Travel Medicine and Infectious Disease 71 (2026) 102980

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

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

Blood smear examination matters: an incidental case of tick-borne relapsing fever in a traveller returning from Senegal

Alessandro Pavesi [a,1], Andrea Ciccarone [a,1], Jacopo Logiudice [a], Benedetta Fioretti [a], Angelica Lenzi [a], Maurizio Gulletta [b], Stefano Di Bella [c], Cristina Bertasio [d], Nadia Vicari [d], Lina Rachele Tomasoni [b], Francesco Castelli [a], Benedetta Rossi [a,b,e,*]

[a] Department of Clinical and Experimental Sciences, Unit of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy
[b] Unit of Infectious and Tropical Diseases, ASST Spedali Civili di Brescia, Brescia, Italy
[c] Clinical Department of Medical, Surgical and Health Sciences, Trieste University, Trieste, Italy
[d] Istituto Zooprofilattico Sperimentale della Lombardia ed Emilia Romagna "Bruno Ubertini", Brescia, Italy
[e] Department of Experimental Medicine and Public Health, School of Advanced Studies, University of Camerino, Camerino, Italy

ARTICLE INFO

Keywords:
Borreliosis
Jarisch-Herxheimer
Blood smear
Ticks
One health
Zoonosis

ABSTRACT

Relapsing fever is caused by various species of *Borrelia* bacteria and is traditionally categorized into louse-borne relapsing fever (LBRF) and tick-borne relapsing fever (TBRF). The epidemiological patterns differ according to the vector: LBRF is typically linked to epidemic outbreaks, while TBRF usually presents with an endemic distribution. Even though TBRF is endemic also in the Mediterranean Basin, diagnosis is mainly incidental in migrants or visiting friends and relatives travelling from sub-Saharan Africa.

We report a case of TBRF with aseptic meningitis caused by *Borrelia crocidurae/duttonii/hispanica* in a 46-year-old Senegalese man, diagnosed through blood smear examination performed during the diagnostic workup for malaria.

Diagnosis of TBRF is still primarily based on the direct detection of spirochetes in blood smear, although novel molecular methods (PCR) have recently been developed. Awareness, especially in non-endemic areas, and a One Health approach are crucial. Such an approach should aim to monitor the spread of *Borrelia* species, their vectors, and animal reservoirs, as well as to study their interactions with the environment and climate.

1. Introduction

Tick-borne relapsing fever (TBRF) is a zoonosis caused by relapsing fever group *Borrelia*, a group of spirochetes transmitted by ticks. TBRF differs from louse-borne relapsing fever (LBRF) in the *Borrelia* species involved (with *Borrelia recurrentis* being responsible for LBRF), as well as in epidemiology, reservoirs, vectors, and clinical presentation [1]. Transmission occurs worldwide, with the exception of Australia and Antarctica, although the precise incidence and prevalence of cases remains unknown [2].

Soft ticks belonging to the *Ornithodoros* spp. are considered the most competent vectors responsible for the transmission of TBRF, particularly in tropical and subtropical rural regions. Major endemic areas are scattered across Africa, Southern Europe, Asia, and Latin America. Here, contact with rodent burrows provides access to intermediate hosts and natural reservoirs of the disease. *Ornithodoros* spp. are vectors for *B. duttonii*, *B. crocidurae*, and *B. hispanica*. Conversely, certain hard ticks, such as *Ixodes* spp. and other *Ixodidae* have recently been recognized as competent vectors for the transmission of *B. miyamotoi*, particularly in temperate continental regions such as Northern Asia and North America, but not well described in West-Africa [3,4].

In the past two decades, fewer than 200 cases TBRF have been reported in Europe, mainly as autochthonous cases in Spain, with sporadic imported or autochthonous in others countries [2]. In Italy, only a few cases have been reported over the past decades [5–7]. Here, we describe a case of TBRF with aseptic meningitis caused by *Borrelia crocidurae/duttonii/hispanica*. From a One Health perspective, we aim to raise awareness in non-endemic countries of both imported and potential

* Corresponding author. Department of Clinical and Experimental Sciences, Unit of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy.
E-mail address: benedetta.rossi19@gmail.com (B. Rossi).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tmaid.2026.102980
Received 3 February 2026; Received in revised form 3 April 2026; Accepted 10 April 2026
Available online 12 April 2026

autochthonous cases, to enhance diagnostic vigilance and expand diagnostic capability, guide timely clinical management, and inform public health strategies.

2. Case report

A 46-year-old Senegalese man, with no significant past medical history and living in Italy since 2013, presented to the Emergency Room on November, 3 2023, after a one-month trip to Senegal (September, 19 - October, 19 2023). He complained of headache beginning one week after his return, and myalgia. Moreover, he reported a 5-day episode of remittent fever that began approximately 10 days after his arrival in Senegal, which was treated as malaria during the trip. He had not received vaccinations or antimalarial prophylaxis. At admission, he was afebrile, with mild thrombocytopenia and anaemia, while renal, hepatic, and inflammatory parameters were within normal ranges. Head computed tomography (CT) was unremarkable, and malaria testing (blood smear, malarial antigens, and PCR for *Plasmodium* spp.) and SARS-CoV-2 swab were negative. He was then admitted to the Neurology Unit for further investigations. On day 4 upon admission, the patient developed fever: blood and urine cultures were collected, and the blood smear was repeated to rule out malaria. Laboratory tests revealed monocytosis, anaemia, thrombocytopenia, and an elevated C-reactive protein. Cultures and malarial testing were negative. The blood smear was reviewed by a Tropical Diseases specialist, who identified spirochetes (Fig. 1).

The patient was subsequently transferred to the Infectious and Tropical Diseases Unit with suspected TBRF. Because of worsening thrombocytopenia (platelets count: 39,000 cell/mm^3), lumbar puncture (LP) was deferred. Oral doxycycline 100 mg twice daily was initiated on day 5. Two hours after the first dose, he developed high fever (39.6 °C), chills, dyspnea and hypotension. A Jarish-Herxheimer reaction was suspected and supportive therapy was promptly provided with intravenous fluids, oxygen support, paracetamol and methylprednisolone, with resolution of symptoms. On day 6, LP was performed: cerebrospinal fluid (CSF) analysis showed normal glucose level (79 mg/dL), with a concomitant blood glucose level glycemia of 124 mg/dL, hyperprotidorrachia (679 mg/L), and pleocytosis (326 cells/μL; 90% lymphocytes, 10% monocytes). CSF and blood sample were sent to the Istituto Zooprofilattico Sperimentale Lombardia ed Emilia Romagna (IZSLER), where real-time PCR on the blood confirmed *Borrelia* spp. and the sequencing of a fragment of 16S rRNA confirmed an identity of 99.72% with *Borrelia crocidurae/duttonii/hispanica (NCBI Accession Number* PX376609*)*. No *Borrelia* spp. DNA was detected in the CSF sample. Considering neurological involvement, antibiotic treatment was switched to intravenous ceftriaxone, leading to gradual clinical improvement and normalization of laboratory parameters. On day 17, the patient was discharged afebrile, without residual headache, and with the recommendation to complete a 14-day course of intravenous ceftriaxone through the Outpatient Parenteral Antimicrobial Therapy (OPAT) program.

3. Discussion

As illustrated by our case, TBRF may be easily misdiagnosed because of its resemblance to other febrile infections, with the most distinctive clinical feature being the relapsing pattern of fever. Its pattern is characterized by approximately 2–7 days of fever, interspersed with afebrile periods of around 10 days, corresponding to phases in which the spirochete evades the immune system. TBRF is usually benign and self-limiting, even though neurological involvement occurs in approximately 10-40% of cases, with manifestations such as dizziness, apathy, or delirium, and with a fatality rate around 2-10% if untreated [8].

In our case, no evidence of *Borrelia* infection was detected in the CSF, despite the presence of signs and symptoms of aseptic meningitis. However, it cannot be established with certainty whether the negative CSF PCR reflected the initiation of doxycycline therapy before lumbar puncture or whether the neurological manifestations are thought to be more frequently related to spirochetemia and high fever rather than direct central nervous system invasion by *Borrelia*. Notably, brain inflammation is a common pathological feature of TBRF. Findings from murine models show that inoculation with *B. turicatae* or *B. crocidurae* induces mild leptomeningeal inflammation characterized by macrophage infiltration and microglial activation in the parenchyma, with only limited numbers of lymphocytes and granulocytes [9]. Another complication related to spirochetemia and the inflammatory response is *Jarisch-Herxheimer* reaction, following the first dose of antibiotic therapy. This reaction is a well-described inflammatory response often occurring after antibiotic initiation in several spirochetal infections, including tick-borne relapsing fever, syphilis, Lyme disease, and

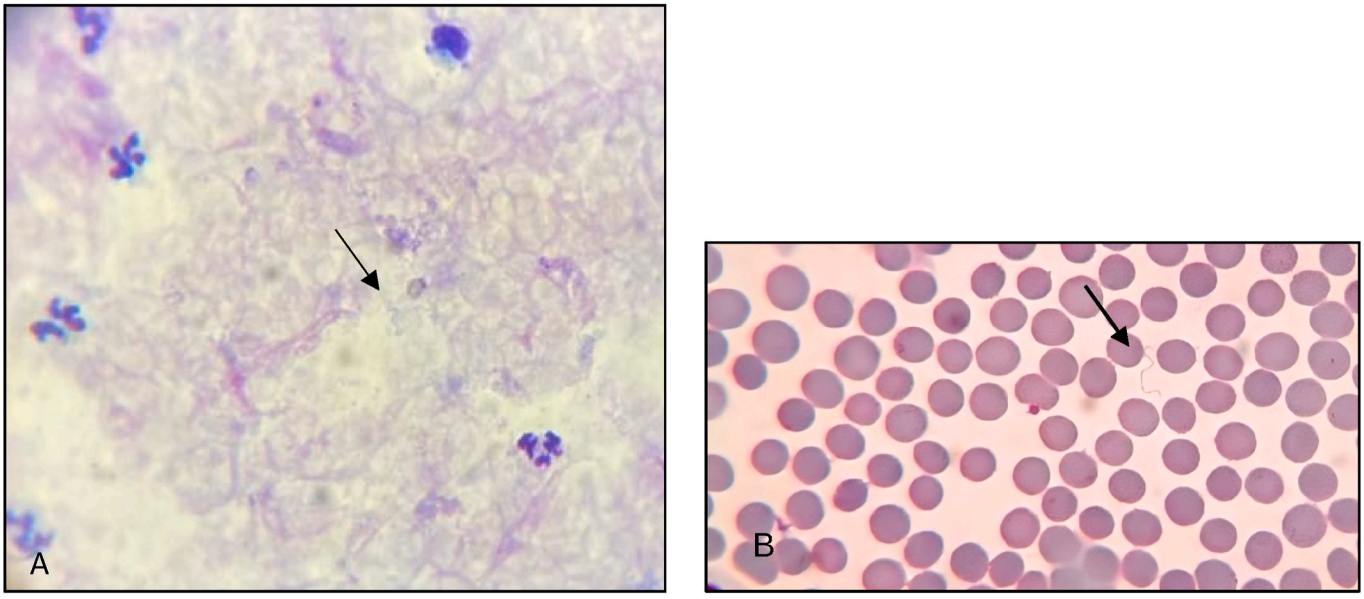

Fig. 1. Spirochetes seen in peripheral blood stained with Giemsa optical microscopy, magnification x100.
A. Thick-blood smear; B. Thin-blood smear with intact blood cells.

leptospirosis.

Due to its overlapping clinical features with malaria and the similar diagnostic approach, TBRF may be diagnosed incidentally. It should therefore be included in the differential diagnosis of relapsing or acute undifferentiated fever in travellers returning from endemic regions. Once malaria has been excluded, other infectious diseases should also be considered, including other tick-borne infections such as African tick-bite fever, as well as acute HIV infection, meningococcal disease, leptospirosis [10]. In selected cases, empirical antimicrobial therapy with ceftriaxone and doxycycline may be considered pending diagnostic confirmation [11]. As rapid diagnostic tests increasingly replace microscopy for malaria, such incidental detection of *Borrelia* on blood smears is likely to decline, potentially exacerbating underdiagnoses of TBRF. Despite this, blood smear examination remains indispensable for the evaluation of hemoparasites. However, the sensitivity of conventional blood smear examination is limited, and cases with low spirochetemia may be missed; therefore, if blood smear results are negative, the diagnosis of TBRF may be significantly delayed. Increasing awareness among frontline clinicians, including emergency department and primary care physicians, is essential to ensure that TBRF is considered in febrile travellers returning from endemic regions and that appropriate specialist evaluation is obtained when needed.

During the primary attack, spirochetemia can be observed on thick- or thin-blood smears using Giemsa staining or dark-field microscopy, remembering that the positivity thresholds are estimated at 10^4 and 10^5 spirochetes per mL of blood, respectively [12].

A higher sensitivity and specificity have been demonstrated with quantitative buffy coat (QBC) fluorescence analysis. The QBC test has been initially designed to facilitate the diagnosis of malaria, and it is based on the centrifugal layering of parasites into a 60-ml blood capillary tube containing acridine orange dye [7]. In a laboratory model conducted in rural area in Ethiopia, the QBC was able to detect spirochetes in human blood down to a concentration of 10 organisms/mm^3, confirming a higher sensitivity compared to blood smear [13]. However, it requires technical expertise and laboratory infrastructure and does not allow species identification. Alternative concentration methods, including simple centrifugation techniques, have also been proposed to improve the sensitivity of microscopic detection of *Borrelia* in blood samples and to enhance DNA extraction for subsequent PCR analysis [14]. While QBC is more sensitive than conventional blood smears, morphological confirmation or molecular testing (PCR) is still necessary for definitive diagnosis. Molecular methods indeed are increasingly used due to their high sensitivity and ability to identify *Borrelia* species, even in samples with very low spirochete loads. Emerging molecular diagnostic approaches, including multiplex PCR assays and next-generation sequencing methods, may further improve the detection and characterization of tick-borne pathogens; however, these technologies are currently largely restricted to specialized or reference laboratories. PCR on blood is expected to have the highest sensitivity during periods of spirochetemia, usually corresponding to febrile episodes. By contrast, evidence on CSF PCR in neurologic TBRF is limited and mainly based on case reports or small case series, suggesting variable and probably low positivity rates. In our case, lumbar puncture was performed after doxycycline initiation, which may have further reduced the sensitivity of CSF PCR. In particular, genes encoding 16S ribosomal RNA, flagellin, and glycerophosphodiester phosphodiesterase appear useful for *Borrelia* taxonomy, as even minor differences in these genes can help differentiate Borrelia species [15]. To date, specific serological assays are not available for most known TBRF species, limiting their diagnostic utility.

. The four main Borrelia species associated with soft tick–borne relapsing fever in Europe are *B. hispanica*, *B. persica, B. caucasica* and *B. crocidurae*, mainly transmitted by Ornithodoros spp. The presence of *Ornithodoros* spp. in Italy is poorly documented: *Ornithodoros maritimus* has been reported in Sardinia, although its competence in transmitting *Borrelia* remains unknown, alongside reports of *Ornithodoros erraticus* [16]. The only case of autochthonous transmission of TBRF described in the literature involved meningitis with cranial polyneuritis and cavernous sinus thrombosis caused by *Borrelia crocidurae*. The pathogen's transmission route remains unclear, as no exposure to *Ornithodoros* ticks was documented [6]. Most tick species present in Italy belong to the genus *Ixodes*. More recently, however, the presence of *B. miyamotoi* has been documented in ticks of the genus *Ixodes* in northeastern Italy and Veneto region, although no confirmed cases of human transmission have been reported [17]. To date, only one autochthonous case of TBRF has been reported in Italy, involving meningitis with cranial polyneuritis and cavernous sinus thrombosis caused by *Borrelia crocidurae* [6]. In our case, the infection was most likely acquired during the patient's recent stay in Senegal, where TBRF is endemic. Therefore, the main implication in many European countries, is not the search for autochthonous cases, but rather increased clinical awareness of imported TBRF in travellers returning from endemic areas. A One Health approach is particularly relevant though in endemic settings, where integrated surveillance of human infections, tick vectors, and animal reservoirs may improve understanding of transmission dynamics, including vector-host interactions, and support the development of more effective diagnostic strategies. For example, the detection of Borrelia DNA within ticks can be considered a valuable research tool, providing useful information about the epidemiology of tick-borne diseases.

4. Conclusion

TBRF remains an underdiagnosed condition and should be considered as a diagnostic hypothesis in the work-up of recurrent fevers, particularly in visiting friends and relatives travelling from endemic regions. While peripheral blood smear remains the diagnostic gold standard, broader adoption of molecular techniques, which are less operator-dependent and allow for species identification, is needed. A One Health, multidisciplinary approach is essential to strengthen surveillance, containment, and diagnostics. In endemic countries with limited reported cases, integrated surveillance systems should include: training of healthcare workers for early clinical recognition, strengthening laboratory networks to expand molecular diagnostics, and monitoring tick vectors through veterinary and environmental networks. Pre-travel counselling, including advice on malaria prophylaxis, recommended vaccinations, and prompt medical evaluation in the event of febrile illness after travel, remains essential for travellers visiting endemic regions**.** These strategies enable timely case detection, facilitate containment of potential outbreaks, and ensure a coordinated public health response even where the disease does not yet represent a major public health concern.

CRediT authorship contribution statement

Alessandro Pavesi: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Andrea Ciccarone:** Writing – original draft, Investigation. **Jacopo Logiudice:** Writing – original draft, Investigation. **Benedetta Fioretti:** Writing – original draft, Investigation. **Angelica Lenzi:** Writing – original draft, Investigation. **Maurizio Gulletta:** Writing – review & editing, Investigation. **Stefano Di Bella:** Writing – review & editing, Visualization. **Cristina Bertasio:** Writing – review & editing, Investigation. **Nadia Vicari:** Writing – original draft, Investigation. **Lina Rachele Tomasoni:** Writing – review & editing, Investigation. **Francesco Castelli:** Writing – review & editing, Supervision. **Benedetta Rossi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Informed consent

The patient provided written informed consent for the publication of clinical data and case-related information.

Ethical approval

Not applicable.

Funding

None to declare, this research received no external funding or financial support.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Warrell DA. Louse-borne relapsing fever (Borrelia recurrentis infection). Epidemiol Infect 2019 Jan;147:e106. https://doi.org/10.1017/S0950268819000116. PubMed PMID: 30869050; PubMed Central PMCID: PMC6518520.

[2] Jakab Á, Kahlig P, Kuenzli E, Neumayr A. Tick borne relapsing fever - a systematic review and analysis of the literature. PLoS Neglected Trop Dis 2022 Feb;16(2): e0010212. https://doi.org/10.1371/journal.pntd.0010212. PubMed PMID: 35171908; PubMed Central PMCID: PMC8887751.

[3] Kubiak K, Szczotko M, Dmitryjuk M. Borrelia miyamotoi-An emerging human tick-borne pathogen in Europe. Microorganisms 2021 Jan 12;9(1):154. https://doi.org/10.3390/microorganisms9010154. PubMed PMID: 33445492; PubMed Central PMCID: PMC7827671.

[4] Domínguez MC, Vergara S, Gómez MC, Roldán ME. Epidemiology of tick-borne relapsing fever in endemic area, Spain. Emerg Infect Dis 2020 May;26(5):849–56. https://doi.org/10.3201/eid2605.190745.

[5] Tordini G, Giaccherini R, Corbisiero R, Zanelli G. Relapsing fever in a traveller from Senegal: determination of borrelia species using molecular methods. Trans R Soc Trop Med Hyg 2006 Oct;100(10):992–4. https://doi.org/10.1016/j.trstmh.2005.11.002. PubMed PMID: 16455121.

[6] Malincarne L, Schiaroli E, Ciervo A, Scaglione V, Paciaroni M, Mancini F, et al. Meningitis with cranial polyneuritis and cavernous sinus thrombosis by borrelia crocidurae: first autochthonous case in Europe. Int J Infect Dis 2019 May;82:30–2. https://doi.org/10.1016/j.ijid.2019.02.028. PubMed PMID: 30818047.

[7] Chatel G, Gulletta M, Matteelli A, Marangoni A, Signorini L, Oladeji O, et al. Short report: diagnosis of tick-borne relapsing fever by the quantitative buffy coat fluorescence method. Am J Trop Med Hyg 1999 May;60(5):738–9. https://doi.org/10.4269/ajtmh.1999.60.738.

[8] Lopez J, Hovius JW, Bergström S. Pathogenesis of relapsing fever. Curr Issues Mol Biol 2021;42:519–50. https://doi.org/10.21775/cimb.042.519. PubMed PMID: 33372163; PubMed Central PMCID: PMC8756760.

[9] Cadavid D, Londoiño D. Understanding tropism and immunopathological mechanisms of relapsing fever spirochaetes. Clin Microbiol Infection 2009 May;15 (5):415–21. https://doi.org/10.1111/j.1469-0691.2009.02785.x.

[10] Bhargava A, Ralph R, Chatterjee B, Bottieau E. Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions. BMJ 2018 Nov; 29:k4766. https://doi.org/10.1136/bmj.k4766.

[11] Camprubí-Ferrer D, Oteo JA, Bottieau E, Genton B, Balerdi-Sarasola L, Portillo A, et al. Doxycycline responding illnesses in returning travellers with undifferentiated non-malaria fever: a European multicentre prospective cohort study. J Trav Med 2023 Feb 18;30(1). https://doi.org/10.1093/jtm/taac094. taac094.

[12] Hovette P, Aubron C, Perrier-Gros-Claude JD, Schieman R, N'Dir MC, Camara P. [value of quantitative buffy coat (QBC) in borreliasis-malaria co-infection]. Med Trop 2001;61(2):196–7. PubMed PMID: 11582881.

[13] Cobey FC, Goldbarg SH, Levine RA, Patton CL. Short report: detection of borrelia (relapsing fever) in rural Ethiopia by means of the quantitative buffy coat technique. Am J Trop Med Hyg 2001 Aug;65(2):164–5. https://doi.org/10.4269/ajtmh.2001.65.164. PubMed PMID: 11508395.

[14] Larsson C, Bergström S. A novel and simple method for laboratory diagnosis of relapsing fever borreliosis. TOMICROJ 2008 Jan 14;2(1):10–2. https://doi.org/10.2174/1874285800802010010.

[15] Faccini-Martínez ÁA, Silva-Ramos CR, Santodomingo AM, Ramírez-Hernández A, Costa FB, Labruna MB, et al. Historical overview and update on relapsing fever group borrelia in Latin America. Parasites Vectors 2022 Jun 8;15(1):196. https://doi.org/10.1186/s13071-022-05289-5. PubMed PMID: 35676728; PubMed Central PMCID: PMC9175325.

[16] Rebaudet S, Parola P. Epidemiology of relapsing fever borreliosis in Europe. FEMS Immunol Med Microbiol 2006 Oct;48(1):11–5. https://doi.org/10.1111/j.1574-695X.2006.00104.x. PubMed PMID: 16965346.

[17] Moro L, Da Rold G, Beltrame A, Formenti F, Mazzi C, Ragusa A, et al. Surveillance of tick-borne pathogens in ticks from humans in the province of Verona, Italy (2018-2022): a prospective study. Microorganisms 2025 Apr 23;13(5):965. https://doi.org/10.3390/microorganisms13050965. PubMed PMID: 40431138; PubMed Central PMCID: PMC12114187.