

About the Author

Dr. Page is an infectious diseases and critical care physician at the Scripps Research Institute and the University of California, San Diego. His research interests include the natural history, epidemiology, and management of infections that cause critical illness in resource-limited settings.

References

1. Queiroz A, Sousa R, Heine C, Cardoso M, Guimarães LH, Machado PR, et al. Association between an emerging disseminated form of leishmaniasis and *Leishmania (Viannia) braziliensis* strain polymorphisms. *J Clin Microbiol*. 2012;50:4028–34. <https://doi.org/10.1128/JCM.02064-12>
2. Machado PR, Rosa ME, Costa D, Mignac M, Silva JS, Schriefer A, et al. Reappraisal of the immunopathogenesis of disseminated leishmaniasis: in situ and systemic immune response. *Trans R Soc Trop Med Hyg*. 2011;105:438–44. <https://doi.org/10.1016/j.trstmh.2011.05.002>
3. Oliveira WN, Dórea AS, Carneiro PP, Nascimento MT, Carvalho LP, Machado PRL, et al. The influence of infection by different *Leishmania (Viannia) braziliensis* isolates on the pathogenesis of disseminated leishmaniasis. *Front Cell Infect Microbiol*. 2021;11:740278. <https://doi.org/10.3389/fcimb.2021.740278>
4. Page B, Lago A, Silva JA, Schriefer A, Lago J, Oliveira L, et al. Influence of intestinal helminth burden on clinical manifestations, therapeutic response, and *Leishmania braziliensis* load in patients with New World cutaneous leishmaniasis. *Am J Trop Med Hyg*. 2021;105:1060–6. <https://doi.org/10.4269/ajtmh.20-1664>
5. Gazzinelli-Guimaraes PH, Nutman TB. Helminth parasites and immune regulation. *F1000 Res*. 2018;7:7. <https://doi.org/10.12688/f1000research.15596.1>
6. O'Neal SE, Guimarães LH, Machado PR, Alcântara L, Morgan DJ, Passos S, et al. Influence of helminth infections on the clinical course of and immune response to *Leishmania braziliensis* cutaneous leishmaniasis. *J Infect Dis*. 2007;195:142–8. <https://doi.org/10.1086/509808>
7. Newlove T, Guimarães LH, Morgan DJ, Alcântara L, Glesby MJ, Carvalho EM, et al. Antihelminthic therapy and antimony in cutaneous leishmaniasis: a randomized, double-blind, placebo-controlled trial in patients co-infected with helminths and *Leishmania braziliensis*. *Am J Trop Med Hyg*. 2011;84:551–5. <https://doi.org/10.4269/ajtmh.2011.10-0423>
8. Azeredo-Coutinho RBG, Pimentel MI, Zanini GM, Madeira MF, Cataldo JJ, Schubach AO, et al. Intestinal helminth coinfection is associated with mucosal lesions and poor response to therapy in American tegumentary leishmaniasis. *Acta Trop*. 2016;154:42–9. <https://doi.org/10.1016/j.actatropica.2015.10.015>
9. World Health Organization. Basic laboratory methods in medical parasitology. Geneva: The Organization; 1991. p. 9–25 [cited 2024 Jan 28]. <https://iris.who.int/handle/10665/40793>
10. Turetz ML, Machado PR, Ko AI, Alves F, Bittencourt A, Almeida RP, et al. Disseminated leishmaniasis: a new and emerging form of leishmaniasis observed in northeastern Brazil. *J Infect Dis*. 2002;186:1829–34. <https://doi.org/10.1086/345772>

Address for correspondence: Brady Page, University of California–San Diego, 9500 Gilman Dr, MC 0507, La Jolla, CA 92093-0507, USA; email: bpage@ucsd.edu

Confirmed Case of Autochthonous Human Babesiosis, Hungary

Dávid Sipos, Ágnes Kappéter, Barbara Réger, Gabriella Kiss, Nóra Takács, Róbert Farkas, István Kucsera, Zoltán Péterfi

Author affiliations: University of Pécs, Pécs, Hungary (D. Sipos, Á. Kappéter, B. Réger, G. Kiss, Z. Péterfi); University of Veterinary Medicine, Budapest, Hungary (N. Takács, R. Farkas); National Public Health Center, Budapest (I. Kucsera)

DOI: <https://doi.org/10.3201/eid3009.240525>

We report a case of autochthonous human babesiosis in Hungary, confirmed by PCR and partial sequencing of the *Babesia* spp. 18S rRNA gene. Babesiosis should be considered during the differential diagnosis of febrile illnesses, and peripheral blood smears to detect *Babesia* spp. should be part of the routine clinical workup.

Since the first description of human babesiosis caused by *Babesia divergens* protozoa in 1956 in the former Yugoslavia, 2 other zoonotic species, *B. venatorum* and *B. microti*, have been isolated in Europe. Unlike in North America, where most identified human cases have been caused by *B. microti*, the predominant pathogen causing babesiosis in Europe is *B. divergens* (1). The rising number of identified human infections in Europe has drawn attention to this emerging tick-borne zoonotic disease. In Europe, *B. microti* has been identified in 25 of 71 confirmed human babesiosis cases, of which 11 were autochthonous (1). Rodents and insectivores are reservoir hosts for *Babesia* spp. parasites, which are transmitted by widespread *Ixodes ricinus* ticks, well-known vectors of other zoonotic pathogens (2). We report a confirmed case of human babesiosis caused by *B. microti* infection in Hungary.

A 64-year-old man who lived in the countryside and worked as a farmer sought care at an emergency department on July 7, 2021, because of fatigue, nausea, vomiting, and a 10-kg weight loss during the past 2 months. His body temperature reached 38.9°C. He was unaware of having any chronic illnesses or tick infestations and did not have a blood transfusion or indicate a travel history outside of Hungary. Routine laboratory tests confirmed slightly elevated bilirubin (2.13 mg/dL), lactate dehydrogenase (760 U/L), alkaline phosphatase (170 U/L), gamma-glutamyl transferase (207 U/L), blood urea nitrogen (36.96 mg/dL), and creatinine (1.27 mg/dL) levels. He also had hyponatremia (120 mEq/L), prominent elevation of

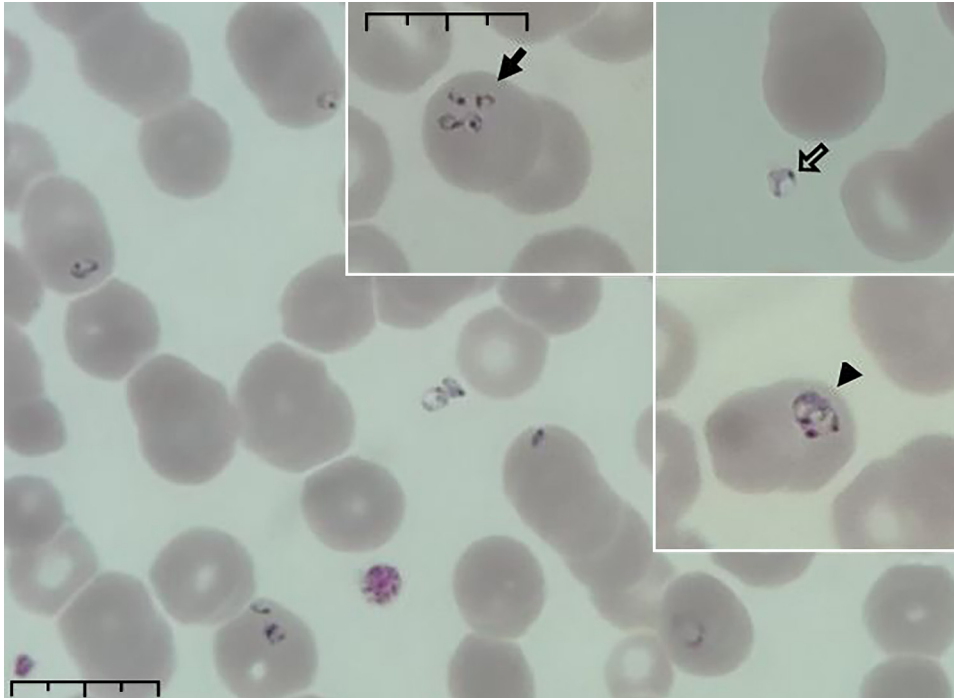


Figure 1. Peripheral blood smear from patient who had a confirmed case of autochthonous human babesiosis, Hungary. Smear shows erythrocytes infected with *Babesia* sp.; smear was stained with May-Grünwald Giemsa stain and examined by using light microscopy. In inset images, solid arrow indicates cells infected with multiple merozoites, open arrow indicates extracellular parasites, and arrowhead indicates vacuolated ring forms (trophozoites). Scale bars indicates 10 μ m.

ultrasensitive C-reactive protein (218.8 mg/L), and new-onset diabetes, as well as slight anemia (hematocrit 37.9%) and an elevated procalcitonin level (1.94 ng/mL). A complete blood count examined by using an automated hematology analyzer (Sysmex, <https://www.sysmex.com>) showed elevated monocyte levels (25%) and thrombocytopenia (78×10^9 platelets/L). We examined peripheral blood smears by using au-

tomated and light microscopy, which confirmed intraerythrocytic ring forms with central vacuoles, some intraerythrocytic tetrads, and extraerythrocytic forms, suggesting babesiosis rather than malaria (Figure 1). Parasites infected 4.5% of erythrocytes. Because of microscopic findings and laboratory results, hospital staff tested blood haptoglobin level, which was 0.0 mg/dL, confirming suspected hemolysis.

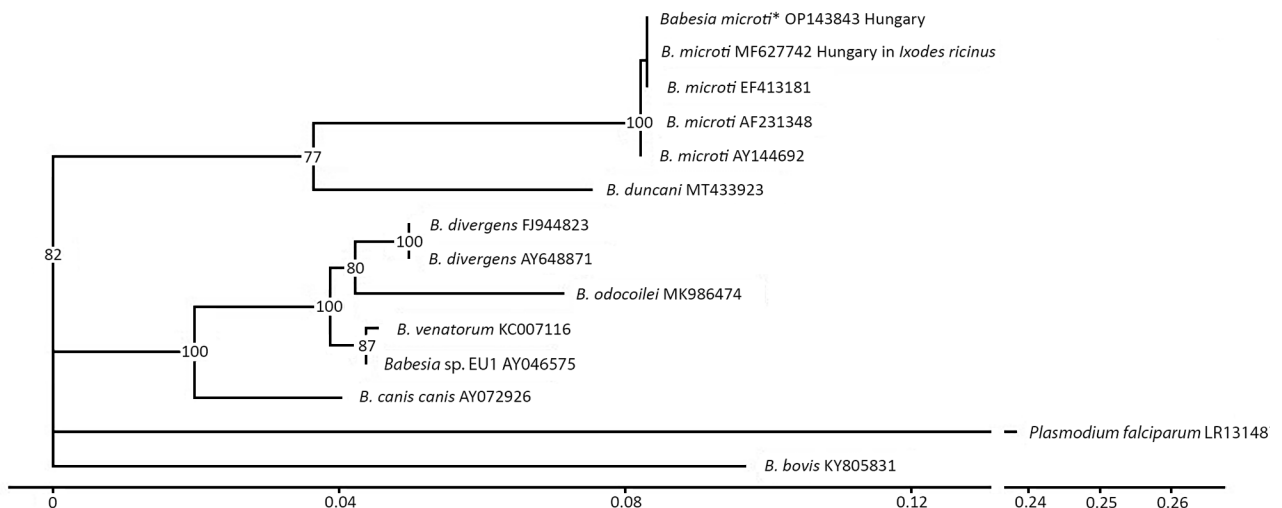


Figure 2. Phylogenetic analysis of *Babesia* spp. in confirmed case of autochthonous human babesiosis, Hungary. Asterisk indicates *B. microti* isolated from the patient in this case study. Phylogenetic tree was constructed by using Ggtree (5) according to multiple sequence alignments created by using MAFFT software (6). Best substitution model (3-parameter model, TPM2u) was selected by using functions of the phangorn version 2.11.1 R package (7) according to the Bayesian information criterion. Neighbor-joining tree was optimized by using the maximum-likelihood method. Bootstrap values were produced by 100 iterations and are indicated at branches. All data processing and plotting were performed in R version 4.4.1 (The R Project for Statistical Computing, <https://www.r-project.org>). GenBank accession numbers are indicated after the species name. Scale bar indicates nucleotide substitutions per site.

Other symptoms appeared during hospitalization, including left subcostal pain, decreased exercise tolerance, constipation, shivering, and new-onset torpidity; blurred vision occurred a few days after admission. Although malaria is not endemic in Hungary, we performed serologic tests for *Plasmodium* spp., which had negative results.

We performed PCR with primers BJ1 and BN2 to amplify a 459-bp fragment of the 18S rRNA gene of *Babesia* sp. (3) at the University of Veterinary Medicine, Budapest; the fragment was sequenced at the University of Szeged, Szeged, Hungary. We deposited the sequence in GenBank (accession no. OP143843.1). Nucleotide BLAST (<https://blast.ncbi.nlm.nih.gov>) analysis of the sequence showed 100% homology to *B. microti* detected in *I. ricinus* ticks and human blood (4). Although the sequence likely represents *B. microti*, further sequencing was not possible, and another closely related *Babesia* species cannot be excluded. We constructed a phylogenetic tree to compare the sequence with other *Babesia* spp. sequences found in GenBank (Figure 2).

Because of the advanced age of the patient and the clinical picture, we administered atovaquone/proguanil and azithromycin for 2 weeks (atovaquone is available in Hungary as an antimalaria drug). The patient became afebrile, and his condition improved. During follow-up examinations, fatigue and blurred vision gradually disappeared, and laboratory results improved. On the eighth day after treatment ended, we were unable to see any parasites through microscopic examination of blood. By the ninth week after treatment, lactate dehydrogenase, haptoglobin, and hemoglobin levels had normalized, and the patient fully recovered.

Although most human babesiosis cases have been imported in Europe, an increasing number of autochthonous *Babesia* spp. infections have been reported, possibly from a greater chance of tick contact because of human behavior changes (e.g., seeking outdoor activities) and a surge in vector population because of climate change. Furthermore, the number of immunocompromised hosts who have a more severe disease course and seek medical care is increasing as well.

In conclusion, although the 2 zoonotic species *B. divergens* and *B. microti* and their *I. ricinus* tick vector can be found in Hungary (8), imported or autochthonous

human babesiosis cases had not been reported in this country. Babesiosis is not an endemic disease in Hungary; thus, clinicians rarely suspect this disease, despite the typical symptoms. Seroepidemiologic findings confirm the possibility of *Babesia* spp. transmission to humans in Europe. The increasing number of reported cases indicates that babesiosis should be considered in the differential diagnosis of patients manifesting fever in Europe. Furthermore, peripheral blood smears to detect this parasite should be a routine part of the workup for febrile illnesses, especially when disease-typical laboratory findings are present.

About the Author

Dr. Sipos is a medical doctor specializing in infectious diseases. His academic interests focus on infections of immunocompromised hosts and differential diagnosis of fever.

References

- Hildebrandt A, Zintl A, Montero E, Hunfeld KP, Gray J. Human babesiosis in Europe. *Pathogens*. 2021;10:1165. <https://doi.org/10.3390/pathogens10091165>
- Yabsley MJ, Shock BC. Natural history of zoonotic *Babesia*: role of wildlife reservoirs. *Int J Parasitol Parasited Wildl*. 2012;2:18–31. <https://doi.org/10.1016/j.ijppaw.2012.11.003>
- Casati S, Sager H, Gern L, Piffaretti JC. Presence of potentially pathogenic *Babesia* sp. for human in *Ixodes ricinus* in Switzerland. *Ann Agric Environ Med*. 2006;13:65–70.
- Moniuszko-Malinowska A, Swiecicka I, Dunaj J, Zajkowska J, Czupryna P, Zambrowski G, et al. Infection with *Babesia microti* in humans with non-specific symptoms in North East Poland. *Infect. Dis*. 2016;48:537–43. <https://doi.org/10.3109/23744235.2016.1164339>
- Xu S, Li L, Luo X, Chen M, Tang W, Zhan L, et al. Ggtree: a serialized data object for visualization of a phylogenetic tree and annotation data. *Imeta*. 2022;1:e56. <https://doi.org/10.1002/imt2.56>
- Katoh K, Standley DM. MAFFT multiple sequence alignment software version 7: improvements in performance and usability. *Mol Biol Evol*. 2013;30:772–80. <https://doi.org/10.1093/molbev/mst010>
- Schliep K, Potts AJ, Morrison DA, Grimm GW. Intertwining phylogenetic trees and networks. *Methods Ecol Evol*. 2017;8:1212–20. <https://doi.org/10.1111/2041-210X.12760>
- Sréter T, Kálmán D, Sréterné Lancz Z, Széll Z, Egyed L. *Babesia microti* and *Anaplasma phagocytophilum*: two emerging zoonotic pathogens in Europe and Hungary. *Orv Hetil*. 2005;146:595–600.

Address for correspondence: Dávid Sipos, University of Pécs, Rákóczi út 2, 7623 Pécs, Hungary; email: sipos.david@pte.hu