Annals of Clinical and Medical Case Reports

Case Report

ISSN 2639-8109 | Volume 5

Atypical Haemolytic Uraemic Syndrome with Isolation of Aepec in the Stool Culture

García SN[1*], Fernández PC[2] and López LG[3]

[1]Servicio de Nefrología del Hospital Universitario Clínico San Carlos de Madrid, Spain

[2]Servicio de Nefrología del Hospital General Universitario de Ciudad Real, Spain

[3]Servicio de Anatomía Patológica del Hospital General Universitario de Ciudad Real, Spain

***Corresponding author:**

Loles Sanchez de la Nieta,
Servicio de Nefrología del Hospital Universitario Clínico San Carlos de Madrid, Spain,
Email: lsanchezdelanieta@icloud.com

Received: 11 Jan 2021
Accepted: 28 Jan 2021
Published: 01 Feb 2021

Citation:

García SN. Atypical Haemolytic Uraemic Syndrome with Isolation of Aepec in the Stool Culture. Ann Clin Med Case Rep. 2021; V5(10): 1-4.

1. Abstract

Thrombotic Microangiopathy (TMA) is based on a vascular endothelial injury and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ malfunction of variable intensity. The etiology includes Thrombotic Thrombocytopenic Purpura (TTP); Hemolytic Uremic Syndrome (HUS), caused by Shiga Toxin-Producing Escherichia Coli (STEC) in 90% of cases; atypical Hemolytic Uremic Syndrome (aHUS), and secondary TMA. Eculizumab is a humanized monoclonal antibody that inhibits the activation of C5 and blocks the formation of the cell membrane attack complex. The efficacy of eculizumab has been demonstrated in aHUS, and recently in secondary TMA.

A case of TMA is described in a 27-year-old woman who suffered diarrhea and vomiting after a programmed hemithyroidectomy. Atypical Enteropathogenic Escherichia Coli (aEPEC) was isolated in the stool culture, and normal result for ADAMTS-13 activity was obtained. We performed genetic and functional complement activity analysis for known mutations with negative result, suggesting a secondary cause of aHUS. The patient showed clinical and analytical recovery after Eculizumab.

EPEC and STEC have the same pathophysiological mechanism characterized by diarrhea, and they share negative “bpf” and positive “eae” genes. The difference between them is that EPEC strains lacks the gene that encodes Shiga toxin. Some authors claim that STEC can become atypical EPEC during infection due to the loss of mobile genetic elements such as verotoxin-encoding plasmids or bacteriophages. Therefore, we propose the possibility of being the first case of HUS due to STEC, in which during the infection process, it has lost these genetic elements isolating aEPEC in the stool culture.

Introduction:

Thrombotic Microangiopathy (TMA) is based on a vascular endothelial injury and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ malfunction of variable intensity [1]. The etiology includes Thrombotic Thrombocytopenic Purpura (TTP); Shiga Toxin–Producing Escherichia Coli Hemolytic Uremic Syndrome (STEC-HUS); atypical hemolytic uremic syndrome (aHUS) due to a dysregulation of the alternative pathway of the complement system, leading to uncontrolled activation of C5 and the formation of the cell membrane attack complex. In addition, TMA can be secondary to different triggering factors such as viral infections, neoplastic processes, drugs, malignant arterial hypertension, bone marrow or solid organ transplantation, pregnancy, postpartum, autoimmune systemic diseases or glomerulonephritis [2]. In some patients it is not possible to find any of the aforementioned causes of TMA, while in others more than one etiology may coexist, leading to a heterogeneous clinic and a difficult diagnosis [3].

Eculizumab, a humanized monoclonal antibody that inhibits the activation of C5 and prevents the formation of the cell membrane attack complex, has demonstrated its efficacy in the treatment of aHUS, and recently in secondary TMAs refractory to the treatment of the TMA-inducing condition [2, 3]. The scientific evidence shows common pathophysiological mechanisms between aHUS and other secondary TMAs in which endothelial injury occurs due to complement activation. This explains the efficacy of Eculizumab in patients with secondary TMA and makes it a treatment option [2, 3].

We describe a case of TMA that presented diarrhea and vomiting, in which atypical Enteropathogenic Escherichia Coli (aEPEC) was isolated in the stool culture. We treated with Eculizumab resulting on a clinical and analytical remission, which remained even after eculizumab discontinuation.

2. Case Report

A 27-year-old woman undergoing scheduled left hemithyroidectomy surgery due to thyroid nodule. In the immediate postoperative period, she presented nausea, vomiting, bilateral lumbar pain and anuria. Physical examination revealed temperature of 36.6ºC, blood pressure of 150-160 / 90-100 mmHg, heart rate 90 bpm and basal oxygen saturation 98%. The cardiopulmonary auscultation: bibasal crackles. The abdomen palpation: Soft, nontender, positive bilateral renal fist percussion. The examination of the extremities showed no edema or skin lesions. In blood tests, blood count: 13,800 leukocytes (91% segmented), hemoglobin 10.2 mg / dl, MCV 88.9 fl., 32,000 platelets / µl. Coagulation test with normal results. Biochemistry: creatinine 5.25 mg / dl, urea 92 mg / dl, total bilirubin 2.3 mg / dl, albumine 2.7 g / dl, LDH 3006 IU / L, CPK 276 IU / L, GOT 149 IU / L, GPT 42 IU / L, amylase 110UI / L, ions in normal range, C-reactive protein 9.1 mg / dl. Venous gasometry with normal results. Abdominal ultrasound and subsequently abdominal CT scan showed multiple irregular areas of cortical hypocaptation in the renal cortical, several of them with slight bulging of the surface, to rule out multiple non-abscessed pyelonephritic areas versus cortical infarction. She was transferred to the Intensive Care Unit (ICU). Urine and blood cultures were requested with negative results. She started with diarrhea, therefore stool culture and immunological study were requested. We obtained the pathological result of the surgical piece of the thyroid: nodular hyperplasia. The result of the immunological study revealed: C3 79.4 mg / dl, with normal result for C4, immunoglobulins G, M, A and proteinogram. ANA, ANCA, lupus anticoagulant, IgM and IgG anticardiolipin antibodies, with negative results. Serology for HBV, HCV, HIV, CMV and EBV negative. Direct Coombs was negative, with undetectable haptoglobin and presence of 3-4% of schistocytes in blood smears. On suspicion of hemolytic uremic syndrome, and with the result of the stool culture still pending, ADAMTs 13 was requested and plasmapheresis was initiated. Hemodialysis was also performed due to anuric renal failure. She received 2 hemodialysis sessions and 3 plasmapheresis sessions on consecutive days, with poor clinical evolution, maintaining microangiopathic hemolytic anemia and thrombocytopenia. Afer that we obtained a result of normal ADAMTs 13 activity. On suspicion of atypical hemolytic uremic syndrome, Eculizumab 900 mg / week was started, after requesting a genetic and functional complement activity analysis. After the first dose of Eculizumab the patient presented progressive analytical improvement and onset of urine output, so after 5 days in the ICU she was discharged to nephrology department. When she started to urinate, urinalysis was requested. Urine protein / creatinine ratio result was 1.21 mg / mg, and in the sediment there were 5-10 red blood cells / field, but in that moment the patient was on her period. Stool culture presented positive result for Escherichia coli, with specific pathogenicity group: atypical Enteropathogen (aEPEC), with a positive result for Intimin gene (eae gene); being negative the result for the rest of genes: Type 1verotoxin, Type 2 verotoxin, CVD432 plasmid, ipaH gene, thermostable toxin (st gene), thermolabile toxin (lt gene) and Adhesin (bfp gene). Renal biopsy: in optical microscopy 27 glomeruli were observed, with global sclerosis in 3 of them. Fibroedema of the mesangial matrix was noticed in hematoxylin-eosin, without an increase in mesangial cellularity. Images of mesangiolysis, capillary dilation and focal thickening of glomerular basement membranes, with images reminiscent of double contours and glomerular arteriole fibrosis. No thrombi in glomerular nor extraglomerular vessels were identified. The interstitium showed mild fibrosis and inflammation of the mononuclear cell, being remarkable the tubular involvement showing acute tubular necrosis. In direct immunofluorescence: no glomerular deposits were observed with any of the studied antiserum (IgG, IgA, IgM, C3, C1q, kappa and lambda) (Figure 1). All this suggested a pathological diagnosis of moderate acute tubular necrosis. There were no active lesions of thrombotic microangiopathy, but there were focal images of mesangiolysis, mesangial fibroedema and double contours. These findings, although nonspecific, were compatible with residual post-treatment lesions of hemolytic uremic syndrome. In electron microscopy there were not relevant findings. The patient recovered normal renal function after the 3rd dose of eculizumab, with creatinine 0.93 mg / dl. After one month of hospital admission, at discharge, the analysis showed hemoglobin 10.3 mg / dl, platelets 270,000 / µl, creatinine 0.75 mg / dl, normal urine sediment and protein / creatinine ratio 0.12 (Table 1). During the follow-up, we obtained the result of the genetic study and functional complement activity analysis: no abnormalities in complement proteins in biochemical and immunological analysis, nor pathogenic variants in complement genes that are involved with the development of aHUS, concluding that the molecular and genetic study suggested a secondary form of aHUS.

The patient, who was diagnosed with acute renal failure due to acute tubular necrosis with aHUS or TMA secondary to aEPEC infection, was finally recovered. She received Eculizumab for 4 months (total 9 doses). Eleven months after recovering renal function and eight months after withdrawing treatment with Eculizumab, she maintains normal values in blood and urine analysis, with normal renal function (Table 1). She has been in follow-up in the nephrology unit first every fifteen days, then monthly and currently every 3 months.

3. Discussion

The triad of non-immune haemolytic anaemia, thrombocytopenia, and acute renal failure, should make us rule out TMA and make a differential diagnosis that establishes the most probable etiology [3]. The result of ADAMTS13< 5-10% is used in the diagnosis of PTT. The isolation of STEC in the stool culture in patients with TMA diagnoses STEC-HUS. The diagnosis of aHUS is made essentially by exclusion, once a deficit of ADAMTS13 (PTT) or STEC infection (STEC-HUS) are ruled out. In addition, before diagnosing aHUS, it is necessary to carry out additional studies to rule out secondary causes of TMA, and perform genetic and functional complement activity studies, considering specific treatment with Eculizumab if the suspicion of aHUS is high [1-4].

In our case, the patient has nausea and vomiting, bilateral lumbar pain, microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Suspecting TMA, ADAMTs 13 is performed with normal result, and in stool culture aEPEC is isolated, which is a strain of E. coli that does not produce Shiga toxin, so PTT and STEC-HUS are initially ruled out. In treatment, plasmapheresis is initiated, without clinical or analytical improvement, so a complementary study is requested and treatment with Eculizumab is initiated. Causes of currently known secondary TMA are ruled out: viral infections, neoplastic processes, drugs, cobalamin C deficiency, malignant arterial hypertension, transplantation, pregnancy or autoimmune diseases.

Table 1: Improvement of blood and urine tests after starting treatment with Eculizumab

	09/13/2018 (first day of admission)	9/15/2018 (First dose of Eculizumab)	09/22/2018 (Second dose of Eculizumab)	09/29/2018 (Third dose of Eculizumab)	10/05/2018 (Fourth dose of Eculizumab)	December 2018 (Nineth dose of Eculizumab)	Currently (August 2019)
Anemia (g/dl)	**10.2**	**7.8**	**8.3**	**8.4**	**8.2**	13.3	13.6
Platelets (miles/µl)	**32**	**43**	438	470	266	328	317
Creatinine (mg/dl)	**5.25**	**5.85**	**5.57**	**3.39**	0.93	0.76	0.81
Urea (mg/dl)	94	109	93	106	34	36	36
LDH (UI/L)	**3006**	**1641**	**424**	168	125	133	133
Bilirrubin (mg/dl)	**2.3**	**2.1**	0.7	0.4	0.5	0.3	0.3

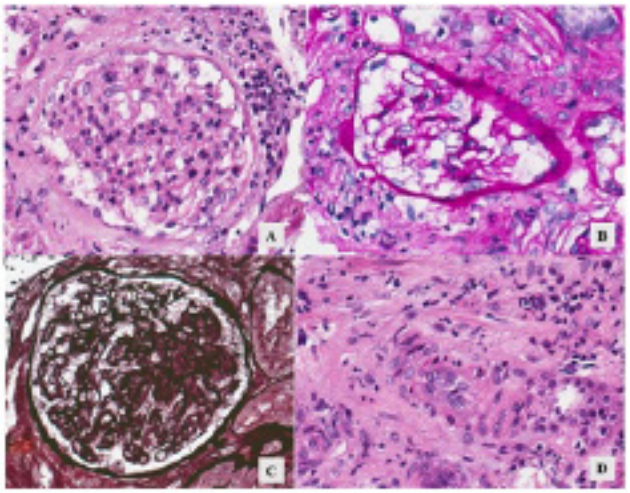

Figure 1: Renal biopsy. A. Representative image of most of the glomeruli with preserved architecture without active lesions due to TMA. HE x20. B. Mesangiolysis observed in a glomerulus. PAS x20. C. Glomerulus with the appearance of double contours. Methenamine silver stain x20. D. Arteriole with prominent endothelium. HE.

Regarding the genetic and molecular complement analysis, several studies have established that approximately 60% of patients with aHUS carry mutations in complement regulatory genes (CFH, MCP, CFI, Thrombomodulin [THBD], or in the C3-convertase components, factor B [FB] and C3). 5-10% of patients with HUS have anti-FH autoantibodies against C-terminal region, with similar consequences to those in FH mutations [3, 11, 12]. It is not ruled out that in the rest there is also an unidentified autoimmunity and / or genetic component (involving complement genes of other types, such as coagulation genes) [3, 13]. In our case, the result of the genetic and molecular study is negative for the known mutations, suggesting that it could be a secondary form of aHUS.

The result of aEPEC in the stool culture of our case, take us to make the differential diagnosis between HUS due to aEPEC versus aHUS. E. coli is a gram negative bacillus that belongs to the Enterobacteriaceae family. There are six E. coli phatotypes involved in diarrheal processes, which differ in virulence factors and pathogenicity mechanisms. These include, enteropathogenic E. coli (EPEC), enterotoxigenic E. coli (ETEC), enteroinvasive E. coli (EIEC), enteroaggregative E. coli (EAEC), diffusely-adherent E. coli (DAEC), adherent-invasive E. coli (AIEC) and shigatoxigenic E. coli (STEC), which has also been described as enterohemorrhagic E. coli (EHEC) and verotoxigenic E. coli (VTEC) [6]. Enteropathogenic E. coli (EPEC) normally produces watery diarrea, as described by Mónica Z. Alonso et al. [7], as it happens in our patient. EPEC strains are divided into typical and atypical, by the ability to express (typical) or not (atypical) a fimbria called BFP ("bundle forming pili") [7]. The STEC (which is shiga toxin producer), is related to 90% of cases of HUS, and is normally preceded by diarrhea that lasts 4 to 10 days, usually bloody [3]. Even so, cases of HUS due to microorganisms different from STEC are also described, such as Shigella dysenteriae type I or Streptococcus pneumoniae [1].

Both EPEC and STEC have in common the pathophysiological mechanism that causes diarrea. It is based on the disorder of the intestinal cell due to the attaching and effacing (A/E) microvilli damage, that is mediated by intimin (encoded by eae gene), and other secreted proteins. In contrast, EPEC and STEC differ in that the latter produces shiga toxin, which is the responsible of the development of bloody diarrhea and HUS. EPEC strains, like the one in our case, lack the genes that encode Shiga toxins [6-9]. Silveyra et al. [10] describes in his article the case of a two-year-old boy with bloody diarrhea in which E. coli O157: H16 was isolated, with positive eae gene, negative bfp and negative shiga toxin, corresponding this isolation to the aEPEC category, the same as in our patient; but unlike his case, in ours there was no bloody diarrhea. Bloody diarrhea due to aEPEC, in the absence of Shiga toxin raises the question of how it could have happened. Some authors, such as Feng et al. [7] or Alonso et al. [8], states that typical STEC and EPEC may become atypical EPEC during the infection due to the loss of mobile genetic elements such as bacteriophages or plasmids encoding verotoxins and adhesion factor (bfp), respectively. Alonso et al. [9] states that the prophages encoding the Shiga toxin are usually stable in the genome of the bacteria, but that some strains of STEC can lose the prophage and, therefore, return to the aEPEC state.

Therefore, we propose the possibility of being the first case of HUS due to STEC, in which during the infection process, it has lost mobile genetic elements such as bacteriophages or plasmids encoding verotoxins, isolating aEPEC in the stool culture. Despite this, we cannot rule out that it is a aHUS, with thyroid surgery or gastrointestinal infection as triggers, in which the genetic and/or autoimmunity implicated component has not been identified, but that has not recurred after withdrawing eculizumab.

1. References

1. Contreras E, De la Rubia J, Del Río-Garma J, et al. Guía diagnóstica y terapéutica de las microangiopatías trombóticas del Grupo Español de Aféresis. Med Clin (Barc). 2015; 144 (7): 331.e1–331.e13
2. Loirat C, Saland J, Bitzan M. Management of hemolytic uremic syndrome. Presse Med. 2012; 41: e115–35.
3. Campistol J.M, Arias M, Ariceta G. et al. Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento

de consenso. Nefrología. 2015; 35 (5): 421-47.

4. Román E, Mendizábal S, Jarque I, et al. Microangiopatía trombótica secundaria y eculizumab: una opción terapéutica razonable. Nefrología. 2017; 37(5): 478-91.
5. Escribano TC, Alonso M. Síndrome hemolítico urémico: estado actual. Medicina Clínica. 2018; 151 (8): 329-35.
6. Farfán-García AE, Ariza-Rojas SC, Vargas-Cárdenas FA, Vargas-Remolina LV. Mecanismos de virulencia de Escherichia coli enteropatógena. Rev Chilena Infectol. 2016; 33(4): 438-50.
7. Alonso M, Sanz M, Padola N, Lucchesi P. Caracterización de cepas de Escherichia coli enteropatogénico (EPEC) aisladas durante el proceso de faena de pollos. Rev Argent Microbiol. 2014; 46(2): 122-5.
8. Feng PC, Keys C, Lacher DW, et al. Clonal relations of atypical enteropathogenic Escherichia coli O157:H16 strains isolated from various sources from several countries. FEMS Microbiol Lett. 2012; 337(2): 126-31.
9. Alonso C A, Mora A, Díaz D, et al. Occurrence and characterization of stx and/or eae-positive Escherichia coli isolated from wildlife, including a typical EPEC strain from a wild boar. Veterinary Microbiology. 2017; 207: 69-73.
10. Silveyra I M, Pereyra A, Alvarez M, et al. Aislamiento de Escherichia coli enteropatógeno O157:H16 de un caso de diarrea infantil y sus contactos familiares en La Pampa, Argentina. Rev Argent Microbiol. 2015; 47 (4): 317-321.
11. Dragon-Durey M-A, Loirat C, Cloarec S, et al. Anti-factor H autoantibodies associated with atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2005; 16(2): 555-63.
12. Jozsi M, Strobel S, Dahse H-M, et al. Anti factor H autoantibodies block C-terminal recognition function of factor H in hemolytic uremic syndrome. Blood. 2007; 110 (5): 1516- 1518.
13. Laurence J, Haller H, Mannucci PM, Nangaku M, Praga M, Cordoba SR. Atypical Hemolytic Uremic Syndrome (aHUS): Essential Aspects of an accurate Diagnosis. Clin Adv Hematol Oncol. 2016; 14 (11) (supl. 11): 1-16.
14. Tsai HM. Untying the knot of thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome. Am J Med. 2013; 126(3): 200-9.
15. Karpac CA, Li X, Terrell DR, et al. Sporadic bloody diarrhea associated thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome: an adult and paediatric comparison. Br J Haematol. 2008; 141(5): 696-707.
16. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011; 6(60) 1-24.
17. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010; 5(10): 1844-59.
18. Vidal JE, Canizález-Román A, Gutiérrez-Jiménez J, Navarro-García F. Molecular pathogenesis, epidemiology and diagnosis of enteropathogenic Escherichia coli. Salud Publica Mex. 2007; 49(5): 376-86.
19. Jajarmi M, Imani Fooladi AA, Badouei MA, Ahmadi A, et al. Virulence genes, Shiga toxin subtypes, major O-serogroups, and phylogenetic background of Shiga toxin-producing Escherichia coli strains isolated from cattle in Iran. Microbial Pathogenesis. 2017; 109: 274-9.
20. Fakhouri F, Delmas Y, Provot F, et al. Insights from the use in clinical practice of eculizumab in adult patients with atypical hemolytic uremic syndrome affecting the native kidneys: An analysis of 19 cases. Am J Kidney Dis. 2014; 63(1): 40-8.