An unusual case of haemolytic uraemic syndrome following endoscopic retrograde cholangiopancreatography rapidly improved with eculizumab

Olivier Taton[1], Myriam Delhaye[1], Patrick Stordeur[2], Timothy Goodship[3], Alain Le Moine[4], Annick Massart[4]

(1) Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, (2) Immunochemistry-Autoimmunity Laboratory, Immunobiology Clinic, Erasme Hospital, Brussels, Belgium ; (3) Institute of Genetic Medicine, Newcastle University, Central Parkway, United Kingdom ; (4) Department of Nephrology, Dialysis and Transplantation, Erasme Hospital, Brussels, Belgium.

Abstract

Atypical haemolytic uraemic syndrome (aHUS) is a rare but life-threatening complement system-related disorder, characterized by renal failure, non-immune haemolytic anaemia and thrombocytopenia. We report on a young woman who developed a pancreatitis-induced aHUS following a routine procedure of endoscopic retrograde cholangiopancreatography. The patient was successively treated by 2 plasma exchanges with fresh frozen plasma and eculizumab, a monoclonal antibody designed to block terminal complement activation. The last treatment resulted in the immediate improvement of haemolytic parameters and to the definitive suspension of plasma exchanges. This is likely the first description of the use of a complement inhibitor to treat post-pancreatitis aHUS. We discussed treatment options and concluded that eculizumab could be a beneficial alternative to plasma exchanges in the management of such complications. (Acta gastroenterol. belg., **2016**, 79, **257-261**).

Key words : acute kidney injury, eculizumab, endoscopic retrograde cholangiopancreatography, haemolytic uraemic syndrome, pancreatitis, thrombotic microangiopathy.

Introduction

Haemolytic Uraemic Syndrome (HUS) is a rare disorder characterized by non-immune (Coombs negative) haemolytic anaemia, thrombocytopenia and renal failure (1). Anaemia is microangiopathic in nature : it results from the fragmentation of red blood cells flowing through small vessels damaged or obstructed by platelet-rich thrombi. Typical HUS usually follows an infection by Shiga-like toxin producing *Escherichia coli* which manifests as bloody diarrhea. However, 10% of HUS cases are said to be "atypical" (aHUS) because of the lack of evidence of a preceding *E.coli* infection. Pregnancy, virus, cancer, drugs or vasculitis can trigger aHUS through endothelial injury. Approximately 70% of aHUS patients carry genetic mutations which impair the regulation of the alternative complement pathway. aHUS may develop into a multisystemic relapsing form. About one third of patients develop end-stage renal disease or die during the first episode. To date, the treatment of aHUS has relied on plasma exchange with fresh frozen plasma, in order to remove and replace abnormal circulating complement proteins or, rarely, autoantibodies. However the efficacy of plasma exchange is controversial (1). Recently, the use of a monoclonal antibody directed against the complement component C5 (eculizumab, (SOLIRIS®) – Alexion Pharmaceuticals, Cheshire, Connecticut), preventing terminal activation of the complement pathway, has dramatically modified the disease outcome (2). Herein, we report a case of aHUS following endoscopic retrograde cholangiopancreatography (ERCP) and its successful treatment by eculizumab.

Case report

A 21-year-old Turkish woman was admitted to our hospital with acute epigastric pain radiating to the back. Four years earlier, she was diagnosed with idiopathic chronic calcifying pancreatitis. The patient did not drink alcohol, had no gallbladder stone nor mutation in the *CFTR* or *PRSS1* genes. During these 4 years, she underwent 8 ERCPs for endoscopic therapy including pancreatic sphincterotomy, extracorporeal shockwave lithotripsy of obstructive pancreatic stones located in the head of pancreas and recurrent pancreatic ductal stenting. Two stents have been inserted in the main pancreatic duct 4 months before this admission. Her medication included tramadol and omeprazole. On admission, laboratory data showed marked inflammation (Table 1). Abdominal computed tomographic scan showed a dilatation of the main pancreatic duct proximal to the first stent (Fig. 1A), as well as migration of the second stent into the right colon (abdominal plain film, Fig. 1B). Two days later, the patient underwent ERCP with removal of the stent and insertion of 3 new stents. Abdominal pain rapidly improved. Laboratory examination showed resolution of the inflammatory syndrome but an increased lipasemia. On the sixth hospital day, she developed a purpuric eruption (Fig. 1C) along with features of a thrombotic microangiopathy (TMA) including thrombocytopenia, anaemia, elevated LDH, increased unconjugated bilirubin, low haptoglobin and presence of schizocytes (Table 1). Plasma exchange with fresh frozen plasma replacement (30 mL/kg, 2 sessions over 2 days) and methylprednisolone (1 mg/kg) were started in the intensive care unit. However a stage 2- acute kidney injury developed on the day after (serum creatinine increased

Correspondence to : Annick Massart, M.D., Department of Nephrology, Dialysis and Transplantation, Erasme Hospital, 808, route de Lennik, 1070 Brussels, Belgium. E-mail : anmassar@ulb.ac.be

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Table 1. — **Evolution of the laboratory findings**

Variable	Day 1	Day 4	Day 6	Day 8	Day 9	Day 17	Day 32
Haemoglobin (12-15.5 g/dL)	13.8	12.7	6.6 ↓	6.2 ↓	7.4 ↓	8.3 ↓	10.8 ↓
Platelets (150-350 ×10³/µL)	395 ↑	235	20 ↓	7 ↓↓	56 ↓	377 ↑	284
WBC (4-10 ×10³/µL)	9.7	14.2 ↑	9.4	17.7 ↑	15.2 ↑	11 ↑	5.2
CRP (0-1 mg/dL)	24 ↑	12 ↑	18 ↑	2.9 ↑	2.3 ↑	0.6	0.1
Urea (15-39 mg/dL)	11	23	65 ↑	81 ↑	89 ↑	55 ↑	37
Creatinine (0.5-1 mg/dL)	0.6	0.7	0.6	1.6 ↑	1.6 ↑	1.3 ↑	0.8
eGFR	115	100	108	48 ↓	39 ↓	52 ↓	95
Lipase (13-60 U/L)	14	2329 ↑	476 ↑	218 ↑	222 ↑	–	–
Total bilirubin (0-1.2 mg/dL)	0.6	2.3 ↑	5 ↑	1.4 ↑	0.9	0.71	0.65
Unconjugated bilirubin (< 0.5 mg/dL)	–	–	3.2 ↑	–	–	–	0.22
LDH (< 244 U/L)	197	497 ↑	2108 ↑	1296 ↑	829 ↑	605 ↑	164
Haptoglobin (30-200 mg/dL)	–	–	< 5 ↓	< 5 ↓	< 5 ↓	9 ↓	–
Schizocytes/1000 RBC	–	–	51 ↑	–	28 ↑	–	–
ADAMTS13 activity (> 40%)	–	–	86	–	–	–	–
aPTT (24-35 s)	29	31	71 ↑	40 ↑	33	–	31.4
PTT (70-130%)	91	68 ↓	47 ↓	74	70	–	89
Fibrinogen (160-400 mg/L)	690 ↑	–	243	206	196	–	302
C3 (72-156 mg/dL)	–	–	99	–	71	103	86
C3d (< 1.2 mg/dL)	–	–	1	–	< 0.4	< 0.4	< 0.4
CFH haemolytic assay (86-103%)	–	–	78 ↓	–	–	–	–

Abbreviations : ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 ; aPTT, activated partial thromboplastin time ; C3/C3d, complement component C3/C3d ; CFH, complement factor H ; CRP, C-reactive protein ; eGFR, estimated glomerular filtration rate ; LDH, lactate deshydrogenase ; PTT, partial thromboplastin time ; RBC, red blood cells ; WBC, white blood cells.

from 0.6 to 1.6 mg/dL with a drop of more than 50% of the glomerular filtration rate) and platelets continued to decline up to 7.000/mm3. Shiga-toxin detection assays in faeces and serum were negative. A diagnosis of aHUS was made. Because of this extremely severe, life-threatening presentation, eculizumab was initiated on day 7 (intravenous, 900 mg per week for 4 weeks then 1200 mg per 2 weeks), immediately after N. *meningitidis* vaccination together with antibiotic prophylaxis. Haemolytic parameters immediately improved (Fig. 2). Steroids were tapered and complementary plasma exchanges were not required. She was discharged home on day 15 and remained on eculizumab for 11 months during which she did not experience recurrent haemolysis or abdominal pain. Her creatinine returned to baseline within 4 months. At month 7, a new ERCP was performed under eculizumab and after intrarectal indomethacin prophylaxis, to remove the remaining pancreatic stents and was uneventful. Interestingly, we found in retrospect that, 2 years before, this patient likely developed a first, unrecognized, episode of TMA, 2 days after therapeutic ERCP. A peak lipasemia – 1989 IU/L (N ≤ 60 UI/L) – was noted on post-ERCP day 1 and the lowest platelet count – 39,000/µL – was noted on post-ERCP day 4 in the context of acute anaemia, elevated LDH and bilirubin. However, no renal injury was noticed. This retrospectively diagnosed less severe episode of TMA recovered spontaneously.

Diagnostic and genetic testing

Manifestations of TMA can be observed in different disorders. A normal level of ADAMTS13 activity in a sample taken before the onset of plasmatherapy allowed us to rule out the diagnosis of thrombotic thrombocytopenic purpura with confidence. Screening for mutations in complement genes (*CFH*, *CFI*, *CD46*, *C3*, *CFB*, *THBD*, *CFHR5*) and copy number variants affecting *CFHR1* and *CFHR3* showed no abnormality. Rarer complex genomic rearrangements involving CFH and CFHR genes were not tested. Autoantibodies against complement factor H were negative on two occasions after steroid withdrawal. Nevertheless, we performed a functional test, based on the fact that sheep erythrocytes do not normally undergo haemolysis in presence of human serum containing upright complement factor H (3). This test was abnormal, which is consistent with pathologic alternative complement activation.

Evolution

At the latest follow-up, 26 months after eculizumab withdrawal, the patient showed no sign of recurrent haemolysis or anaemia, nor renal dysfunction despite mild pancreatic pain attacks, however not leading to new ERCP procedures. Finally, she became pregnant and gave birth to a child uneventfully.

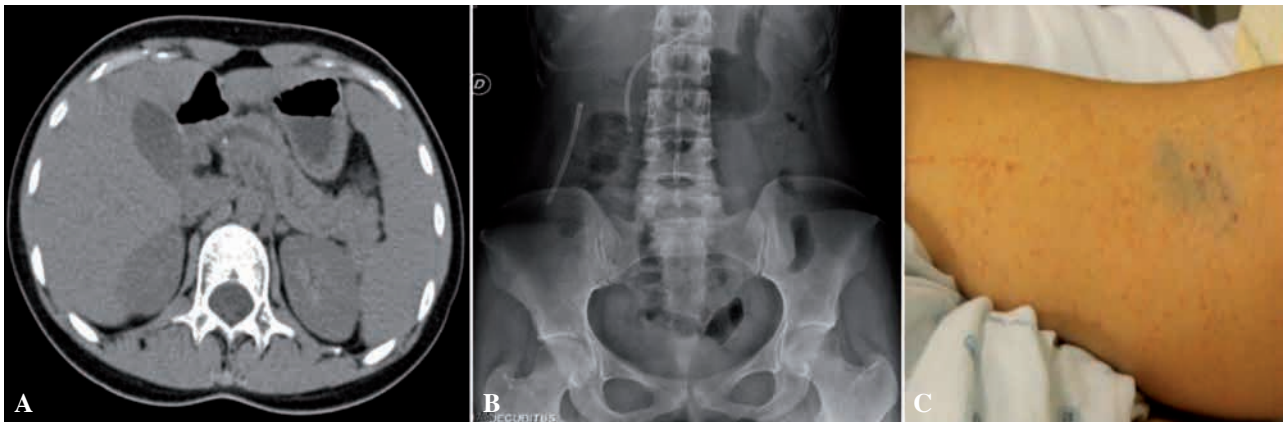

Fig. 1. — Radiological and clinical manifestations.
(A) Unenhanced CT scan performed at admission showed main pancreatic duct dilatation, (B) Abdominal X-ray showed only one pancreatic stent in place while the second stent moved to the right colon, (C) Purpuric eruption on the right arm on hospital day 6.

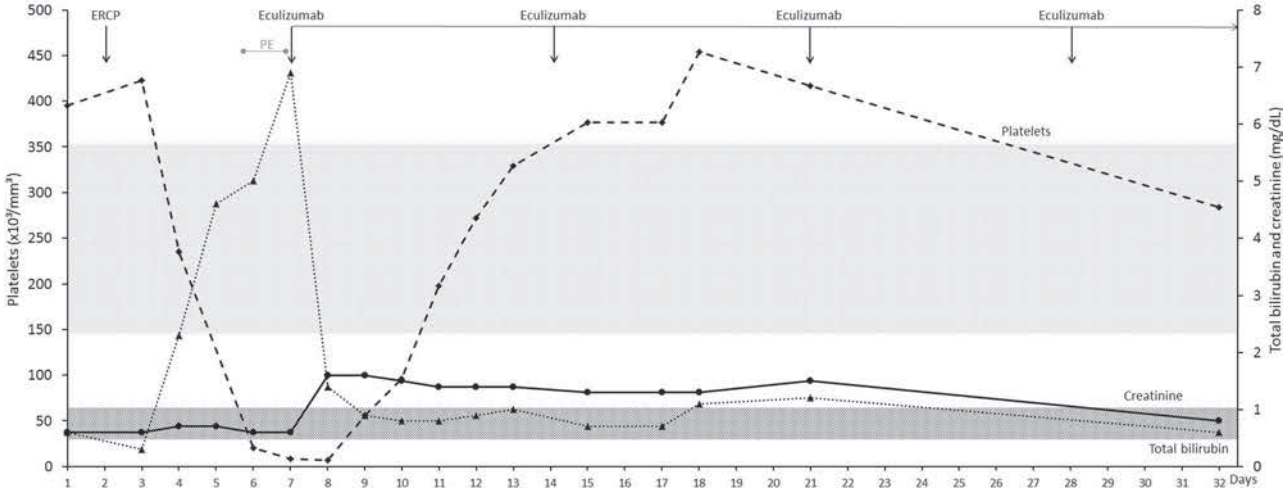

Fig. 2. — Biochemical evolution and treatment.
Evolution of platelet count (dashed line), creatinine (plain line) and total bilirubin (dotted line) during the hospitalization, from admission to discharge. The dark grey zone represents normal reference ranges for creatinine and the light grey zone for platelet count. ERCP and eculizumab injection are indicated by black arrows. The grey and black lines represent the periods of time during which plasma exchanges (PE) and eculizumab were administered, respectively.

Discussion

As herein reported, aHUS was an unexpected event following a routine ERCP for pancreatic stent exchange. This complication has been rarely reported previously (4-7). We postulate that post-ERCP pancreatitis (PEP) was the likely trigger of aHUS in our patient, as suggested by the clear association, on 2 occasions, of aHUS with pancreatitis following ERCP. PEP is the most frequent complication with an incidence of 3.5% (8). Several independent patient-related and procedure-related risk factors for PEP have been previously reported (9) and updated (10). Among them, female gender, previous pancreatitis, previous PEP, younger age, nondilated extrahepatic bile ducts and normal serum bilirubin were indeed present in our patient. On the contrary, as our patient was previously endoscopically treated for advanced chronic pancreatitis, none procedure-related risk factors was involved. Effective PEP prevention has been demonstrated by using 100 mg of diclofenac or indomethacin administered rectally immediately before or after ERCP in patients at high as well as low risk for PEP (10). This is the reason why we also used intrarectal indomethacin prophylaxis in our patient during the last ERCP aimed to definitively remove the pancreatic stents.

Post-ERCP aHUS observed in this case can be considered as a variant of pancreatitis-associated aHUS. Our patient presented only biological pancreatitis because there was no abdominal pain or radiological feature of acute pancreatitis. However, the induced inflammatory

cascade could have led to endothelial injury and aHUS in a predisposed patient (11). Importantly, the negative results of the genetic testing do not rule out this possibility in our patient because 30% of aHUS-causing mutations remain currently unknown (1). Also, the presence of an abnormal haemolytic assay strongly argues for a susceptibility to develop aHUS (12,13). It is interesting to note that pancreatitis was also described as a consequence, and not a cause, of aHUS (14). Subtle interplay exists between pancreatitis and thrombotic microangiopathic disorders (11) ; this raises the possibility of a common mechanism underlying both idiopathic chronic pancreatitis and aHUS susceptibility in this patient.

A median delay of 3 days to develop aHUS after the onset of pancreatitis has been reported (6,15) with a median of 10 sessions of plasma exchange to achieve remission (15). According to two reports (6,16), 50 to 87% of patients presenting with renal involvement (n = 7/14 and 7/8, respectively) required haemodialysis. It is well established that even modest increases in serum creatinine, dramatically increase both mortality and length of stay (17). In contrast to all these facts, our patient who had developed a severe aHUS with a stage 2 - acute kidney injury (AKIN classification), received only 2 sessions of plasma exchange and went back home 1 week after initiation of eculizumab. Ultimately, she completely recovered from her renal failure. This favorable outcome is consistent with previous studies reporting dramatic renal improvement following eculizumab administration in the setting of aHUS (2). Hence, although not proved, this excellent outcome suggests a beneficial therapeutic effect of eculizumab in our patient. Besides efficacy considerations, eculizumab administration should reduce the rate of complications due to plasma exchanges (17) including anaphylaxis reaction to plasma derivatives, catheter insertion complications such as pneumothorax, infections and venous thrombosis (1). On the other hand, eculizumab was associated with an increased incidence of meningococcal infections, as reported in the setting of paroxysmal nocturnal haemoglobinuria ; an orphan disease for which eculizumab was designed for. This adverse event seems to be less critical in the setting of aHUS and it is partly prevented by prophylactic vaccination and/or antiobiotherapy (2).

To date, eculizumab prohibitive cost of approximately € 4.600 per 300 mg vial severely limits patient access (18). We propose that the efficacy, duration of administration and cost-effectiveness of eculizumab be evaluated further in other patients suffering from pancreatitis associated HUS.

Conclusion

This report illustrates that 1) aHUS could complicate an usual ERCP procedure ; physicians should be concerned because of the need for urgent management. 2) Eculizumab, an anti-complement drug, could be a beneficial alternative to the conventional plasma exchange therapy in the setting of aHUS following acute pancreatitis.

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References

1. LOIRAT C., FREMEAUX-BACCHI V. Atypical hemolytic uremic syndrome. *Orphanet. J. Rare Dis*., 2011, **6** : 60.
2. LEGENDRE C.M., LICHT C., MUUS P., GREENBAUM L.A., BABU S., BEDROSIAN C. *et al*. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N. Engl. J. Med*., 2013, **368** : 2169-81.
3. ROUMENINA L.T., LOIRAT C., DRAGON-DUREY M.A., HALBWACHS-MECARELLI L., SAUTES-FRIDMAN C., FREMEAUX-BACCHI V. Alternative complement pathway assessment in patients with atypical HUS. *J. Immunol. Methods*, 2011, **365** : 8-26.
4. NGUYEN N.Q., MADDERN G.J., BERRY D.P. Endoscopic retrograde cholangiopancreatography-induced haemolytic uraemic syndrome. *Aust. N. Z. J. Surg*., 2000, **70** : 235-236.
5. BONG J.J., AMMORI B.J., MCMAHON M.J., KUMAR A., TURNEY J.H., NORFOLK D.R. Thrombotic microangiopathy in acute pancreatitis. *Pancreas*, 2002, **25** : 107-109.
6. SWISHER K.K., DOAN J.T., VESELY S.K., KWAAN H.C., KIM B., LAMMLE B. *et al*. Pancreatitis preceding acute episodes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome : report of five patients with a systematic review of published reports. *Haematologica*, 2007, **92** : 936-943.
7. JELIAZKOVA P., NOE S., JOST P., SARKAR O., KUCHLE C., SCHMID R.M. *et al*. Postendoscopic retrograde cholangiopancreatography pancreatitis : a rare cause of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Eur. J. Gastroenterol. Hepatol*., 2011, **23** : 825-827.
8. DUMONCEAU J.M., ANDRIULLI A., DEVIERE J., MARIANI A., RIGAUX J., BARON T.H., TESTONI P.A. Prophylaxis of post-ERCP pancreatitis : European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*, 2010, **42** : 503-515.
9. MASCI E., MARIANI A., CURIONI S., TESTONI P.A. Risk factors for pancreatitis following endoscopic retrograde cholangiopancreatography : a meta-analysis. *Endoscopy*, 2003, **35** : 830-834.
10. DUMONCEAU J.M., ANDRIULLI A., ELMUNZER B.J., MARIANI A., MEISTER T., DEVIERE J. *et al*. Prophylaxis of post-ERCP pancreatitis : European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. *Endoscopy*, 2014, **46** : 799-815.
11. THACHIL J. Lessons from acute pancreatitis-induced thrombotic thrombocytopenic purpura. *Eur. J. Intern. Med*., 2009, **20** : 739-743.
12. MASSART A., GOLMARVI S., HACHIMI-IDRISSI S., BROEDERS E., TOURNAY Y., NORTIER J. *et al*. Complement factor H functional assay may help to monitor atypical haemolytic uraemic syndrome : a pilot study. *Acta Clin. Belg*., 2013, **68** : 9-14.
13. ROUMENINA LT., ROQUIGNY R., BLANC C., POULAIN N., NGO S., DRAGON-DUREY M.A. *et al*. Functional Evaluation of Factor H Genetic and Acquired Abnormalities : Applications for Atypical Hemolytic Uremic Syndrome (aHUS). In : GADJEVA M. (ed). The Complement Sytem : Methods and Protocols, Methods in Molecular Biology. New York : Springer Science + Business Media, 2014, p. 237-247.
14. ROBITAILLE P., GONTHIER M., GRIGNON A., RUSSO P. Pancreatic injury in the hemolytic-uremic syndrome. *Pediatr. Nephrol*., 1997, **11** : 631-632.
15. MC DONALD V., LAFFAN M., BENJAMIN S., BEVAN D., MACHIN S., SCULLY M.A. Thrombotic thrombocytopenic purpura precipitated by acute pancreatitis : a report of seven cases from a regional UK TTP registry. *Br. J. Haematol*., 2009, **144** : 430-433.
16. BOYER A., CHADDA K., SALAH A., BONMARCHAND G. Thrombotic microangiopathy : an atypical cause of acute renal failure in patients with acute pancreatitis. *Intensive Care Med*., 2004, **30** : 1235-1239.

17. CHERTOW G.M., BURDICK E., HONOUR M., BONVENTRE J.V., BATES D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.*, 2005, **16** : 3365-3370.

18. ZUBER J., FAKHOURI F., ROUMENINA L.T., LOIRAT C., FREMEAUX-BACCHI V. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat. Rev. Nephrol.*, 2012, **8** : 643-657.