, normal level of ADAMTS activity, and lack of predisposing factors seen in typical HUS. We planned to perform genetic analysis for the patient and the donor candidate (mother). The variations found on exon 7 of the CFH gene had not been reported previously. According to PolyPhen analysis, this mutation was reported as a potential cause for aHUS. We decided to perform Ktx under eculizumab prophylaxis. Weekly administration of prophylaxis was extended to 1 month. The graft functioned immediately after Ktx. The patient has completed his first year uneventfully in our follow-up, with a creatinine 0.79 mg/dl at his last control visit.

**Conclusions:** We found favorable results of an aHUS case successfully treated with kidney transplantation combined with short-term prophylactic eculizumab therapy.

**MeSH Keywords:** **Complement C5 • Hemolytic-Uremic Syndrome • Kidney Transplantation**

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## Background

Hemolytic uremic syndrome (HUS) is a rare disease characterized by the triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia (TCP), and acute kidney injury (AKI), with an annual incidence of 6.1 cases per 100 000 children aged less than 5 years. Its overall incidence including adults is 1 to 2 cases per 100 000 [1].

Typical (acquired) HUS is triggered by infectious agents that produce powerful Shiga-like exotoxins (STEC-HUS), whereas atypical HUS (aHUS) develops as a result of genetic or acquired conditions or can be idiopathic [1–3]. Atypical HUS, with an overall incidence of 1–2 cases per 100 000, is usually classified as a very rare disease [4]. The primary kidney pathology is thrombotic microangiopathy (TMA), frequently accompanied by acute kidney injury in aHUS [5]. A progression to end-stage renal disease (ESRD) from acute kidney injury is observed in 60% of aHUS cases, and mortality rate can be as high as 8% [1,4–6]. Atypical HUS is a catastrophic disease that can result in sudden and progressive vital organ failure and premature death [7,8].

Generally, STEC-HUS, aHUS, and thrombotic thrombocytopenic purpura (TTP) are all diseases of complement activation [9]; however, plasma exchange (PE), which is the standard treatment for TTP, has a limited role for patients with a diagnosis of aHUS [10], and there have been no well-controlled trials showing PE or plasma infusion (PI) to be either safe or effective in aHUS [7]. Eculizumab (ECU), a first-in-class humanized monoclonal anti-C5 antibody that has been successful in the treatment of paroxysmal nocturnal hemoglobinuria, a disorder of complement-induced hemolytic anemia, received approval for the treatment of aHUS in the US and EU in late 2011 [11,12]. ECU binds specifically to the complement protein C5, halting the complement cascade and inhibiting production of cell-killing protein complexes [13]. All relevant prospective controlled studies [14] have documented the efficacy of ECU in the treatment of aHUS. ECU directly inhibits the activation of the membrane attack complex (MAC) through C5 and has achieved encouraging outcomes in all series [14]. ECU efficacy was also documented in aHUS recurrence after renal transplantation [15].

Recent studies have documented a mutation in proteins involved in complement C3 and complement regulatory proteins, such as complement factor H (CFH), I (CFI), B (CFB), and membrane cofactor protein (MCP), in more than 50% of aHUS patients [16]. CFH, MCP, CFI, C3, CFB, thrombomodulin (THBD), and complement factor H-related (CFHR) proteins 1, 3, and 4 are the most common mutations. CFH-dependent mutations, which are among the major regulators of the alternative pathway, are the most frequently observed group [17,18], with high

recurrence rates and predictor of negative response to therapy. CFH mutation is also a bad prognostic factor for kidney transplantation; graft dysfunction develops in 80% of the patients within 2 years [19].

Currently, kidney transplantation is accepted as the best treatment modality for ESRD. However, patients with aHUS who undergo kidney transplantation have a poor prognosis, and they are at high risk for recurrence, which is associated with graft loss [19,20]. Patients with a documented mutation in complement regulatory proteins (with the exception of MCP) have especially high risk, which ranges from 45% to 90% [1,21–23]. The process of recurrent aHUS is difficult to treat. Although PE and PI have been successful in some patients with aHUS in the past [5,24], many patients do not respond (are resistant) or need continued weekly treatment (are plasma-dependent). There are no well-controlled trials showing PE or PI to be either safe or effective in aHUS [7]. Prophylactic plasma therapy in kidney transplantation seemed to reduce the risk of aHUS recurrence, but without reaching statistical significance, in a retrospective study [21]. An alternative option is liver-kidney transplant, but it can only be used in a restricted group of patients; therefore, aHUS patients usually are not offered transplantation and these patients may have to remain on dialysis therapy for the rest of their lives. The entrance of ECU in clinical practice has raised a hope for patients with aHUS, particularly for patients who are awaiting kidney transplantation. There are many case reports documenting favorable response to ECU in patients with recurrent aHUS after transplantation [25–27]. Many patients have been transplanted successfully with ECU given prophylactically. Experts now recommend prophylactic treatment with ECU for all aHUS patients who are at medium or high risk for disease recurrence after transplantation [15].

In this paper, we present a new case of aHUS patient, who underwent successful kidney transplantation in our center with the use of prophylactic ECU therapy.

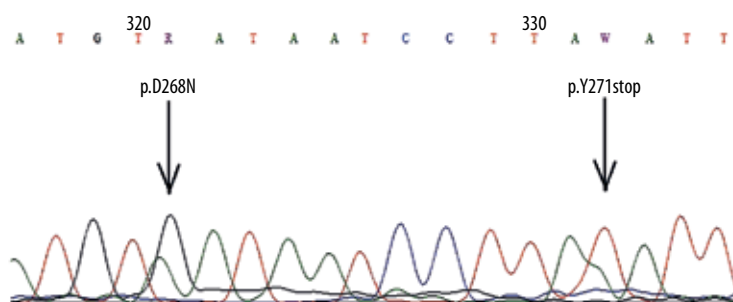
## Case Report

We herein report the case of an 18-year-old Kosovan male patient referred to our department 5 March 2014 for kidney transplantation from a medical center in his home town Pristina, Kosovo.

According to medical history, his symptoms rapidly progressed to ESRD, and he started to have hemodialysis (HD) eight months ago. At initial diagnosis his hemoglobin, platelet, indirect bilirubin, LDH, BUN and creatinine levels were 6.6 g/dL, 100.000/mm<sup>3</sup>, 2.9 mg/dL, 660 IU/L, 98 mg/dL, and 13 mg/dL, respectively. His renal ultrasonography showed bilaterally echogenic kidneys, and his serum C3 and C4 levels were normal.

**Table 1.** Identified variants on CFH gene.

Exon	DNA sequence variation	Effect	Reference
7	Heterozygous	p.D268N	–
7	Heterozygous	p.Y271X	–
9	c.1204C>T, homozygous	p.H402Y	rs1061170
10	c.1419 G>T, heterozygous	p.A473A	rs2274700
12	Heterozygous	p.Q672Q	rs3753396

**Figure 1.** Stop kodon mutation on exon 7.

During hospitalization there were no laboratory evidence for intravascular hemolysis, and LDH, C4, platelet, and bilirubin levels were normal but C3 level was 69 mg/dl (82–182). We considered HUS for the ESRD etiology because the case was presenting the classical triad of the disease. We ruled-out typical HUS, as there were no predisposing factors such as drug usage, infection, and diarrhea in his detailed medical history. Also, because ADAMTS13 levels within normal ranges, we ruled-out TTP.

As pre-transplant evaluation, we performed genetic analysis bearing in the mind that complement genes strongly predict graft outcome and recurrence as well in renal transplant recipients with aHUS. His mother agreed to be the donor, and HLA compatibility and lymphocyte cross-match tests were performed. Genetic analysis of the donor candidate (mother) was done for a possible mild form of aHUS, which we could not determine from her medical history. He had 2 mismatches and 1 negative cross-match test with the donor.

Subsequently, for genetic analysis, exons identified by using genomic DNA as a template were amplified and sequenced, including the non-coding regions that are approximately 20 base-pairs long. Sequence data obtained were then compared to reference sequences. Three variants that usually do not lead to aHUS were identified on CFH gene (Table 1). Two of these variations were found to be synonymous mutations, and they were not expected to lead any amino acid changes (p.Q672Q and p.A473A); p.H402Y variation on exon 9 was indicated to be a polymorphism, which can be observed also in healthy

individuals. However, variations on exon 7 were absent from both the literature and the database. It was also determined that p.Y271X (p.Tyr271stop) mutation on exon 7 generated a stop codon that may lead to the formation of a short form of the protein (Figure 1). CFI gene analysis was normal.

According to PolyPhen analysis and 3D modeling, this mutation was reported as a potential causative agent for aHUS. No mutations were detected by genetic analyses carried out on the mother (donor) and the father.

Transplantation was delayed approximately 14 weeks after admission as we awaited genetic testing and ECU availability. Until 17 June 2014 (transplantation day) we continued HD therapy 3 times weekly. Starting from hospitalization, we also started to use sevelamer hydrochloride and calcitriol orally 3 times daily and erythropoietin injection intravenously 3 times weekly. No drug- and HD-related adverse effects were seen during this period.

ECU prophylaxis was selected for follow-up procedure after renal transplantation. Before starting ECU, informed consent was obtained.

Currently, the drug is not registered in Turkey and we must have medical and ethical approval from the health authority (Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy) in order to use ECU. After he has been vaccinated with meningococcal, pneumococcal, and influenza vaccinations, we administered 900 mg ECU preoperatively. Weekly

administration of this prophylaxis dosage was extended to 1 month (total 5 doses). He did not receive any plasma exchange or infusion.

For immunosuppression, we used tacrolimus 1 mg orally twice daily, mycophenolate mofetil 1000 mg orally twice daily, and a rapid discontinuation of prednisolone protocol (starting with 500 mg intravenous on transplantation day, and tapering the dosage to 30 mg orally on postoperative day 10). We also used once-daily oral valganciclovir 450 mg, trimethoprim, nystatin for prophylaxis and lansoprazole orally once daily for gastroprotection.

There was no problem during the operation. The graft functioning was determined to be normal following transplantation; creatinine levels were 2.8 mg/dL, 1.1 mg/dL, and 0.98 mg/dL on day 1, day 4 and day 7, respectively. In the next week his vital signs and all laboratory parameters were good and his graft function remained excellent. Therefore, we discharged the patient on 30 June 2014 (14 days after transplantation) and sent him to his home country, Kosovo.

We are following the case with weekly laboratory parameters that are done at Kosovo. Follow-up visits were done 3 and 6 months after transplantation. One year after transplantation, the patient had no signs of anemia or thrombocytopenia; LDH and bilirubin levels were normal, and his creatinine level was 0.76 mg/dL. Therefore, we discontinued valganciclovir, tmp/smx, and nystatin at the 6-month follow-up visit.

## Discussion

The differential diagnosis of 3 entities with similar clinical pathology – HUS, aHUS, and TTP – can be challenging for clinicians. Although the neurological symptoms are major criteria for TTP diagnosis, they can also be detected in HUS and, less frequently, in aHUS cases [28]. In our case, the ADAMTS13 level was detected to be within normal ranges; therefore, we ruled-out TTP [29]. For HUS, diagnosis might not always be possible through clinical, anamnestic, or laboratory tests. Diarrhea is a crucial parameter in the discrimination of typical and atypical cases. However, it should be noted that non-bloody diarrhea can be among the initial symptoms of aHUS in 15–39% of cases [30,31].

Genetic mutations, which are abundantly encountered in aHUS patients are not always necessary for diagnosis, and they do not provide short-term results. Nevertheless, genetic testing is necessary in patients who are about to undergo transplantation from a first-degree relative.

Mutations related to distinct complement factors have been discovered in almost 70% of patients diagnosed with aHUS, 30% of them being CFH mutations. The majority of these mutations are loss-of-function mutations [32]. Yet, mutations in combination with other factors – CFH/CFH-related protein hybrid gene formation, as well as antibodies against CFH – may all contribute to the pathogenesis of aHUS [33]. Disease activation is observed in 50% of the mutation-bearing family members of the patients diagnosed with atypical HUS [34,35]. The database of genetic mutations is expanding each day, with developments that enhance the depth of this field. The relation between disease and novel mutations not yet recorded in the literature will be documented by future reports of rare cases. Occasionally, administration of prophylactic ECU may conceal this relationship.

Hypertension, infections, pregnancy, medications, surgery, and stem cell transplantation are among the etiological factors [36]. Nevertheless, the fact that genetic tests are not a necessity for treatment, and that they are not applicable to every patient, suggests that the remaining etiologies are less important than anticipated.

Although plasmapheresis treatment has been used, prognosis is considerably unfavorable with native kidneys and in aHUS that develops after transplantation. Long-term follow-ups show that risk of death and ESRD reach 80% in patients who develop aHUS in a native kidney, due to a CFH mutation [23,33]. Relapse rates of 50–60% has been observed following renal transplantation. The average period of relapse is 1–3 months and the related graft loss rate was reported as 60% [23]. Though plasmapheresis is not successful in the treatment of relapses after transplantation, these relapses have been shown to be significantly hindered through successive plasmapheresis applied pre-transplantation [36,37].

Studies have shown that anti-C5 antibody ECU is effective in aHUS cases that develop in native and transplanted kidneys [15,38–40]. Similarly, it has been demonstrated that administration of prophylactic ECU prevents relapse in all transplants with aHUS diagnosis [16]. It is generally accepted to initiate infusions within the first week. Even though it is well tolerated, the major risk for ECU therapy is infection. Meningococcal, pneumococcal, and influenza vaccination are recommended prior to ECU therapy in pediatric patients. In adults, however, meningococcal vaccination is sufficient [31].

Transplantation from a living donor is recommended. Prolonged cold ischemia and immunological problems encountered in cadaver donors increase the likelihood of aHUS recurrence. Likewise, it is generally accepted that first-degree relatives should be avoided as donors in aHUS cases [41]. Only after detailed genetic analysis is it possible for the mother, father,

and siblings to become donors. Even though the donor was the mother in our case, in-depth genetic analysis was applied both on the mother and the father, and all possible risks have been excluded, in all aspects.

It is well known that ECU enables transplantation in ESRD patients diagnosed with aHUS. Another alternative in this regard is the tandem transplantation of liver and kidney; however, the applicability of this method is restricted to certain patient groups [42]. Although the apparent increase in genetic mutations, together with their etiological roles, is in correlation with the developments related to this field, they bring about certain concerns, such as the duration and cost of the therapy.

The ideal procedure in transplantation is a weekly dosage of 900 mg for the first 4 weeks, with 1200 mg on week 5 and once every 2 weeks in perpetuity [43]. Nevertheless, the annual cost of medication is a major drawback. Thus, only the first 5 doses could be given in this case.

Another point is the necessity of prophylaxis procedures. Studies show that fast diagnosis and ECU therapy are as effective as prophylaxis on relapses that develop after transplantation [16,44]. Relapse has been detected in 3 out of 10 aHUS-diagnosed patients being followed without treatment but who had already undergone initial ECU therapy after transplantation. Recovery in all parameters has been achieved after supplemental doses of ECU in patients who performed urinary hemoglobinuria scanning by means of dipstick at home [44]. A critical point in this respect is the rate of access to early diagnosis and treatment, especially for patients unable to receive continuous therapy.

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Checking non-genetic factors has also proved to be a significantly preventive approach. Keeping the donor's ischemic period short, minimizing the risk of acute rejection, applying minimal or no doses of calcineurin and mTOR inhibitors, and optimizing hypertension and volumetric control have been demonstrated to increase the success of transplantation, even in the absence of ECU treatment [41,45].

Despite financial drawbacks, being pivotal in responding to problems accompanied by various complement-related mechanisms, apart from aHUS and PNH therapies, ECU utilization is usually the sole treatment. However, although ECU seems to be the absolute cure for TMA-related diseases, questions regarding the ideal procedure to follow are in accordance with health policies and supplies that differ among countries.

## Conclusions

We found favorable short-term results with prophylactic ECU, although we used just the initial phase of the dosing regimen. We believe that more studies are needed to determine the optimum dosage and duration of prophylactic treatments including eculizumab for a successful kidney transplantation for aHUS patients. There is still much research to be performed in order to precisely determine the dosage and length of treatment with this drug. Therefore, we believe that further research is needed to determine whether ECU is useful for successful transplantations, and controlled randomized trials, including cost-effectiveness studies, are necessary.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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