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Diagnosis of Louse-Borne Relapsing Fever despite Negative Microscopy in Two Asylum Seekers from Eastern Africa

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Abstract. We report two cases of louse-borne relapsing fever observed at our Institution in June 2016. Both patients were young asylum seekers from Africa who had recently arrived in Milan, Italy. Notably, direct microscopic examination of peripheral blood smears was repeatedly negative for the presence of spirochetes and the diagnosis, supported by clinical and epidemiologic evidence, required molecular confirmation by polymerase chain reaction amplification of DNA extracted from blood and sequencing of the amplified products.

Louse-borne relapsing fever (LBRF), caused by *Borrelia recurrentis* and transmitted by the body louse (*Pediculus humanus*), is a neglected infectious disease that has been responsible for huge outbreaks in the past but has virtually disappeared from Europe since the end of World War II.[1,2] War, famine, overcrowding, and poor living conditions are recognized risk factors favoring the re-emergence of this disease.

From June to December 2015, around 50 cases of LBRF were described among asylum seekers from Eastern Africa arriving to Europe with reports from Germany, Italy, Belgium, Switzerland, the Netherlands, and Finland.[3–19] The latest report of imported LBRF in Europe regards a patient observed in Italy in June 2016 and coming from Mali.[20] In all published instances described as yet, migrants had stationed in overcrowded refugee camps in Libya before arriving to Italy after having crossed the Mediterranean Sea, with the exception of two patients who were probably infected in Turin, Italy, while sheltered in the same asylum as other individuals with the disease.[5]

We report herein two additional cases of LBRF in refugees from Somalia and Sudan who were admitted to our Department of Infectious Diseases in Milan, Italy, in June 2016. We describe their clinical presentation, the difficulties encountered in diagnosing the disease, and finally we review all cases of LBRF imported to Europe thus far.

PATIENT 1

On June 17, 2016, a 30-year-old Somali man was conducted from a center for asylum seekers located in Milan to our Emergency Department because of fever and suspected malaria. The patient had arrived in Italy 2 weeks earlier after a 4-month stay in Libya. He complained of fever, severe headache, vomiting, and knee arthralgias of 7 days duration. Of note, the patient mentioned an episode of "malaria" that occurred during his stay in Libya that resolved without specific treatment. On admission, physical examination was notable for arterial hypotension (80/50 mm Hg), tachycardia (120 bpm), and fever (38°C) with normal oxygen saturation while breathing ambient air (97%). Laboratory analysis showed elevated C-reactive protein (CRP) (364.5 mg/L), anemia (hemoglobin: 9.4 g/dL), thrombocytopenia (PLTs: 81,000/μL), and leukocytosis (white blood cells: 22,180/μL) with neutrophilia (20,405/μL), acute kidney injury (serum creatinine: 1.86 mg/dL), elevated bilirubin (2.85 mg/dL), D-dimer (1,713 mg/dL), fibrinogen (954 mg/dL), and an increased prothrombin activity (INR 1.68). The chest X-ray was reportedly unremarkable. A rapid malaria antigen test was negative, as well as direct microscopic examination of May-Grunwald-Giemsa (MGG) thin and Giemsa-stained thick blood smears (400 and 200 microscopic fields examined, respectively) which were sent to the microbiology laboratory for the detection of malaria parasites and spirochetes. Standard blood cultures eventually yielded negative results. No infestation by body lice could be found neither on the patient nor his clothing (the latter had been immediately changed on his arrival to Italy). The patient was hospitalized with a working diagnosis of LBRF and started with empirical oral doxycycline, 100 mg bid. A second blood smear obtained the following day for microscopic examination also turned negative for malaria parasites and spirochetes.

However, broad-range DNA polymerase chain reaction (PCR) of the patient's peripheral blood obtained at admission with primers 806r and 515PL that amplify a 328 base pair (bp) fragment of the small ribosomal DNA gene (16 sRNA), followed by direct sequencing of the amplified product, was positive for *B. recurrentis*/*B. duttonii.* In addition, PCR using *Borrelia* genus-specific primers B188 and B181 was also positive, with sequenced 350 bp amplicons showing a 100% identity with *B. recurrentis* and *B. duttonii*.[21]

The patient had an uneventful recovery and voluntarily abandoned the hospital after 3 days of antimicrobial therapy.

PATIENT 2

On June 26, 2016, a 26-year-old Sudanese man who was hosted in the same center for asylum seekers as patient 1 was referred to our Emergency Department because of headache, epistaxis, hematuria, abdominal pain, and diffuse arthralgias that had begun 6 days earlier. He had resided in Libya for

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1 year before arriving in Italy on June 11th after a journey by sea of 37 days. Upon admission, he was afebrile (36.7°C) with a normal blood pressure (120/60 mm Hg), tachycardia (90 bpm), and normal oxygen percutaneous saturation while breathing ambient air (97%). The physical examination was notable for scleral icterus. Laboratory analyses showed increased CRP levels (428.7 mg/dL), moderate anemia (Hb: 12 g/dL), a normal white blood cell count (7,300/μL), severe thrombocytopenia (6,000/μL), increased serum lactate dehydrogenase concentration (696 U/L), and prothrombin activity (INR: 1.4), moderate kidney injury (serum creatinine: 1.25 mg/dL), a markedly elevated bilirubin (12.32 mg/dL; direct 9.5 mg/dL), and increased fibrinogen (897 mg/dL). The chest X-ray was normal. Blood films (thin and thick smears stained with MGG and Giemsa) were negative for malaria parasites as well as spirochetes. Peripheral blood examinations by direct microscopy were repeated for the next three consecutive days and always gave negative results. The patient was finally hospitalized at the Department of Infectious Diseases and empirically started with oral doxycycline 100 mg bid because the clinical picture, laboratory findings, and travel history were highly evocative of LBRF. A rapid improvement of his clinical conditions followed the introduction of antibiotic therapy: on the fourth day of hospitalization, the platelet count was 112,000/μL and the total bilirubin concentration decreased to 2.6 mg/dL. However, treatment with doxycycline was interrupted after 3 days because of growing concentrations of liver transaminases (i.e., alanine transaminase: 150 U/L and aspartate transaminase: 278 U/L). Serologic tests were negative for hepatitis A, B, C, Chikungunya, dengue viruses, and Leptospira. Indirect immunofluorescence assays for the detection of antibodies against *B. recurrentis*, *B. duttonii*, and *B. crocidurae* were similarly negative. No treatment-induced Jarisch–Herxheimer reaction was noted. The patient was discharged on the fifth day of hospitalization in good clinical health.

DNA extracted from peripheral blood was subjected to PCR amplification using broad-range and *Borrelia* genus-specific primers, as described previously. While broad-range 16 rDNA PCR gave a negative result, the *Borrelia*-specific PCR was positive and sequencing of the amplified product revealed 100% identity with *B. recurrentis* and *B. duttonii*.

Definitive microbiology identification. Retrospective identification of the species of *Borrelia* was performed at the URMITE laboratory in Marseille. From the samples of both patients, we succeeded in amplifying a 344-bp fragment of the *flab* gene using the primers and conditions as described previously.[10,22] The comparison with the GenBank database sequences identified both sequences as *B. recurrentis* with 100% identity with several *B. recurrentis* isolates, including strain A1 (CP000993).

DISCUSSION

We report herein two additional cases of LBRF observed among African asylum seekers in Italy who were diagnosed in June 2016. To our knowledge, they represent a new observation of disease occurrence in Europe after those initially reported between June and December 2015.[3–19] Both cases were highly suggestive for LBRF based on their clinical presentation and epidemiologic features even if direct microscopic examination of patient blood smears was repeatedly negative. It should be emphasized that in our patients that the correct diagnosis was possible because of the high index of clinical suspicion due to our previous experience with LBRF and, ultimately, only by molecular testing.[10] However, in the absence of the latter, the diagnosis of LBRF may be overlooked.

As shown in Table 1, LBRF is a febrile disease that requires differentiation form several other infectious diseases such as malaria, bacterial sepsis, leptospirosis, dengue fever, meningitis, and typhoid fever. In all cases recently observed in Europe, the patient's travel history correctly elicited the request of a blood smear examination by direct microscopy to rule-out the diagnosis of malaria. This allowed the serendipitous observation of spirochetes in more than 90% of patients (Table 1). Nevertheless, it should be noted that in at least three cases the diagnosis was initially missed and was obtained only retrospectively on revision of the peripheral blood smears by an expert microscopist.[3,7,12] The sensitivity of a blood smear is approximately 70% in febrile patients but decreases to less than 5% during an afebrile period.[23] Thrombocytopenia was present in 90% of imported LBRF cases in Europe, and it is the most frequent hematologic alteration observed in the disease. Mild elevations of both liver transaminases and bilirubin are commonly reported (Table 1). Altogether, these laboratory findings may raise the initial suspicion of malaria as well as of viral hepatitis. Indeed, malaria can coexist with LBRF as documented in 3.6% of patients recently diagnosed in Europe (Table 1), a prevalence rate that is very similar to the one observed in Ethiopia, where both diseases are endemic.[24]

The second patient we describe here was notable for severe thrombocytopenia and hemorrhagic manifestations at presentation (i.e., epistaxis and hematuria).[12] A bleeding diathesis is indeed a common finding in LBRF with epistaxis being the most frequent manifestation even if hemoptysis and hematuria may also occur, findings that could direct the clinician toward a diagnosis of hemorrhagic fever or tuberculosis (the latter when cough and radiographic abnormalities coexist).[2,12]

The association of severe thrombocytopenia, leukocytosis, and hypotension is commonly encountered in severe sepsis and/or septic shock. In addition, very high levels of both CRP and procalcitonin (PCT) are reported as almost universal findings among patients with LBRF observed in Europe.[3–20] (Table 1). Both CRP and PCT are well-known biomarkers of the inflammatory response, and PCT is increasingly used in patients who are admitted to the intensive care unit to guide early antibiotic therapy when an undifferentiated infection or sepsis are suspected and the results of blood cultures are still pending.[25,26] These facts may explain why many patients with LBRF have been initially treated empirically with broad-spectrum antibiotics (i.e., ceftriaxone, piperacillin-tazobactam, or meropenem).[3,4,7,10,12,13,18,19] Because a Jarisch–Herxheimer reaction characterized by high spiking fever, severe hypotension, agitation, or confusion can be frequently precipitated among patients with LBRF after the first antibiotic administration (i.e., 62% prevalence rate in the recent European experience—see Table 1 for details), an erroneous diagnosis of sepsis can be further pursued. In fact, in the current European experience, at least 10 patients with LBRF (18.2%) required admission to the intensive care unit, and one of them died of multiorgan failure.[3,9,13,18]

In this regard, it is also interesting to mention that two recent reviews dealing with diagnosis and management of critically ill migrants did not consider LBRF as a possible infectious cause.[27,28]

TABLE 1

Clinical and laboratory characteristics of cases of Louse-borne relapsing fever imported in Europe, June 2015–June 2016 compared with an historical case file*

N† patients	55‡	62
Sex, *N* (%)	52 (94.5) M, 3 (5.9) F	46 (74.2) M, 16 (25.8) F
Age, years median (range)	20 (13–35)	20§ (10–49)
Country of origin, *N*† (%)	Somalia 46 (83.6), Eritrea 6 (11.8), Ethiopia 1 (1.8), Sudan 1 (1.8), Mali (1.8)	Ethiopia 62 (100)
Fever	51/55 (92.7%)	97%
Fever > 38°C	26/37 (70.3%)	94%
Headache	23/45 (51.1%)	87%
Malaise	11/45 (24.4%)	NR
Chills	3/45 (6.7%)	90%
Myalgia	15/45 (33.3%)	78%
Abdominal pain	10/45 (22.2%)	68%
Jaundice	20/39 (51%)	34%
Vomiting	10/45 (22.2%)	34%
Diarrhea	2/45 (4.4%)	NR
Urinary symptoms	5/45 (11.1%)	NR
Cough	4/45 (8.9%)	53%
Bleeding	4/45 (8.9%)†	23%‖
Meningism	3/55 (5.5%)	39%
Hypotension (systolic pressure under 90 mm Hg)	6/34 (17.6%)	12%
Body lice recovered	12/55 (21.8%)	NR
JHR	34/55 (61.8%)	100%
Concomitant malaria	2/55 (3.6%)	0
Blood smears positive	52/55 (94.5%)	62/62 (100)
Death	1/55 (1.8%)	3/62 (4.8%)
Anemia (Hb < 12 g/dL)	31/39 (79.5%)	41/44 (93.1%)
Hb g/dl, median (range)	10.7 (4.8–14.8)	12§ (8.5–15.2)
Leukocitosis (WBC > 11,000/μL)	16/38 (42.1%)	14/44 (31.8%)
Leukopenia (WBC < 4,000/μL)	4/38 (10.5%)	NR
WBC/μL, median (range)	9,400 (1,600–25,500)	8,230§ (2,900–24,400)
Thrombocytopenia (PLTs < 150,000/μL)	49/54 (90.7%)	34/37 (91.9%)
< 50,000/μL	25/54 (46.3%)	NR
Platelets/μL, median (range)	69,500 (4,000–610,000)	136,000§ (41,000–295,000)
C Reactive Protein, mg/dL, median (range)	284 (55–440.9)	NA
Increased	47/47 (100%)	
PCT, ng/mL, median, (range)	13,93 (0.95–62.1)	NA
Increased	19/20 (95%)	
AST U/L, median (range)	114 (30–282)	169 (4–1,050)
Increased	6/7 (85.7%)	20/33 (60.6%)
ALT U/L, median (range)	48 (7–489)	43 (18–65)
Increased	16/35 (45.7%)	8/10 (80%)
Bilirubin, total mg/dL	1.8 (0.3–12.3)	7§ (0.3–38.4)
Increased	31/38 (81.6%)	22/37 (59.5%)
Serum creatinine, mg/dL, median (range)	2.4 (0.9–4.7)	NR
Increased	7/35 (20%)	

* Ref. 2.
† 2 epistaxis, 1 hematuria, 1 hemoptysis.
‡ Including the two patients described herein.
§ Mean value; ALT = alanine aminotransferase; AST = aspartate aminotransferase; JHR = Jarisch–Herxheimer reaction; PCT = procalcitonin.
‖ Epistaxis; NA = not available; NR = not reported.

Furthermore, concerning the differential diagnosis, icteric patients with fever, headache, myalgias, conjunctival injection or hemorrhages, thrombocytopenia, leukocitosis, and renal failure may be suspected to be affected by leptospirosis, although this infection is rarely reported among migrants.

Likewise, meningitis can be suspected when the patient presents with severe headache and confusion, symptoms that can accompany the high fevers seen in LBRF. Indeed, in previous experiences, meningismus has been reported in up to 38% of patients with the disease.[2] However, the review of all published cases observed thus far in Europe documented a single case of meningeal involvement, with three patients undergoing lumbar puncture.[11,19,20]

In the present report, we discovered that both migrants were hosted a few days apart in the same center in Milan, a situation that could raise the possibility of local acquisition of the infection, as already reported in two individuals diagnosed with LBRF in Turin.[5] Although this issue cannot be formally ruled-out (the incubation period of LBRF is about 1 week), it should be noted that both patients were free of lice during their arrival in Milan, and no other case of LBRF was observed among migrants housed in the same center.

In conclusion, our experience highlights the many pitfalls that physicians may encounter in the diagnosis of LBRF among migrants: language barriers, negative blood microscopy, overlooked spirochetes in blood, clinical presentations mimicking other life-threatening infections (i.e., *P. falciparum* malaria, sepsis, leptospirosis, and meningitis), Jarisch–Herxheimer reactions, and the need of molecular techniques to rule-out the infection when suspicion is high but direct microscopic examination of peripheral blood is unrevealing.

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