Thrombotic Thrombocytopenic Purpura in a Patient with Brucella Infection Is Highly Responsive to Combined Plasma Infusion and Antimicrobial Therapy

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by thrombocytopenia as well as microangiopathic hemolytic anemia and often accompanied by fever, renal failure and neurologic abnormalities. In adults, TTP is idiopathic in about one third of cases. However, in the rest, TTP is encountered in a variety of clinical situations such as viral, bacterial and mycobacterial infections, drug reactions, connective tissue disease, solid tumors, bone marrow transplantation and pregnancy [1]. Brucella infection as a causative agent of microangiopathic hemolytic anemia has been reported [2]. A case of TTP in a patient with brucellosis is reported here.

Case Report

A 51-year-old man was admitted to the hospital, complaining of a 2-day history of moderate confusion, low mood and dysarthria. Four months before admission, he had consulted a local practitioner for back pain, generalized weakness, anorexia, fever, jaundice, hematuria, dark urine, urinary tract symptoms, nausea and vomiting. Gentamycin (80 mg twice daily, 14 days) and a non-steroidal anti-inflammatory drug were administered. However, the symptoms persisted. On examination, the patient appeared...
chronically ill and was unable to speak. The vital signs were normal, except for a slightly raised temperature (38.5°C). The patient was anemic but had no clubbing, lymphadenopathy, skin rash or joint swelling. His sclera were icteric, and petechial-purpuric skin lesions were present on both legs. Neurological examination revealed diminished consciousness with a Glasgow coma scale score of 7 and +1 neck rigidity. Respiratory and cardiovascular system examinations were unremarkable. There was a history of frequent consumption of raw milk and regular direct contact with infected animals. Also, he lives in an area endemic for brucellosis. The family history was negative for diabetes mellitus and hypertension.

Laboratory tests showed: white blood cell count of 9,600/mm³ with 66% neutrophils, 21% lymphocytes, 12% monocytes and 1% basophilia; hemoglobin 7.1 g/dl; platelets 18,000/mm³; reticuloocyte index 6.7%; erythrocyte sedimentation rate 120 mm/h; prothrombin time 13 s; international normalized ratio 1.1 and activated partial thromboplastin time 29.6 s. The fibrinogen level was normal, but the D-dimer level was higher (180 ng/ml) than normal (15–150 ng/ml). The peripheral blood film showed fragmented erythrocytes and a complete absence of platelets. The bone marrow aspirate was normal, except for an increased number of megakaryocytes. The direct antiglobulin test was negative. Liver function tests showed the following values: alanine aminotransferase 93 U/l, aspartate aminotransferase 95 U/l, lactate dehydrogenase (LDH) 2,726 U/l (<450 U/l) and total bilirubin 2.7 mg/dl (2.0 mg/dl indirect). The patient showed signs of mild renal dysfunction, with blood urea nitrogen 51 mg/dl and creatinine 2.4 mg/dl. The urine was positive for urobilinogen and protein, and the sediment contained 7 white blood cells per high-power field; the red blood cells and the erythrocytes were too numerous to count. The HBsAg, anti-HCV IgM, anti-HAV IgM, anti-HBc IgM, anti-HIV and HIV tests were negative, but anti-HBs IgG proved positive. Abdominal ultrasonography revealed splenomegaly (155 mm). The chest radiograph was normal. While investigating the etiology of fever and back pain, a positive agglutination test (Wright agglutination test) for brucellosis was documented at a titer of 1:160 on the 7th day after admission. Initially, TTP associated with brucellosis was suspected. However, examination of a lumbar puncture cerebrospinal fluid sample was normal (protein 45 mg/dl; glucose 40 mg/dl, no lymphocytes/mm³), and the agglutination test was negative. Enzyme-linked immunosorbent assay of cerebrospinal fluid was not done for brucellosis. Magnetic resonance imaging of the brain was normal except for a minimal central cortical atrophy. There were none of the most frequent features of neurobrucellosis such as meningitis, meningonecephalitis, polyradiculoneuritis or cranial nerve palsies. With these clinical and laboratory findings, the patient was diagnosed as having TTP due to brucellosis. Steroid therapy (methylprednisolone 1 mg/kg) plus fresh frozen plasma replacement (15 mg/kg, twice daily) were commenced. The patient was started on a combination of doxycycline (100 mg twice daily, for 6 weeks) and trimethoprim-sulfamethoxazole (160/800 mg twice daily) for brucellosis.

Unfortunately therapeutic plasma exchange, though treatment of choice, was not performed because of financial constraints; instead, plasma infusion was done. There were signs of recovery from the 7th day onwards, with the patient gaining full consciousness by day 25. The hemoglobin level was 7.5, 9.5 and 11.1 g/dl on the 7th, 15th and 25th day, respectively. During the follow-up tests on days 7, 15 and 25, platelets and LDH were 30 × 10^9, 60 × 10^9, 152 × 10^9/l and 2,500, 1,240 and 404 U/l, respectively.

Steroid therapy was discontinued, and the patient was discharged on the 30th day, with maintenance therapy of doxycycline and trimethoprim-sulfamethoxazole. There were no neurological sequelae on follow-up after treatment completion (6 weeks). The patient had normal clinical and laboratory values at 1.5 years.

**Discussion**

A pentad of signs and symptoms has been associated with TTP: thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal failure and fever, as was the case with this patient.

Brucellosis is an important zoonotic disease, since it remains a worldwide public health problem. The use of a rifampicin-containing regimen is generally avoided in our region due to concerns regarding induction of rifampicin resistance, which may be problematic as in endemic tuberculosis [3–6]. Humans acquire the infection through the consumption of raw milk products, cheese and raw meat or direct animal exposure [7]. In Turkey, about 18,000 new cases of brucellosis are diagnosed each year. The prevalence of seropositivity in the Turkish population varies from 2.6 to 14.4%, depending upon the geographical location [8]. Thus, this patient, being from an area with a high incidence of brucellosis, displayed a high level of seropositivity. In patients with brucellosis pancytopenia, incidence is found in 3–21% of cases. Brucella infection as a causative agent of microangiopathic hemolytic anemia has been reported [2]. Microangiopathic hemolytic anemia caused by bacterial agents may occur due to release of circulating endotoxins and/or immune complexes in the circulation, which may result in alterations in the function of several organs [2].

The patient in this study showed hemolytic anemia, thrombocytopenia, schistocytes in the blood smear, reticulocytosis, increased serum LDH, fever, neurological abnormalities and renal impairment. The diagnosis of acute brucellosis was based on the presence of clinical signs and symptoms with ≥1:160 tube agglutination test [9].

Plasma infusion and exchange are usually employed with the rationale of restoring a component that is missing in the patient’s plasma, possibly an enzyme, that by modulating protease activity of Willebrand factor in handling may prevent abnormal fragmentation of that molecule during the acute phase of the disease [10].
been suggested that fresh-frozen plasma infusions may have an effect similar to plasma exchange, provided that patients can tolerate the volume load [11]. In this patient, a rapid improvement in platelet count, LDH level, hemolytic anemia and neurologic symptoms was observed with treatment of fresh-frozen plasma infusions combined with specific antimicrobial therapy. Therefore, in this case, it was thought that TTP was due to brucella infection. Therapies (i.e. plasma exchange or infusion) aimed at stopping the microangiopathic process and TTP should always be tried. However, this approach is seldom effective in secondary forms, where the outcome mainly depends on the prognosis of the underlying condition [12]. Therefore, specific therapy should be started as soon as the diagnosis of the predisposing condition has been established in order to effect disease recovery and minimize the risk of sequelae. The treatment recommendation is to continue therapy until complete disease remission is achieved. Although short-term plasmapheresis may be applied as an urgent therapy, in addition to antimicrobial therapy, in infection-induced thrombotic microangiopathy, the therapy of underlying infection together with plasma was successful in this case of brucellosis-induced TTP.

**Conclusion**

This report shows that therapy of underlying infection together with plasma infusion may be a successful treatment option for brucellosis-induced TTP.

**References**