International Journal of Infectious Diseases 38 (2015) 83–85

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

A case of severe babesiosis treated successfully with exchange transfusion☆

Esra Tanyel [a,*], Nil Guler [b], Murat Hokelek [c], Fatma Ulger [d], Mustafa Sunbul [a]

[a] Department of Infectious Disease and Clinical Microbiology, Faculty of Medicine, Ondokuz Mayıs University, Samsun 55139, Turkey
[b] Department of Hematology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[c] Department of Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey
[d] Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form 13 July 2015
Accepted 21 July 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Babesia divergens
Severe babesiosis
Treatment
Exchange transfusion

SUMMARY

Babesiosis is a zoonotic disease that may be asymptomatic or result in severe clinical conditions, with severe hemolysis, hepatic, and renal failure, in humans. Clinical symptoms depend on the species and immune status of the host. The disease is especially severe in those of advanced age, those with an immune deficiency, and the splenectomized. A severe case of babesiosis that developed in a splenectomy patient is presented here; the patient was admitted from a rural region with severe anemia and a deterioration in her general condition, with an initial diagnosis of malaria. In such situations, an exchange transfusion (ET), in addition to antimicrobial treatment, could be lifesaving.

1. Introduction

Babesiosis is a zoonotic disease that is caused by an intraerythrocytic protozoan; it is frequently transmitted through deer ticks (*Ixodes scapularis*).[1–3] Although human babesiosis is often transmitted through tick bites, it can also be transmitted through transfusions or transplacentally or perinatally. Humans are an accidental host in babesiosis.[4,5] The main *Babesia* species that produce the disease in humans are *Babesia microti*, *Babesia divergens*, and *Babesia bovis*.[1] In a study conducted in Turkey, the IgG antibody seropositivity for *B. microti* with the indirect fluorescence antibody method was found to be 6.23% (17/273) in people living in rural areas of Sinop.[6] A severe clinical picture including hemolysis, HIV-derived immunosuppression, renal–hepatic failure, and hypotension can develop, particularly in patients who have undergone a splenectomy.[4,5,7–9] Clindamycin + quinine or atovaquone + azithromycin are the preferred antimicrobial treatments.

A case of severe babesiosis that developed in a woman living in the countryside is presented here. The patient had undergone a splenectomy 15 years previously due to a firearm injury.

2. Case report

In August 2014, a 28-year-old housewife was admitted to health center in Ordu province with complaints of malaise, jaundice, and general impairment. She had severe anemia (hemoglobin 5.5 g/dl), and so was referred to the hematology department. A large number of signet ring forms were observed within the erythrocytes in the peripheral smear. Consequently she was hospitalized in the infectious diseases clinic with an initial diagnosis of malaria.

The patient had a tendency to sleep, so her medical history was obtained from her relatives. It was learned that she had been experiencing her complaints for approximately 1 month and that she was living in a rural area. She had not traveled to any other cities or countries. Fifteen years earlier she had undergone a splenectomy due to a firearm injury. Upon physical examination, the patient's body temperature was 37.8 °C, her blood pressure was 110/70 mmHg, her respiratory rate was 24 breaths/min, her pulse was 110 beats/min, her sclera and skin were icteric, and her

☆ This case was presented at the Turkish EKMUD Congress in Antalya, Turkey, 2015, as a secondary presentation in the Turkish language.

* Corresponding author. Tel.: +90 506 2488521.
E-mail address: estanyel@yahoo.com.tr (E. Tanyel).

http://dx.doi.org/10.1016/j.ijid.2015.07.019

liver was palpable. In terms of laboratory findings, the white blood cell count was 17.6 × 10^9/l (neutrophils 72%, lymphocytes 11%), hemoglobin was 5.5 g/dl, hematocrit was 13.2%, platelet count was 114 × 10^9/l, aspartate aminotransferase (AST) was 469 U/l (normal range 8–46 U/l), alanine aminotransferase (ALT) was 89 U/l (normal range 0–35 U/l), total/direct bilirubin was 10.6/2.9 mg/dl, lactate dehydrogenase (LDH) was 4053 U/l (normal range 0–480 U/l), creatine phosphokinase (CPK) was 1576 U/l (normal range 35–195 U/l), and creatinine was 2.5 mg/dl (normal range 0.4–1.4 mg/dl). Tests for hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), and antibody to HIV (anti-HIV) were all negative, as was a Brucella tube agglutination test. In the peripheral blood samples, a large number of ring-shaped parasites (>50%) were observed within the erythrocytes on Giemsa staining (Figure 1).

The patient was diagnosed with babesiosis according to the history and the evaluation of the preparations. Treatment with quinine (3 × 650 mg, orally) + clindamycin (4 × 600 mg, intravenous) was initiated. Patient blood samples were sent to Cerrahpaşa University and the causative agent was identified as *Babesia divergens* by PCR.

DNA was extracted with a commercial nucleic acid isolation kit (Roche, Germany), in accordance with the manufacturer's protocol. *Babesia spp* DNA was investigated by PCR. For PCR amplification of the 18s rRNA gene, the forward primer GACACAGGGAGGTAGTGACAAG and reverse primer CTAAGAATTTCACCTCTGACAGT were used.[10] The reaction mixture contained 25 μl of ready-to-use PCR Master Kit (containing dNTPs, Taq DNA polymerase, and $MgCl_2$; Thermo, Finland), 1 μl of each primer (final concentration 25 pMol), and 10 μl of template, in a final volume of 50 μl. The PCR amplification was performed with the following program: 94 °C for 2 min, followed by 40 cycles of 94 °C for 45 s, 54 °C for 45 s and 72 °C for 60 s. The PCR reaction was ended with a final extension at 72 °C for 10 min. The amplified PCR product was controlled by electrophoresis on 1.5% agarose gel in 0.5× Tris–borate–ethylenediaminetetraacetic acid (TBE) buffer, stained with ethidium bromide, and visualized under UV light using a transilluminator.

The positive PCR product was purified using the High Pure PCR Purification Kit (Roche, Germany) following the manufacturer's protocol, and then bidirectional DNA sequencing was performed with BigDye 3.1 sequencing chemistry (Life Technologies, USA). Chromatograms were edited and aligned with DNASTAR software. Database searches and sequence comparisons were performed with the BLAST tool provided by the National Centre for Biotechnology (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The DNA sequence showed 100% similarity to the *Babesia divergens* isolate DP-1576b 18S ribosomal RNA gene, partial sequence (GenBank accession number **JX083979.1**)

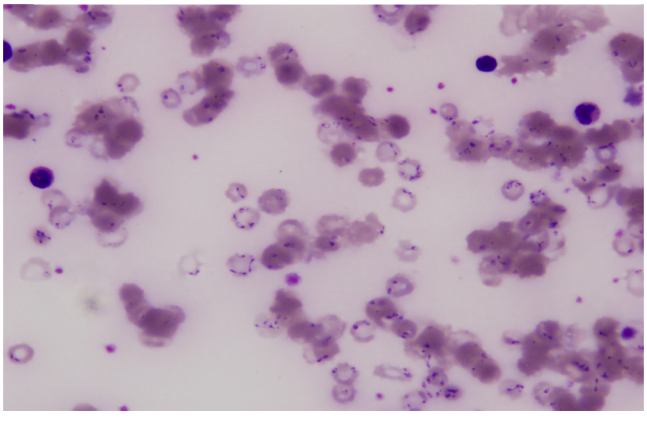

Figure 1. Giemsa stain of a thin blood smear showing ring forms of intraerythrocytic trophozoites of *Babesia divergens* before the exchange transfusion.

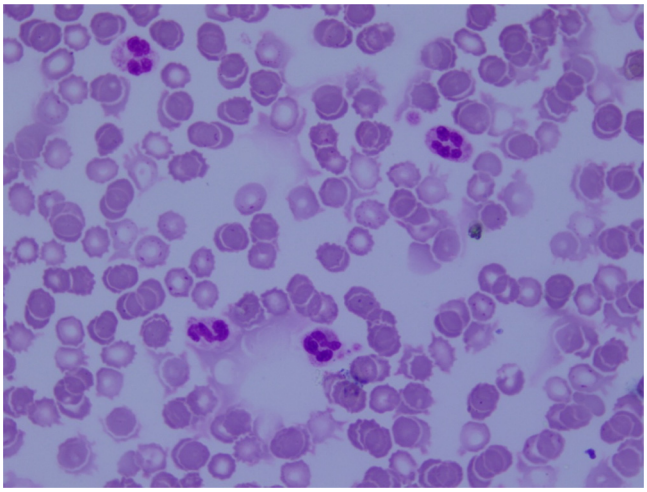

Figure 2. Giemsa stain of a thin blood smear after the exchange transfusion.

As the patient's clinical condition was poor and she had severe findings of babesiosis, she was referred to the hematology clinic and an exchange transfusion (ET) was performed. The parasitemia was initially >50%, and this decreased significantly (<10%) with erythrocyte ET (Figure 2). Within 48 h after the ET, the parasitemia had decreased significantly and it became undetectable on peripheral blood smear. The quinine and clindamycin therapy was completed at the end of 10 days and the patient was discharged.

3. Discussion

Babesiosis, which is transmitted through tick bites and can cause severe clinical conditions in immunocompromised patients, is a disease that can be diagnosed with thin and/or thick smears. The causative agent is observed as a round or oval shape within the erythrocyte. Although the brown pigment deposits (hemozoin) that are observed for the *Plasmodium* species are not observed in babesiosis, its merozoites are tetrad in structure. Furthermore, different from malaria, the presence of sudden excessive hemolysis, due to asynchronous production and non-periodic symptoms, is typical in babesiosis.[1] When the data from Turkey were investigated, it was found that although local cases of malaria have decreased over the years, important malaria cases have been observed.[11–14] When signet ring forms are observed within erythrocytes in peripheral smears in the presence of an epidemiological history and periodic high fever, malaria could be considered as the primary diagnosis.[15,16]

In the present case, malaria was assumed to be the initial diagnosis, since the ring-shaped parasites were observed within the erythrocytes in the first evaluation, and the region around Turkey is not endemic for human babesiosis. However, the absence of an epidemiological history, the presence of a large number of ring forms within a single erythrocyte, the extreme anemia, previous splenectomy, and the absence of a periodic high fever suggested babesiosis. Furthermore, the patient had no history of known tick contact, she had not traveled to endemic regions, she had no history of working in stock farming, and she had no recent history of blood transfusions for the transmission of babesiosis.

In the literature, it is mentioned that *B. divergens* is frequently isolated in human babesiosis cases reported in Europe and that it

causes a severe disease in patients who have undergone a splenectomy and are immunosuppressed.[3–5,7,8] However, no case report was found in a literature search using PubMed and Science Citation Index.[17–19] The present case is the first case reported from Turkey as an international report in which *B. divergens* was detected in blood samples by PCR. *Babesia ovis, Babesia bigemina*, and *B. microti* have been isolated in ticks from sheep and goats in the Black Sea region of Turkey.[20,21]

All active babesiosis cases should be treated.[5] A combination of either atovaquone + azithromycin or quinine + clindamycin for 7–10 days is the preferred treatment.[4,5] It has been reported that a more successful outcome could be obtained from clindamycin + quinine therapy in >10% of the cases with organ failure or parasitemia.[9] In the current case, the combination quinine + clindamycin was preferred in the first instance, due to the presence of high parasitemia and the deterioration in the patient's general condition.

An ET with erythrocytes or whole blood may be conducted in cases of severe babesiosis (high parasitemia >10%, severe hemolysis (hemoglobin <10 g/dl), splenectomy, coma, hypotension, congestive heart failure, pulmonary edema, and heart failure) in addition to antimicrobial treatment.[1,3,5,22] The aim of this method is to exchange the erythrocytes containing parasites and remove the toxic harmful metabolites.[3,4,9] As the *Babesia* species has no exoerythrocytic phase, the removal of erythrocytes with parasites is curative.[1,4,22] In a study including asplenic patients under immunosuppressive therapy who had been diagnosed with babesiosis, it was demonstrated that parasitemia decreased with ET treatment with whole blood and/or erythrocytes; it was also reported that ET together with medical therapy is lifesaving.[22] In a study investigating 34 cases diagnosed with babesiosis and their complications, a significant decrease in parasite load was reported in seven cases with high parasitemia.[23] In an asplenic female who was diagnosed with babesiosis, it was reported that the parasitemia rate of 13% decreased to 0.3% after ET.[24] In the present case, the parasitemia was initially >50%, and it decreased significantly with erythrocyte ET. The parasitemia decreased to <10% after erythrocyte ET in the present case in which the patient was in a poor general condition, had a tendency to sleep, and had extreme anemia. Therefore, ET may have been lifesaving in the present asplenic case.

In conclusion, babesiosis is a disease that can be diagnosed with a detailed epidemiological history and an examination of thin and/or thick smear preparations, which is a simple and rapid method. Treatment should be initiated promptly, as the disease may become progressively more severe in immunocompromised and asplenic individuals. ET can be lifesaving in patients with extreme cases of the disease and a high parasite load; therefore, it could be performed in addition to medical therapy.

Conflict of interest: The authors state that they have no conflict of interest.

References

1. Krause PJ. Babesiosis. *Semin Pediatr Infect Dis* 2000;**11**:182–8.
2. Diuk-Wasser MA, Liu Y, Steeves TK, Folsom-O'Keefe, Dardick KR, Lepore Bent SJ, et al. Monitoring human babesiosis emergence through vector, surveillance, New England, USA. *Emerg Infect Dis* 2014;**20**:225–31.
3. Weiss LM. Babesiosis in humans: a treatment review. *Expert Opin Pharmacother* 2002;**3**:1109–15.
4. Hildebrandt A, Gray JS, Hunfeld KP. Human babesiosis in Europe: what clinicians need to know. *Infection* 2013;**41**:1057–72.
5. Kavanaugh MJ, Decker CF. Babesiosis. *Dis Mon* 2012;**3**:55–60.
6. Poyraz O, Gunes T. Sinop Yoresinde Kirsal Kesimde Yasayan Insanlarda Babesia microti Seroprevalansi. *Turkiye Parazitoloji Dergisi* 2010;**34**:81–5.
7. Mørch K, Holmaas G, Frolander PS, Kristoffersen EK. Severe human *Babesia divergens* infection in Norway. *Int J Infect Dis* 2015;**33**:37–8.
8. González LM, Castro E, Lobo CA, Richart A, Ramiro R, González-Camacho F, Luque D, Velasco AC, Montero E. First report of *Babesia divergens* infection in an HIV patient. *Int J Infect Dis* 2015;**33**:202–4.
9. Semel ME, Tavakkolizadeh A, Gates JD. Babesiosis in the immediate postoperative period after splenectomy for trauma. *Surg Infect* 2009;**10**:553–6.
10. Nijhof AM, Penzhorn BL, Lynen G, Mollel JO, Morkel P, Bekker CP, Jongejan F. *Babesia bicornis* sp. nov. and *Theileria bicornis* sp. nov.: tick-borne parasites associated with mortality in the black rhinoceros (*Dicerosbicornis*). *J Clin Microbiol* 2003;**41**:2249–54.
11. Altun S, Kocak Tufan Z, Kacar M, Ataman Hatipoglu C, Kınıklı S, Pekcan Demiroz A. A case of malaria with uveitis, hyperglycemia, and rash in a Turkish radiologist who went to Africa. *Turkiye Parazitol Derg* 2014;**38**:258–60.
12. Aksoy Gokmen A, Pektas B, Oncel K, Ozdemir OA, Cavus I, Ozbilgin A. The investigation of malaria cases in Manisa between 2008–2012. *Turkiye Parazitol Derg* 2014;**38**:151–4.
13. Demiraslan H, Erdoğan E, Türe Z, Kuk S, Yazar S, Metan G. Evaluation of imported *Plasmodium falciparum* malaria cases: the use of polymerase chain reaction in diagnosis. *Mikrobiyol Bul* 2013;**47**:668–76.
14. Yilmaz H, Cicek B, Ulger F, Esen S, Hokelek M, Kilic S, Sunbul M. Experience of erythrocyte exchange in severe *Plasmodium falciparum* malaria. Flora The Journal of Infectious Disease and Clinical Microbiology, ID number: 00126860007438.
15. Powel VI, Grima K. Exchange transfusion for malaria and Babesia infection. *Transfus Med Rev* 2002;**16**:239–50.
16. Holler JG, Röser D, Nielsen HV, Eickhardt S, Chen M, Lester A, et al. A case of human babesiosis in Denmark. *Trav Med Infect Dis* 2013;**11**:324–8.
17. Aydin MF, Aktas M, Dumanli N. Molecular identification of Theileria and Babesia in sheep and goats in the Black Sea Region in Turkey. *Parasitol Res* 2013;**12**:2817–24.
18. Inci A, Yazar S, Tuncbilek A. Vectors and vector-borne diseases in Turkey. *Vet J Ankara Univ* 2013;**60**:281–96.
19. Acici M, Umur S, Guvenc T. Seroprevalence of equine babesiosis in the Black Sea region of Turkey. *Parasitology Int* 2008;**57**:198–200.
20. Aydin MF, Aktas M, Dumanli N. Molecular identification of Theileria and Babesia in ticks collected from sheep and goats in the Black Sea region of Turkey. 2015;114:65-9.
21. The Epidemiology of *Babesia bovis* and *Babesia bigemina* in cattle in Turkey. TAGEM/HS/05/01/02/98. Istanbul Pendik Veteriner Kontrol Enstitusu;
22. Dorman SE, Cannon ME, Telford SR, Frank KM, Churchill WH. Fulminant babesiosis treated with clindamycin, quinine, and whole-blood exchange transfusion. *Transfusion* 2000;**40**:375–80.
23. Hatcher JC, Greenberg PD, Antique J, Jimenez-Lucho VE. Severe babesiosis in Long Island: review of 34 cases and their complications. *Clin Infect Dis* 2001;**32**:1117–25.
24. Cahill KM, Benach JL, Reich LM. Red cell exchange: treatment of babesiosis in a splenectomized patient. *Transfusion* 2000;**21**:193–8.