Atypical Hemolytic-Uremic Syndrome related to systemic infection with Actinomyces spp. – Case report

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Abstract:

Hemolytic-uremic syndrome (HUS) is a clinical entity characterized by acute renal failure, microangiopathic (nonimmune) hemolytic anemia and thrombocytopenia.

Hemolytic-uremic syndrome is classified into two forms, based on whether it is associated with diarrhea: D+HUS and D-HUS. Atypical hemolytic-uremic syndrome or D-HUS is less common than D+HUS and accounts for 5-10% of all cases. It may occur at all ages, but is most frequent in adults and presents without prodromal diarrhea. Atypical HUS has a poor prognosis, with 25% deaths rates and progression to end-stage renal disease in half the patients.

We present the case of a 46-year-old female patient diagnosed with atypical hemolytic-uremic syndrome, treated with conventional therapeutic plasma exchange (TPE) and dialysis, initially without evidence of an etiological factor for her condition. The evolution was marked by slowly hematological and renal function recovery and, concomitantly, by the deterioration of the respiratory function and the occurrence of the fever. She needed respiratory supportive therapy and the imaging tests showed the presence of a pulmonary alveolar-interstitial infiltrate. Also, the blood cultures became positive for Actinomyces spp. She was started on typical antibiotics against actinomycosis: I.V. Amoxicillin. The respiratory symptoms and radiologic images gradually improved. She was discharged in good condition, with mild anemia and residual renal insufficiency and with the recommendations to continue taking Amoxicilin/Clavulanic acid p.o for a period of 2 months.

Although the Actinomyces spp. systemic infection became obvious late in the patient clinical evolution, we consider that it might represent the trigger for atypical hemolytic-uremic syndrome. We discuss the characteristics of atypical HUS and its pathological background.

In the atypical form of hemolytic-uremic syndrome (D-HUS) various triggers have been identified: nonenteric infections, viruses, drugs, pregnancy, malignancies, SLE, transplantation. The absence of diarrhea in HUS-like setting makes the diagnosis difficult. Predominant renal impairment favors HUS in the absence of other evident possible causes. A variety of systemic infections can mimic all clinical features of HUS and often the etiology is not evident until after therapeutic plasma exchange (TPE) is started. Thus it is especially important to promptly make the diagnosis and begin treatment in the setting of HUS because renal failure is progressive and may be fatal if left untreated until the trigger is found.

Case presentation

A 46 year-old female patient, without remarkable medical history, was admitted to the Surgical Department presenting with severe right upper quadrant abdominal pain, nausea and vomiting. Acute cholecystitis was suspected. The biochemistry and the complete blood count tests performed in the preoperative screening showed severe thrombocytopenia (PLT= $23x10^9$/L), anemia (Hb= 10 g/dL) and acute renal impairment (creatinine= 8.12 mg/dL, urea= 143 mg/dL and K^+= 6,2 mmol/L), therefore she was admitted to the Intensive Care Unit and the medical opinion of a specialist in hematology was required.

Further laboratory investigations revealed a serum lactate dehydrogenase (LDH) of 1500 U/L (160-200), haptoglobin of <0.30 g/L (0.30-2.00), a normal absolute reticulocyte count. A blood film was obtained. It showed numerous red cell fragments, acantocytes, helmet cells and polychromasia. The coagulation parameters, hepatic function tests and serum amylase and lipase were within normal limits. Coombs test was negative.

The patient body temperature was normal and the physical examination revealed pallor, ecchymosis at venipuncture sites, painful abdomen, Murphy sign positive, blood pressure slightly raised and tachycardia. The neurological examination was normal. Urine output was < 15 mL/hour. Abdominal computed tomography with I.V. contrast showed no evidence of tumor lesions or pancreatitis.

She reported no drug intake, and no significant family history.

A clinical diagnosis of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS-TTP) was made. Dialysis was started after the biochemistry and urine output failed to respond to hydration over the first 24 hours. A course of plasma exchange was initiated using 1 plasma volume per day for 5 days. A favorable response was seen with the increase in urine output and rapid reduction in LDH.

Possible triggers of HUS-TTP were considered. Serum βhCG pregnancy test was negative. C3 and C4 complement levels were normal. Virology test for CMV and HIV were negative. A stool sample was negative for E. Coli O157.

After 5 days of therapy, while the hematological and renal functions were slowly recovering, hypoxemic acute respiratory failure and fever interfered. Thoracic rx exam showed bilateral alveolar-interstitial infiltrates and bilateral pleural effusion. Empiric large spectrum antibiotics, assisted respiratory support and pleural drainage were initiated, but the general evolution tended to deteriorate despite the favorable course of the hematological and renal parameters.

The blood cultures became positive for Actinomyces spp. (in the presence of Klebsiella spp colonization) infection. The antibiotherapy was changed to specific antibiotics against actinomycosis: I.V. Amoxicillin/Clavulanic acid 3x2g/day. The respiratory dysfunction and the radiologic modifications gradually resolved.

The patient was discharged in a good clinical condition, with the persistence of a mild anemia (Hb= 10.5 g/dL) and residual renal impairment (creatinine= 2 mg/dL, urea= 83 mg/dL).
The treatment recommendations were to continue the administration of oral Amoxicilin for a period of 2 months.

Discussion:

Hemolytic-uremic syndrome (HUS) is a clinical entity characterized by progressive renal failure, microangiopathic (nonimmune) hemolytic anemia and thrombocytopenia.

Hemolytic-uremic syndrome is classified into two forms, based on whether it is associated with diarrhea: D+HUS and D-HUS.

The typical D+ type (epidemic form) of HUS occurs more often in children and young adults and it is caused by the infection with Escherichia coli serotypes O157:H7, O111:H8, O103:H2, or others, which produce Shiga-like toxin (Shiga-like-associated HUS). Acute renal failure occurs in 55-70% of patients, but they have a favorable prognosis, and as many as 70-85% of patients recover renal function.

Non-Shiga-like toxin associated HUS or atypical hemolytic-uremic syndrome is less common than Shiga-like-associated HUS and accounts for 5-10% of all cases. It may occur at all ages, but is most frequent in adults and presents without prodromal diarrhea. Atypical HUS has a poor prognosis, with 25% deaths rates and progression to end-stage renal disease in half the patients. Atypical HUS can be sporadic or familial, and it seems to be associated with abnormalities of the complement regulatory proteins.

In sporadic atypical HUS various triggers have been identified: nonenteric bacteria, viruses, drugs, malignancies, transplantation, pregnancy.
Approximately 50% of sporadic cases appear to be idiopathic.

Atypical HUS that develops in patients with family history of the disease is classified as familial atypical HUS and it is associated with genetic abnormalities of the complement regulatory proteins.

Damage to endothelial cells is the primary event in the pathogenesis of hemolytic-uremic syndrome. The histological lesions, indistinguishable between both forms of HUS, are characterized by thickening of arterioles and capillaries, endothelial swelling and detachment and subendothelial accumulation of proteins and cell debris. The result is formation of platelet microtrombi which obstruct the vessels. Hemolysis occurs and fragmented or distorted erythrocytes appear on blood smears. Lesions typically affect the kidney, although the brain, heart, lungs, gastrointestinal tract, and pancreas may be involved.

Reduced serum levels of complement fraction C3 have been reported in patients with atypical HUS. A low C3 level reflects complement activation and consumption. Granular C3 deposits in glomeruli and arterioles during acute disease are consistent with the activation of complement and local C3 consumption. Several factors that contribute to complement regulation are expressed on or bound to endothelium. Normally, complement regulation remains intact when the activities of one or two regulators are partially reduced. However, triggers, such as infections, that are associated with inflammation and complement activation may lead to endothelial damage, since the vascular endothelium may require multiple regulators for protection.

A variety of mutations in members of the complement pathway have been described in patients with atypical hemolytic-uremic syndrome, not only in the familial subtype but also in the sporadic form: mutations in complement factor H (CFH - plasma regulator of the alternative pathway), in membrane cofactor protein (MCP), in CFI (complement factor I) or in C3. Abnormalities in genes encoding for complement modulatory proteins have been shown to predispose humans to atypical HUS rather than cause it. In the presence of events that enhance alternative pathway activation, carriers of complement mutations present excessive C3b formation and deposition on vascular endothelium. An uncontrolled level of C3 convertase leads to more C3b molecules and to more C5 convertase, initiating the formation of the membrane-attack complex. Complement-mediated endothelial

injury creates a prothrombotic state through exposure of subendothelial collagen, von Willebrand factor and fibrinogen.

On the other hand, in some cases of atypical HUS, anti-CFH autoantibodies can develop.

The diagnosis of HUS is usually raised by the presence of its 3 cardinal features: acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia, in the absence of other evident possible causes. The adult age of the patient and the absence of bloody diarrhea prodrome sustain the presence of atypical form of HUS.

There are conditions in the differential diagnosis with symptoms that can overlap or mimic those of HUS, thus it is important to diagnose correctly and treat appropriately.

In our patient, the acute renal failure associated with thrombocytopenia and fragmented erythrocytes on peripheral blood smear, suggested the presence of HUS-TTP.

Adult HUS and thrombotic thrombocytopenic purpura (TPP) have many common features, but, with the discovery of von Willebrand factor (vWF)-cleaving metalloprotease ADAMTS13, hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (TPP) are clearly different diseases despite their clinical similarities. Patients with HUS consistently have normal ADAMTS13 levels, a feature that distinguishes them from most patients with TTP.

In our case, the absence of the fever and the normal neurological status in conjunction with the severe progressive renal failure which dominated the clinical picture favored HUS diagnosis. We mention that laboratory test for ADAMTS13 (AD integrin-like and metalloproteinase with thrombospondin type 13 motifs) activity could not be done. Also, other conditions associated with microangiopathic hemolytic anemia (MAHA) were excluded: DIC, antiphospholipid antibodies syndrome, HELLP syndrome.

We looked for possible HUS triggers: pregnancy, systemic lupus erythematosus, viral or bacterial infections, drugs, malignancies, but none of these were evident at diagnosis.

The rationale of using therapeutic plasma exchange for treating atypical HUS is still unclear. The plasma exchange or infusion has been successfully used since decades and has been associated with an important decrease in mortality. Plasma exchange allows for the provision of larger amounts of plasma than would be possible with infusion while avoiding fluid overload. However, clinical trials using plasma therapy in patients with HUS are few and they do not distinguish between D+HUS and atypical HUS.

The recent HUS treatment guidelines recommend starting plasma therapy as early as possible, within 24 hours of presentation, in parallel with conservative therapy (dialysis, transfusion, antihypertensive treatment, etc.). This is suggested on the basis that plasma exchange would remove mutant complement proteins (circulating plasma factors such as CFH, CFI, CFB and C3) responsible for the disease and autoantibodies to CFH, while restitution with fresh frozen plasma (FFP) restores the functional proteins.

Actinomycosis is a subacute to chronic bacterial infection caused by Actinomyces spp., an anaerobic gram-positive bacillus. It is characterized by contiguous spread, suppurative and granulomatous inflammation, and formation of multiple abscesses and sinus tracts that may discharge sulfur granules. The most common clinical forms of actinomycosis are oral-cervical (lumpy jaw), thoracic, and abdominal. In women, pelvic actinomycosis is possible as a complication of intrauterine device (IUD) placement. Also, actinomycosis may present as a disseminated hematogenous infection of multiple organs.

Actinomycetes are prominent among the normal flora of the oral cavity but less prominent in the lower gastrointestinal tract and female genital tract. Because these microorganisms are not virulent, they require a break in the integrity of the mucous membranes and the presence of devitalized tissue to invade deeper body structures and to cause human illness.

Furthermore, actinomycosis is generally a polymicrobial infection. Establishment of human infection may require the presence of such companion bacteria, which participate in the production of infection by elaborating a toxin or enzyme or by inhibiting host defenses. These companion bacteria appear to act as copathogens that enhance the relatively low invasiveness of actinomycetes. Specifically, they may be responsible for the early manifestations of actinomycosis and for treatment failures.

In our patient, the pulmonary and then systemic actinomycosis were evident late in the clinical course, after the TPE was started and the hematological and renal parameters were partially recovered. This might be due to the difficulty to culture and identify the microorganism because of its fastidious and slow growth up to two weeks or more.

In the absence of other identified causes, the infection with Actinomyces spp. remains the only possible trigger for atypical HUS. Once the microorganism was isolated and the specific antibiotics were initiated, the pulmonary dysfunction improved and the clinical course was favourable.

We searched in the medical literature and did not find any reference for Actinomyces infection as putative cause for HUS. Our patient might be the first case of HUS related to actinomycosis.

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