

Leptospirosis in Travelers Returning from the Dominican Republic

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Leptospirosis is probably the most widespread zoonosis in the world.¹ Infection of humans occurs after indirect or direct exposure to urine of rodents, livestock, or a wide range of other mammals infected with *Leptospira interrogans* or other *Leptospira* species pathogenic to humans.² Incidence of the disease is higher in warmer than in temperate countries,³ and in developing than in affluent countries.^{4,5} Leptospirosis predominates in rural areas, although urban epidemics are emerging, with larger outbreaks in various regions throughout the world.⁶ Human infection occurs through exposure to water and soil contaminated by infected animal urine. It is an occupational risk of farmers, veterinarians, miners, abattoir and

sewer workers and has been associated with canoeing, wading, and swimming in contaminated lakes and rivers.^{7,8} In many tropical countries, dogs are a significant reservoir for isolated human infections and outbreaks.⁷ Occasional outbreaks in a recreational setting have been described among certain high-risk groups, such as white-water rafters and athletes.^{8,9} In the early phase of illness when initiation of appropriate chemotherapy is most successful, it can be easily mistaken for a range of other infectious diseases, sometimes with severe consequences.⁶

Case Reports

From December 2000 to September 2001, four patients who acquired leptospirosis independently from each other in the Dominican Republic have been diagnosed and treated at the Charité, Humboldt University, Berlin, Germany.

Patient 1 — In December 2000, a 60-year-old German man presented with an acute onset of fever, chills, cephalgias, and myalgias 3 days after return from a 3-week holiday in a tourist resort at the Playa Dorada near Puerto Plata. In the course of disease, he developed mild hepatic (aspartate aminotransferase [AST]: 70 U/L; alanine aminotransferase [ALT]: 94 U/L; total bilirubin: 1.9 mg/dL; normal hepatic ultrasound), renal (creatinine: normal; blood urea nitrogen [BUN]: 52 mg/dL; initially discrete proteinuria and erythrocythemia; normal renal ultrasound), and pulmonary involvement (no dyspnea; no abnormal physical findings but a discrete infiltration in the lower field of the right lung on the chest x-ray). C-reactive protein (CRP) was moderately raised to 6.6 mg/L. A full blood count showed a borderline leukocytosis of 11.20/nL but no other abnormalities. Routine blood cultures remained sterile. As for the other patients, a quantitative *Leptospira* immunoglobulin M (IgM) and immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) was performed with a commercially available test kit (Serion, Würzburg, Germany) utilizing genus-specific *Leptospira biflexa* antigen. IgM was positive with 1,136 U/mL, as well as IgG with 28.6 U/mL (Table). Malaria, dengue fever, brucellosis, rickettsiosis, hantavirus infection, viral hepatitis as well as other possible diagnoses were excluded. Our patient recovered fully

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Table Summary of Serologic Findings

Patient	Days after onset of symptoms	IgM (U/mL)*	Serology (ELISA) IgG (U/m)†	Leptospira interrogans serovar (MAT) reference < 1:100	Severity of Disease
1	8	> 500	18.2	bataviae (1:1600‡)	moderate
	10	> 500	16.8		
2	14	51.0	6.2	bataviae (1:100§)	severe
	16	73.0	6.2		
	38	41.6	5.7		
3	3	41.0	negative	bataviae (1:100)	moderate
	23	20.2	negative		
4	32	>500	10.0	copenhageni (1:12800#)	moderate
	67	>500	11.6		

MAT = microscopic agglutination test.

* < 5 U/mL negative; 5 to 9 U/mL borderline; > 9 positive.

† < 15 U/mL negative; 15 to 20 U/mL borderline ; > 20 positive.

‡ Cross reactions within this specimen: *Leptospira interrogans* serovar bratislava 1:200; *Leptospira interrogans* serovar copenhageni 1:200; *Leptospira interrogans* serovar hardjo 1:100.

§ cross reactions within this specimen: none.

|| cross reactions within this specimen: *Leptospira interrogans* serovar hardjo 1:100.

cross reactions within this specimen: *Leptospira interrogans* serovar autumnalis 1:400; *Leptospira interrogans* serovar bataviae 1:400; *Leptospira interrogans* serovar bratislava 1:400.

physically, and abnormal laboratory values returned to normal within 7 days after initiation of oral chemotherapy with amoxicillin/clavulanate (500/125 mg tid).

In this patient, the risk factor was probably river rafting at the end of the second week, but unfortunately he did not recall the name and location of the river.

Patient 2—In April 2001, a 25-year-old woman from the Dominican Republic but living in Germany for years returned from a 3-week visit to relatives and friends back home. Nine days after her return to Berlin, she fell suddenly ill with severe arthralgias, myalgias, a febrile continua of greater than 39°C, an erythematous rash and, initially, watery diarrhea. Her condition deteriorated, and she developed a small, hemodynamically irrelevant pericardial effusion, hepatic involvement (AST: 63 U/L; ALT: 112 U/L), and rhabdomyolysis (myoglobin: 1,354 µg/L; creatine kinase: 1,998 U/L; muscle-brain 59 U/L; hydroxybutyrate dehydrogenase: 506 U/L; lactate dehydrogenase [LDH]: 760 U/L) but only mild renal impairment (creatinine: 1.3 mg/dL, BUN: 66). CRP was raised to 32.8 mg/L. A full blood count showed a moderate leukocytosis of 14.41/nL but no other abnormalities. Routine blood cultures remained sterile, but *Leptospira* IgM was positive (51 U/mL, whereas IgG was borderline with 6.2 U/mL (see Table). Other potential single or additional causes of disease, including malaria, dengue fever, viral hepatitis, hantavirus infection, rickettsiosis, and brucellosis, were excluded. She received initial symptomatic treatment in our intensive care unit and amoxicillin/clavulanate (1000/200 mg tid intra-

venously for 10 days) and recovered within 4 weeks after admission.

During her holidays, she stayed most of the time with relatives in Santiago/Los Ciruelitos and in Santo Domingo under very basic living conditions, with stray dogs in abundance around in the quarter. Apart from bathing in heavily chlorinated pools during a trip to Samana, she did not have any leisure freshwater exposure.

Patient 3 — In May 2001, a 39-year-old German woman presented 1 day after her return from a 3-week diving holiday with an acute onset of high fever (continually greater than 39°C), chills, headaches, myalgias, diffuse abdominal pain, a pale erythematous rash, a tender left kidney region, and an initial bout of watery diarrhea. During the following days, she developed a mild renal but no hepatic or pulmonary involvement. CRP was raised to 16.2 mg/L. A full blood count showed a moderate leukocytosis of 12.05/nL but no other abnormalities. Routine blood cultures remained sterile, but *Leptospira* IgM turned out to be positive on day 3 (see Table). Malaria, dengue fever, hantavirus infection, brucellosis, rickettsiosis, and other possible diseases were excluded. Her fever defervesced, and her symptoms resolved completely. Laboratory values returned to normal within 5 days after initiation of chemotherapy with amoxicillin/clavulanate, which was administered intravenously for 3 days (1000/200 mg tid) followed by an oral course (500/125 mg tid) for another 7 days.

She had spent most of the time nearby her beach resort in Juan Dolio. Particular risk factors, such as jun-

gle trips or recreational freshwater exposure apart from bathing in chlorinated pools, were not identified.

Patient 4 — In September 2001, a 21-year-old German man presented with generalized weakness and jaundice 2 days after he had returned from a 6-week holiday. He reported that 2 weeks into his journey (4 weeks prior to presentation), he had been afflicted with an acute febrile illness with high fever, chills, myalgias, nausea, and later with jaundice. He had been seen by a local physician who administered antipyretics, but no further diagnostic effort was made. Ten days later, his fever defervesced, and he recovered slowly. When he was seen in our outpatient clinic, CRP was slightly raised to 0.8 mg/L (normal less than 0.6 mg/L). A full blood count still showed a moderate leukocytosis of 11.7/nL. Total bilirubin was slightly elevated (3.4 mg/dL), as were AST (20 U/L) and ALT (21 U/L). Creatinine was borderline with 1.2 mg/dL, whereas BUN was normal (33 mg/dL). Further diagnostics revealed a positive *Leptospira* serology (IgM greater than 500 U/L, IgG 10.0 U/L) (see Table). As expected, blood and urine cultures for 12 weeks on selective media remained negative. Malaria, dengue fever, brucellosis, rickettsiosis, hantavirus infection, viral hepatitis as well as other possible diagnoses were excluded. As he was already recovering spontaneously at that time, no antibiotic therapy was initiated. He had spent most of the time in Mao, where he stayed with a native family. Because of a badly healing ulcer on his right foot, he walked in sandals or with bare feet most of the time.

Discussion

Although the cases reported here are unrelated, they represent a remarkable accumulation of leptospirosis in travelers to the Dominican Republic, returning to Germany. TropNetEurop,¹⁰ a recently established sentinel surveillance network for infectious diseases imported from the tropics currently consists of about 40 major European clinical institutions and covers approximately 10% of all travelers returning sick from the tropics. No further cases of leptospirosis imported from the Dominican Republic were detected during the same period of time. Of the 52 cases of leptospirosis recorded for the year 2001 at the German Center for Infectious Diseases Epidemiology, the vast majority were autochthonous cases. We believe that our cluster of cases does not reflect any epidemiologic change but an altered pattern of activities of, and locations visited, by travelers.

The Table reflects the difficulty of achieving serologic proof in all cases. With the high IgM response by ELISA in case 1, and a high titer by microscopic agglutination test (MAT), used as the confirmatory test, despite having practically a single sample due to the later loss to follow-up of the patient, the serologic confirmation of

the diagnosis is convincing. Both cases 2 (the patient clinically worst afflicted) and 3 have to be considered as possible but not proven cases. Other possible diagnoses were excluded, and the clinical pictures appear to reflect the often atypical pattern of symptoms and signs. Serologic evidence is weak, with moderate IgM levels and failure of demonstration of the development of an IgG response in the respective ELISAs. Moreover, the corresponding MAT results did not rise above borderline level in both cases. Again, both patients did not return for follow-up investigations after recovery. Although the IgG response (ELISA) for patient 4 remained negative, IgM-ELISA from paired sera and MAT results were convincing.

For all patients, the MAT was performed in a German reference laboratory using 12 different serovars of pathogenic *Leptospira* species. Interestingly, there is evidence that at least one patient appeared to be infected with *Leptospira interrogans* serovar bataviae, with weaker evidence of infection with the same serovar in a further two cases. In contrast, a total of 643 serum samples from humans with suspected leptospirosis were tested with the MAT in the reference laboratory of the Dominican Republic in 2000 and the first 3 months in 2001. Approximately, 115 tested positive for various serovars, predominantly *L. interrogans* serovar icterohaemorrhagiae (40/34.8%), pomona (25/21.7%), and canicola (21/18.3%) but none for bataviae. Although the occurrence of some serovars is restricted to certain host species thus facilitating identification of particular risk factors for infection of humans, this does not apply to *L. interrogans* serovar bataviae, which has been found in multiple species.⁷

As demonstrated, sound clinical judgment should not be misguided by ambiguous laboratory results. If indicated, a preemptive therapeutic attempt has to be made on the grounds of a well-founded clinical suspicion.

Standard therapy consists of doxycyclin for mild or penicillin G⁵ for severe cases. As in our patients, a broad-spectrum penicillin in standard dose might be chosen in the first place to account for possible other bacterial agents that have to be considered prior to the definite establishment of the correct diagnosis in due course.

For certain groups or single persons running a particularly activity-related high risk or for visitors to defined areas with a known elevated risk, such as urban areas with an outbreak underway, it might be useful to recommend the application of precautionary measurements such as wearing protective clothing or the avoidance of exposure to freshwater with fresh cuts and abrasions. In these cases, chemoprophylaxis with doxycyclin should be considered. The decision might be easier if the destination is a malarious area, too, for which chemoprophylaxis with doxycycline might be pondered.

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At Simpson Bay in Saint Martin. Submitted by Danielle Gyurech, MD and Julian Schilling, MD.