CASE REPORT

VIA MEDICA

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Hemolytic uremic syndrome in a patient with acute pancreatitis

ABSTRACT

A 40-year-old female patient with no previous medical history was admitted to the Department of Surgery due to symptoms of acute pancreatitis (AP). On the 3rd day of her hospitalization, significant anemia with thrombocytopenia and signs of acute kidney injury with oliguria were observed. In the course of differential diagnosis, after excluding sepsis and bleeding, based on the presence of hemolysis parameters (schistocytes in blood, low haptoglobin concentration, and high lactate dehydrogenase concentration), hemolytic uremic syndrome (HUS) was diagnosed. Treatment with plasmapheresis and steroids was implemented, resulting in inhibition of hemolysis, normalization of the number of platelets, and improvement of renal function. Given the lack of *E. coli* enterotoxin and *Shiga* toxin in the feces, STEC HUS was excluded, and the regular ADAMS-13 activity excluded atypical HUS. The entire clinical picture, including an excellent response to the treatment, allowed for the diagnosis of HUS as a complication of acute pancreatitis.

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INTRODUCTION

Hemolytic-uremic syndrome (HUS) belongs to thrombotic microangiopathy (TMA) — a group of diseases caused by damage to the endothelium of small vessels, accompanied by thrombotic changes causing ischemia or necrosis of the organ affected. Another common clinical manifestation of TMA, next to HUS, is thrombotic thrombocytopenic purpura (TTP). A common feature of HUS and TTP is the co-existence of symptoms of hemolytic anemia, thrombocytopenia, and organ failure, with HUS patients' predominant conditions associated with acute kidney injury (oliguria/anuria, acute kidney injury, proteinuria, erythrocyturia). In contrast, changes in the central nervous system (CNS) are typical of TPP (confusion, seizures, blindness, signs of CNS bleeding). The factor enabling HUS/TTP differentiation is assessment of ADAMTS 13 metalloproteinase activity: HUS shows regular ADAMTS 13 protease activity, while in TTP the activity is reduced.

Some of TMA syndromes have a primary cause. They are related to the presence of ADAMTS 13 metalloproteinase deficiency in the course of genetic mutations (e.g. congenital thrombotic thrombocytopenic purpura), genetic changes responsible for the mutations in genes coding proteins controlling the activation of the alternative complement system (factor H [CFH], factor I [CFI], factor B [CFB], CD 46/MCP [*membrain cofactor protein*], component C3), congenital disorders of vitamin B12 metabolism caused by mutations in the MMAHC gene (methylmalonic aciduria and homocystinuria type C) or genetic coagulation disorders caused by mutations in the genes encoding plasminogen, thrombomodulin, and diacylglycerol kinase epsilon.

The acquired forms of TMA have diverse etiology. For example, they may be the result of autoantibodies against ADAMTS 13 proteinase or the presence of Shiga toxin (*Shiga toxin-mediated HUS*, ST-HUS) produced by *E.coli* and *Shigella dysenteriae*. In addition, TMA may be secondary to other bacterial infections: *Salmonella, Yersinia, Campylobacter, Clostridium, or Streptococcus pneumoniae*, to viral infections, e.g. cytomegalovirus (CMV), HIV, HBV, HCV, HHV 6, parvovirus B19,

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influenza A, varicella and herpes zoster virus, fungal infections including *Aspergillus, Candida albicans*, as well as to the use of drugs (*drug-mediated TMA, DITMA*) from the group of i.e. calcineurin inhibitors, mTOR inhibitors, antibiotics (ciprofloxacin, metronidazole, trimethoprim-sulfamethoxazole), or others, e.g. valganciclovir, quinine, gemcitabine, vincristine, clopidogrel, ticlopidine, simvastatin, and bleomycin. In addition, TMA can also be a clinical manifestation of some autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome, systemic sclerosis) and neoplasms. It can also occur in patients after bone marrow or vascular transplantation or in patients with cardiovascular diseases (cyanotic heart diseases, valvular prostheses, or devices to assist heart function).

HUS/TTP diagnostics, due to the severe clinical course of TMA and the need for immediate implementation of specific treatment, require rapid identification of potential causes of thrombotic microangiopathy.

The diagnosis of HUS/TTP is based on symptoms of hemolytic anemia and thrombocytopenia, accompanied by signs of organ damage. Therefore, as part of laboratory diagnostics, first of all, a complete blood count with a smear for the presence of erythrocyte fragments (schistocytes) should be performed, as well as the concentration of haptoglobin, lactate dehydrogenase (LDH), total bilirubin, and direct Coombs tests. In addition, a stool test is necessary to detect *Shiga* toxin or *E. coli* enterotoxin to identify HUS caused by infection. At the same time, to distinguish TTP from HUS, the activity of ADAMTS 13 and anti-ADAMTS 13 antibodies should be determined in the patient's serum (collected before the administration of plasma!).

The following diagnostics stages attempt to determine the probable pathogenesis of this diverse group of diseases. TMA's clinical symptoms may suggest its cause, but they are not specific enough to make a conclusive diagnosis.

Therefore, the diagnostics of TMA should additionally:
— look for bacterial, viral, and fungal infections: cultures of blood, urine, bronchoalveolar lavage, and stool for the presence of *Shiga* toxin,
— assess organ damage: AST, ALT, amylase, lipase, creatinine, imaging tests depending on the patient's clinical condition (chest X-ray, abdominal ultrasound, computer tomography),
— identify systemic diseases: ANA and ANCA antibodies, lupus anticoagulant, anticardiolipin antibodies, antibodies against β2-glycoprotein I,
— include a pregnancy test, β HCG in women of childbearing potential (HELLP syndrome [Hemolytic anemia, Elevated Liver enzymes, Low Platelet count] in pregnant women with hemolysis, elevated liver enzymes occur in TMA),
— determine vitamin B12 deficiency,
— diagnose the complement system (antibodies against factors H, I, deficiency of factors H, B, I, mutations of the genes encoding CFH, CFI, CFB, C3, MCP).

Treatment of TMA, due to an imminent life-threatening condition for the patient, should be initiated as soon as possible after the diagnosis is made.

Treatment with therapeutic plasmapheresis (PF) should be started in patients with TTP. If a patient is in a hospital center where such treatment is unavailable, fresh frozen plasma (FFP) transfusions should be started in the amount of 25–30 mL/kg body weight (bw), and the patient should be referred as soon as possible to a specialist center that can perform PF procedures. PF treatments should be performed daily with a plasma exchange of 40–60 mL/kg bw and continued until PLT number > 150 000/mm^3 for two consecutive days. At the same time, steroids should be administered — in patients without severe neurological symptoms, prednisone at a dose of 1 mg/kg body weight, and in extreme cases, methylprednisolone at 125 mg *i.v.* up to four times a day. After the patient's clinical condition is stabilized and PF treatments are completed, steroids should be discontinued within 2–3 weeks. In the absence of the effect of the applied PF, rituximab at a dose of 375 mg/m^2 can be used once a week for four consecutive weeks as an adjunct to the current treatment. Prophylactic infusion of platelet concentrate should be avoided but there are exceptions to that: active, clinically significant bleeding and protection from invasive procedures e.g. making vascular access to PF. In addition, red blood cell transfusion should be performed in the case of symptomatic anemia.

Management of complement-mediated HUS should be aimed at targeted treatment with eculizumab as soon as possible. In Poland, as part of the NFZ program, it is possible to administer this humanized monoclonal

antibody against the complement C5 molecule in several centers (including Gdańsk, Warsaw, Wroclaw, and Lodz). In adult patients, eculizumab is initially administered at a dose of 900 mg i.v. once a week for four consecutive weeks, followed by 1 200 mg i.v. every two weeks indefinitely. It should be remembered that the treatment with eculizumab should not be initiated in patients with untreated Neisseria meningitidis infection or in patients not currently vaccinated against Neisseria meningitidis (unless they receive prophylactic antibiotics for two weeks after vaccination). Patients under 18 should be vaccinated against Haemophilus influenzae and pneumococcal infections. TTP treatment is as described above. Moreover, renal replacement therapy (hemodialysis) is often used to treat acute kidney injury, especially in patients with anuria, electrolyte imbalance should be corrected, and nutritional treatment implemented.

CASE REPORT

A 40-year-old female patient with no previous medical history was admitted to the surgery department due to severe pain in the mesogastrium, without accompanying nausea, vomiting, and without changes in the rhythm of bowel movements, fever, or other symptoms of infection. The patient did not take any medications chronically but had been drinking alcohol regularly, several times a week for several years (on average, about 500 mL of beer and 500 mL of high-percentage alcohol per week in the previous year). The patient systematically, once a year, had medical check-ups (morphology, creatinine, glucose concentration, urinalysis), the results of which were normal until then. Before admission, the patient was vaccinated twice against the SARS-CoV-2 virus (Pfizer vaccine).

Abnormalities on physical examination on admission revealed abdominal pain to superficial and deep palpation with preserved peristalsis; however, the Blumberg sign, as well as Chelmonski, Rovsing, Jaworski, and Goldflam signs were negative. Blood pressure values were normal (124/73 mmHg), and daily diuresis was approximately 1500 mL.

In laboratory tests, the following notable results were observed: increased lipase concentration → 3000 U/L (N < 67 U/L), with normal amylase concentration 125 IU/L, and peripheral blood leukocytosis (WBC) 20 thou-sand/mm³, with normal hemoglobin (Hb) — 15.7 g/dL, the number of red blood cells (RBC) 4.51 million/mm³, and the number of platelets (PLT) 295 thousand/mm³. The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum bilirubin, ammonia, urea, and electrolytes were within normal limits. The concentration of C-reactive protein (CRP) was 7.2 mg/L (normal < 5 mg/L). Renal function was normal with creatinine (sCr) 0.79 mg/dL, eGFR$_{CKD-EPI\ 2021}$ 95 mL/min/1.73 m². The values of coagulological parameters, apart from the concentration of D-dimer (1130 ng/mL; N < 500 ng/mL), were within the normal range. The COVID-19 PCR test was negative.

Imaging tests (ultrasound and abdominal CT scan) revealed signs of pancreatitis. Acute pancreatitis was diagnosed based on the overall clinical picture. Broad-spectrum antibiotic therapy (piperacillin with tazobactam), fluid therapy, parenteral nutrition, and then enteral nutrition with *Nutrison Peptisorb* were used. On the third day of hospitalization in the surgical department, the patient reported a significant deterioration in general condition followed by decreased diuresis (daily urine collection was 600 mL), increased peripheral edema accompanied by dyspnea, and diarrhea (5 loose stools/day). Physical examination showed yellowing of the skin and sclera, the presence of small petechiae on the dorsal sides of both hands, and fluid overload features: swelling of the lower limbs reaching 2/3 of the shin, also in the sacral area; jugular vein congestion with a positive hepato-jugular sign; above the lungs, on both sides, a decrease in vocal fremitus below the angles of the shoulder blades, dull percussion note and no alveolar murmur in this area. The abdomen was still tender and distended, and the liver was sticking out three fingers from under the right costal arch. Laboratory tests showed progressive anemization (Hgb 11.9 g/dL, RBC 3.9 million/mm³) with accompanying thrombocytopenia (PLT 96 thousand/mm³), leukocytosis 17.8 thou-sand/mm³. In addition, there was an increase in CRP to 276 mg/L, with a low concentration of procalcitonin 0.76 ng/mL [(N < 0.5 ng/mL), hyperbilirubinemia 7.58 mg/dL (N 0.30––1.2 mg/dL)]. The activity of AST and ALT remained within the normal range, the lipase concentration was 1076 U/L, and the amylase 376 U/L (Tab. 1). Because of the signs of acute kidney injury (creatinine concentration of 1.8 mg/dL, eGFR$_{CKD-EPI\ 2021}$ 36 mL/

Table 1. Results of examination of the patient during hospitalization and outpatient care

LABORATORY PARAMETER	TEST DATE									
	Department of Surgery			Department of Nephrology					Nephrology outpatient care	
	06.12.21	08.12.21	09.12.21	10.12.21	11.12.21	12.12.21	14.12.21	20.12.21	31.12.21	08.02.22
RBC (mln/mm³)	4.51	3.9	1.9	2.67	2.8	2.33	2.78	2.98	3.12	3.81
Hgb (g/dL)	15.7	11.9	6.5	8.3	8.6	7.2	8.6	9.3	9.8	11.4
WBC (thou./mm³)	20	17.8	13	16.6	21.2	23	21.7	11.3	10.8	7.8
PLT (thou./mm³)	295	96	15	31	61	109	193	570	340	346
Creatinine (mg/dL)	0.79	1.8	3.09	3.07	2.89	2.49	1.64	1.05	1.2	0.76
eGFRCKD-EPI 2021 (ml/min/1.73 m²)	95	36	18	18	20	23	40	69	59	96
Urea (mg/dL)	32	65	171	155	170	157	–	31	–	–
LDH (U/L)	–	–	2236	2233	866	647	432	274	190	142
Total bilirubin (mg/dL)	0.64	7.58	12.97	8.61	7.14	3.33	1.57	1.32	1.1	0.98
Amylase(U/L)	125	376	79	129	–	–	–	–	–	–
Lipase(U/L)	> 3000	1076	241	392	–	–	–	–	67	70
AST (U/L)	37	42	68	58	–	63	63	–	42	33
ALT(U/L)	27	16	18	16	–	42	43	–	23	18
CRP (mg/L)	7.2	276	278	214	108	26.7	22	6.8	5.6	4.1
Haptoglobin (g/L)	–	–	–	< 0.1	–	–	–		–	–
PLASMAPHERESIS	–	–	–	X (1)	X (2)	X (3)	X (5)	–	–	–
Methylprednisolone (mg)	–	–	–	250 mg	125 mg	125	125	16 mg	12 mg	–

/min/1.73 m², then 3.09 mg/dL, eGFR$_{CKD-EPI\ 2021}$ 18 mL/min/1.73 m², urea 171 mg/dL) and in the absence of obvious signs of bleeding on clinical examination, the consulting nephrologist raised suspicion of hemolytic uremic syndrome, which was confirmed after detection of signs of hemolysis: increased total bilirubin to 13 mg/dL, LDH 2233 U/L (N < 247 U/L), decreased haptoglobin (< 0.1 g/L), and the presence of schistocytes in peripheral blood smear. Table 1 presents the results of laboratory tests from the patient's entire hospitalization. The patient was transferred to the nephrology department for further diagnosis and treatment.

The material was secured to determine the activity of ADAMTS 13 and presence of *Shiga* toxin. Two units of FFP and three units of red blood cell concentrate were transfused. Daily plasmapheresis (PF) treatments were started with a plasma exchange of 40 mL/kg bw, simultaneously including methylprednisolone (MP) intravenously initially at a dose of 250 mg/day, then 125 mg — infusions were used after each PF (625 mg total administered) then converted to oral MP at 16 mg/day with dose reduction until withdrawal after six weeks. After the first PF treatment, an improvement in the patient's general condition was observed, less dyspnea, increased diuresis to 1000 mL, stabilization of blood count parameters, and renal excretory function (Tab. 1). The PF treatments were continued for the next five days until the PTL level stabilized > 150 thousand/mm³.

The treatment resulted in a significant improvement in the patient's clinical condition, restoration of diuresis (2000–2500 mL/d), and improvement in renal excretory function (creatinine concentration 1.05 mg/dL, eGFR$_{CKD-EPI\ 2021}$ 69 mL/min/1.73 m²), decreased features of hemolysis, normalized the parameters of inflammation. The results of ADAMTS metalloproteinase activity 13–72% (N 40–130%) and the metalloproteinase inhibitor ADAMTS 13–7 U/mL (N < 12 U/mL) were obtained. *Shiga* toxin/enterotoxins in the feces were not detected. Therefore, STEC HUS was excluded as a cause of TMA and atypical HUS was excluded too. The patient was discharged home on the 16th day of hospitalization in excellent general condition, with the recommendation for nephrological outpatient care.

DISCUSSION

Based on the results of laboratory tests, the patient was diagnosed with HUS, probably secondary to acute pancreatitis. Although the patient presented all the features of HUS, due to the history of alcohol abuse, hepatorenal syndrome was initially taken into account in the differential diagnosis of acute kidney injury, which was excluded due to the absence of cirrhosis. Inflammation and developing sepsis could be another potential cause. Toxic kidney injury (non-consumable alcohol) was also taken into account. Before the nephrological consultation at the surgery clinic, extensive diagnostics of anemization were performed, excluding gastrointestinal, retroperitoneal, and vaginal bleeding.

HUS secondary to acute pancreatitis, diagnosed in our patient, is extremely rare. Only about 30 such cases have been described in the literature so far. In most of the described patients, as in our patient, AP developed due to alcohol abuse. The average time from the onset of AP symptoms to the appearance of signs of acute kidney injury and hemolysis indicators is three days. According to the literature data, nearly 30% of patients diagnosed with HUS in the course of AP require renal replacement therapy. However, the prognosis in this form of TMA is fairly good, and in most cases, the normal excretory function of the kidneys is restored, and intravascular hemolysis is inhibited. The pathomechanism of HUS development in patients with AP remains unclear. It has been suggested that AP can damage the vascular endothelium by increasing the release of pro-inflammatory cytokines, e.g. TNF α, interleukins 1, 6, and 8, as well as proteases which by modifying the circulating von Willebrand factor, promote platelet aggregation through the loss of its anti-thrombogenic properties by the endothelium. A clinically significant problem is the question of whether we are dealing with acute pancreatitis as a manifestation of HUS or whether HUS is a disease secondary to acute pancreatitis. Genetic mutations in the complement system will indicate the former pathomechanism. However, waiting for the results of genetic tests usually takes many weeks, which cannot be lost due to the urgency of starting the patient's treatment. On the other hand, a history of alcohol abuse and symptoms of acute pancreatitis, followed by the appearance of markers of hemolysis, may very likely indicate HUS etiology secondary to acute pancreatitis. A factor worth considering is the patient's consumption of alcohol together with tonic that contains quinine. It has been suggested that tonic quinine may trigger the development of microangiopathies by activating quinine-dependent reactive antibodies on platelets.

In general, treatment for this form of HUS typically involves administering FFP or performing PF treatments. Of course, the targeted therapy with eculizumab can be used, which in the above case should not, and indeed was not used because the disease is not caused by genetically determined dysfunction of the complement system but by a completely reversible episode of acute pancreatitis.

SUMMARY

HUS should be considered in the differential diagnosis of acute renal injury associated with inflammation. Thrombotic microangiopathies are rare diseases with a serious prognosis and a wide variety of clinical symptoms. Determining the form of TMA facilitates a rational choice of further therapeutic and prophylactic treatment related to preventing disease recurrences and complications.

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