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The Case | Hemolysis and acute renal failure

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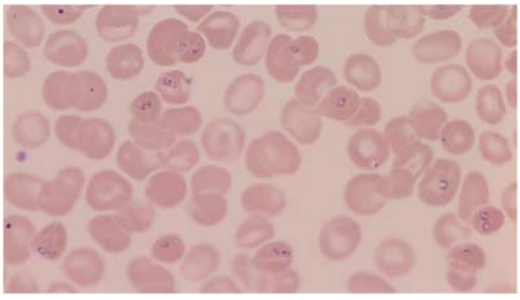

Figure 1 | Peripheral blood (Giemsa staining, print magnification 300 d.p.i.).

A 68-year-old Caucasian man was admitted to the nephrology department in October 2010 with recurrent fever, hemolysis, and acute renal failure.

On review of his record, the patient was suffering from hemolytic anemia since July 2010 (suspected autoimmune hemolytic anemia with positive direct Coombs test) and transient thrombocytopenia. Therapy with prednisolone resulted in clinical improvement. Subsequently T-cell large granular lymphocyte leukemia was suspected and treated with methotrexate at 10 mg per week from 23 July 2010 until 10 September 2010. The patient had previously received splenectomy for hairy cell leukemia in 1986 (and had been in remission since).

On admission, the physical examination was normal. Laboratory tests showed a serum creatinine concentration of 2.4 mg/dl. Lactate dehydrogenase was elevated (2235 U/l). Red blood count showed a normocytic normochromic anemia, with hemoglobin of 7.2 mg/dl. The peripheral smear is shown in Figure 1. Additional signs of hemolysis, such as decreased haptoglobin and hyperbilirubinemia (1.27 mg/dl), were present. The reticulocyte count was elevated (8.9%). Antinuclear antibodies were elevated (1:320), but other immunological parameters (antimitochondrial antibodies, antineutrophilic cytoplasmic antibodies, and antinuclear antibodies subsets) were negative. ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-13 activity was 83%. Urine tested on dipstick was positive for heme with very few red blood cells.

During the previous hospitalization in September 2010, thoracical and abdominal contrast-enhanced computed tomography revealed no signs of infection or process of malignancy.

A renal biopsy showed moderate acute tubular injury and minimal interstitial inflammation.

What is your diagnosis?

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The Diagnosis | Babesiosis

The diagnosis of babesiosis was established on the basis of the piriform shape and the plasmodium-like appearance of the intraerythrocytic parasites (parasitemia ~30%), as shown in Figure 1.

Testing for specific immunoglobulin (Ig) M and IgG antibodies against *Babesia* spp. by immunofluorescence assay was positive (1:1024). PCR from whole blood confirmed *Babesia venatorum*, the recently described species (*EU1* isolates), clustering within the *B. divergens* complex. Serology excluded coinfections with *Borrelia burgdorferi*, *Rickettsia* spp., early summer meningitis-encephalitis, and ehrlichiosis.

Table 1 | Differential diagnosis of hemolysis and acute renal failure

	Pathogenesis	Signs and symptoms	Lab findings
HUS		Acute renal failure, microangiopathic anemia	PT and aPTT normal, thrombocytopenia, microangiopathic hemolytic anemia, ADAMTS-13 activity normal, Coombs test negative, schistocytes, hematuria, proteinuria
HUS (D+)	Infection with shiga-like toxin-producing *Escherichia coli* (often children)	Diarrhea, abdominal cramps, vomiting, fever, neurological involvement possible	Stool cultures, antibodies against shiga-like toxin-producing *E. coli*
Atypical HUS (HUS (D−))			
Familial HUS	Genetic abnormalities of proteins involved in the regulation of complement system → mutation in factor *H, I, B* genes (complement regulatory proteins), mutation in *MCP* gene encoding membrane cofactor protein, heterozygous mutations in the complement *C3* gene		Mutation analysis, PCR C3↓, C4 normal
Sporadic HUS	Viral infections, drugs, malignancies, transplantation, pregnancy, scleroderma, lupus, antiphospholipid syndrome, idiopathic		
TTP (*Moschowitz syndrome*)		Prodrome of fatigue, nausea, pallor, petechiae, purpura, epistaxis, fever, jaundice, neurological deficits, abdominal pain, hepatomegaly, splenomegaly, multiple organ involvement	PT and aPTT normal, thrombocytopenia, microangiopathic hemolytic anemia, Coombs test negative, schistocytes, hematuria, proteinuria
Sporadic TTP	Pregnancy, transplantation, drugs, HIV, lupus, malignancies		
Idiopathic TTP	Autoantibody-mediated ADAMTS-13 deficiency		ADAMTS-13 activity reduced
Hereditary TTP	Homozygous or double heterozygous ADAMTS-13 mutations		
Hemolytic anemia			
PNH (*Marchiafava–Micheli syndrome*)	Non-malignant clonal expansion of one or several hematopoietic stem cells with acquired somatic mutation of *PIG-A* gene → deficiency in glycosyl-phosphatidyl-inositol-anchored complement regulatory proteins CD55 and CD59	Clinical evidence of paroxysmal intravascular hemolysis with fatigue, shortness of breath, palpitations, thrombosis (pulmonary embolism, portal venous thrombosis, mesenteric ischemia, stroke), renal failure, hemoglobinuria	Hemolytic anemia with or without thrombopenia or neutropenia, Coombs test negative, hematuria, hemosiderinuria, thrombosis, acetylcholinesterasis deficiency in erythrocytes, sugar lysis test for screening, more specific Ham's acid hemolysis test, if positive → flow cytometry for CD55 and CD59
Autoimmune hemolytic anemia	Warm autoantibodies (mostly IgG), eventually triggered by non-steroidal anti-inflammatory drugs and cephalosporins; associated with infections, autoimmune disease, malignancies	Signs of intravascular hemolysis with fatigue, shortness of breath, jaundice, splenomegaly, renal failure	Hemolytic anemia, Coombs test positive, hematuria
Infectious anemia	Malaria, thick borne disease		Hemolytic anemia, Coombs test might be positive, hematuria, peripheral blood smear with protists

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; aPTT, activated partial thromboplastin time; HUS, hemolytic uremic syndrome; HUS (D+), diarrheal HUS; HUS (D−), nondiarrheal HUS; IgG, immunoglobulin G; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura.

Babesiosis, a worldwide disease, was primarily known as a zoonotic-emerging tick-transmitted disease of mainly veterinary importance in cattle but also in horses, sheep, pigs, deer, and dogs.[1] Infections in humans are accidental. In the northern and mid-western regions of the United States, the main etiological agent of human babesiosis is *B. microti,* whereas most cases in Europe have been caused by *B. divergens.* These infections mainly occurred in asplenic patients.[2]

Symptoms of *B. divergens* infection tend to appear with abrupt onset following an incubation period of 1–3 weeks. Clinical manifestations of severe illness due to babesiosis may include a shock-like picture with renal failure and pulmonary edema.[2]

Babesia venatorum (EU 1) was first described by Herwaldt *et al*.[3] So far, only three cases of human babesiosis, where *Babesia* spp. *EU 1* was identified, have been reported.

The clinical manifestations in the described cases were mild to moderate, with fatigue, dark urine, headache, jaundice, lethargy, and fever (39° C). The parasitemia ranged from 1 to 30%. All the three cases recovered after therapy. In the follow-up, eventually no parasitemia was found.

A confusing aspect of babesiosis—direct Coombs-positive hemolytic anemia—may lead to a delay in diagnosis as in our case.

In October 2010, treatment with quinine (500 mg, t.i.d., p.o.) and clindamycin (600 mg, t.i.d., p.o.) was initiated and continued for 10 days. The dosage of the prednisolone therapy was tapered slowly. The patient showed good clinical response to treatment, and parasites could no longer be detected in peripheral blood smears.

In summary, we conclude that in unusual cases of hemolysis and acute renal failure babesiosis should be considered especially in immunocompromised subjects such as patients after splenectomy, as in the presented report. Adequate diagnosis and appropriate treatment lead to rapid remission (Table 1).

DISCLOSURE

All the authors declared no competing interests.

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