Title: Leptospirosis in Spanish travelers returning from Chiang Mai: a case series

Keywords: Leptospirosis; Thailand; imported diseases; zoonosis; travel
Authors:

Natalia Rodríguez-Valero1, Helena Moza Moriño2, Miguel J. Martínez3, Aida Peiró3, Ines Oliveira1, Marta Bodro4, Joan Gómez-Junyent1, Joaquim Gascon1, Jose Muñoz1

1. ISGlobal, Barcelona Centre for International Health Research (CRESIB), Hospital Clínic (Department of International Health)-Universitat de Barcelona, Barcelona, Spain
2. Department of International Health, Hospital Universitario Virgen de la Salud, Toledo, Spain
3. Department of Clinical Microbiology, Hospital Clinic de Barcelona, Spain
4. Department of Infectious Diseases, Hospital Clinic Barcelona, Spain

Corresponding author: Rodriguez-Valero, Natalia M.D.; Department of Tropical Medicine and International Health, Hospital Clinic Barcelona. ISGlobal, Barcelona Centre for International Health Research (CRESIB), Hospital Clínic-Universitat de Barcelona C/Rosselló 132 2º2ª, 08036, Barcelona (Spain)
Email: natalia.rodriguez@isglobal.org Phone: +34932271857/+34658263216

Alternate corresponding author: Muñoz, Jose PhD; Department of Tropical Medicine and International Health, Hospital Clinic Barcelona. ISGlobal, Barcelona Centre for International Health Research (CRESIB), Hospital Clínic-Universitat de Barcelona C/Rosselló 132 4º2ª, 08036, Barcelona (Spain)
Email: jose.munoz@isglobal.org Phone: Tel.932275400 Ext.4135
Abstract

Background: Leptospirosis is an important zoonosis worldwide, nevertheless is often poor recognized in non tropical settings. In Thailand is becoming an emerging disease and Chiang Mai could become a popular spot to acquire the disease amongst travelers.

Methods: We describe three cases of imported leptospirosis undifferentiated fever after travelling to Thailand during the summer of 2015 diagnosed at two Spanish hospitals.

Results: Our three patients probably acquired leptospirosis while swimming in freshwater around Chiang Mai, a Thailand’s northern region with moderate incidence of leptospirosis. Travelers had normal white blood cell counts and low platelets, suggesting leptospirosis after ruling out other imported diseases such as malaria, dengue or typhoid.

Conclusion As recent findings point out, low platelets and normal white blood cell counts are clinical features that could help the clinician to suspect Leptospirosis infection. It should be always considered as a cause of fever, particularly if travelers come from a tropical country and have had contact with water or flooding, especially during rainy season.
Leptospirosis is an important zoonosis worldwide, nevertheless is often poor recognized in non tropical settings. In Thailand is becoming an emerging disease(1) and Chiang Mai could become a popular spot to acquire the disease amongst travelers. It should be always considered as a cause of fever, particularly if travelers come from a tropical country especially in those who performed any whitewater sport or other activities such as trekking, adventure races or spelunking.(2)

**Case 1**

A healthy 34 year-old Spanish male was treated at the Tropical Medicine outpatient clinic in Hospital Clinic of Barcelona after a trip to Thailand, from July 27 to August 17 2015. He visited Bangkok, Chiang Mai, Krabi and Kho Tao. On August 12th he started with high-grade fever and severe myalgia and he sought medical attention in a Bangkok’s hospital. There, the patient reported trekking and on August the 8th, he swam in freshwater in Chiang Mai, at Mae Taman River spot area. Physical examination was normal and the main laboratory findings were: 120,000 platelets/mm3, normal white blood cell count (WBC) (7300 WBC/mm3), lymphopenia (513 lymphocytes/mm3), aspartate transaminase (AST) 67 U/L, alanine transaminase (ALT) 71 U/L, creatinine 1.14mg/dL, and urea 7.7mg/dL. Chest X-ray and urinalysis did not show abnormalities. Ceftriaxone 2g plus doxicicline 200mg, once daily, were initiated empirically by Thailand doctors, after ruling out malaria by antigen rapid test. Influenza virus serology, polymerase chain reaction (PCR) for dengue in serum and PCR for leptospira in urine were negative, while PCR for leptospira in serum was positive. He was discharged five days later without any medical complication. On August 27, leptospirosis was confirmed by microscopic agglutination test (MAT) 1/320 at Hospital Clinic in Barcelona, the highest titre was for serogroup Canicola.
Case 2

A 24 year-old Spanish healthy female was seen at the outpatient tropical medicine clinic in Barcelona after a trip to Thailand. From July 30 to August 16th she visited Bangkok (3 days), Ayutthaya (1 day), Sukhothai (1 day), Chiang Mai (5 days) where she practiced trekking and also swam in freshwater, Krabi (1 day, where she visited Railay) and Ko Lipe (1 day). On August 17th she started with low-grade fever, lumbar pain, myalgia and she visited a regional hospital in Barcelona, there a bloodsmear showed no malaria parasites. On August 20 she presented at the Hospital Clinic in Barcelona with high fever, vomiting and diarrhoea and she was hospitalized.

Physical examination revealed skin lesions consistent with insect bites on the legs.

Blood test showed WBC 8500/mm3, haemoglobin 11.2g/L, thrombocytopenia (88000/mm3), alkaline phosphatase 342U/L, Gamma-glutamyl transferase 337, ALT 88U/L, bilirrubin 2.1mg/dL. Antigen rapid test and thick smear for malaria as well as PCR for dengue in serum were negative. No antibiotic was initiated at that time.

High fever persisted, and on August 26 a lumbar puncture was made, showing pleocytosis with lymphocytic predominance with negative Gram stain and culture. The results were consistent with aseptic meningitis. Ceftriaxone plus doxicicline were started empirically. Serology confirmed the diagnosis (initial MAT 1/80 and 1/640 9 days after), although no specific serogroup could reliably be identified and PCR for leptospira in serum. Two days after being diagnosed of meningitis, she started with bilateral ptosis and ocular discomfort and acute anterior uveitis was confirmed by Ophtalmology, probably associated to leptospirosis, she was treated with topical
steroids. She was discharged on August 26. The patient was completely recovered one month after discharge.

Case 3

A 28 year-old man, previously healthy, was visited at the outpatient clinic in the Hospital Virgen de la Salud in Toledo (Spain), three days after his return from a trip to Thailand-Cambodia, from August 8th to the 23th 2015. He visited Bangkok for two days, Chiang Mai for three days, including an elephant park, where he performed activities such as trekking and swimming in natural pools and waterfalls and also had contact with elephants. He visited Angkor Valley in Cambodia for three days and he finally spent 4 days in Ko Phi Phi. On August the 23rd, he developed high fever (41°C), along with chills and shivers, migratory arthralgia, intense muscular pain (in the lumbar area and calves) and prostration. Physical examination did not show abnormalities.

Laboratory findings showed 120,000 platelets/mm3, normal number of WBC (5500 WBC/mm3), AST 56 U/l, ALT 108 U/l, creatinine 0.88 mg/dl, urea 15mg/dL, total bilirubin 3.0 mg/dL; direct bilirubin 2.40 mg/dL. Urinanalysis: red blood cells 250/μL; bilirubin 3 mg/dL; white blood cells: 100/μL; proteins 500 mg/dL; urine culture was negative. Malaria smear, Dengue PCR, chest x-ray and an abdominal ultrasound did not show any anomalies. Doxicicline 100mg every 12h was initiated empirically. During the treatment, a slight transaminase increase was detected. The patient was managed at the Travel Clinic, ending with clinical and laboratory recovery. MAT serology was found at high titres in patient from a non-endemic country (MAT>1280) suggesting Leptospirosis as the probable cause of the clinical picture.

Discussion
Leptospirosis is one of the major bacterial zoonosis worldwide, caused mainly by direct or indirect contact (through water, food or soil) with urine from an infected animal, particularly mammals. It is recently estimated that leptospirosis causes 1.03 million cases (95% CI 0.43-1.75) and 58900 deaths (95% CI 23800-95900) per year globally, significantly distributed in tropical countries.(3)

Leptospirosis is increasing amongst travelers returning from South-east Asia(4). It is also an emergent zoonosis in Thailand (1), (5), which is considered a high incidence country where cases are up to 48.9 leptospirosis per million population annually (6).

Thailand is a very common destination among Spanish travellers. In our travel clinic during 2015 in Hospital Clinic in Barcelona, 10.1% out of 14977 travellers seeking pre-travel advice visited Thailand, being the most common destination among our travelers that year. Once in Thailand, Chiang Mai is one of the favourite destinations. Chiang Mai is a rural area of northern Thailand where travelers often go to trek, to visit Elephant game parks and to perform water recreational activities; thus increasing the odds of leptospirosis transmission by contact with moist soils, flooding, water or animals(7). Incubation periods of our patients along with epidemiology suggest that leptospirosis was probably acquired in Chiang Mai during rainy season (July-August), when most of autochthonous leptospirosis cases occur in the north in Thai population(8),(9). Patient number 1 had a 4 days incubation period after swimming in Chiang Mai and he only visited Bangkok before became ill, where he did not have any epidemiological risk. In case 2 the incubation period was 6-14 days, and she did not have any other risk as she visited monumental areas and also Bangkok without contact with water, flooding or animals. For the third patient the incubation period was 10-13 days, and Chiang Mai was the only spot where he swam in fresh water or trekked, he
only visited the beach in the south and he denied having contact there with animals, fresh or flooding water.

Leptospirosis incidence rate in northern Thailand (Chiang Mai) during 2015 was 1.42/100.000 population(10), nevertheless northeastern and southern regions hold the highest incidence rates across the country (median of 5.43 and 5.36/100.000 population respectively) (10). There are recent reports of leptospirosis amongst travelers who visited Thailand(11),(12), interestingly since 2013 there have been reports of cases in travelers specifically returning from Chiang Mai. In 2013 our group in Spain reported an imported case acquired after canoeing in the Ping River, the main river of Chiang Mai (13); another Japanese traveler acquired leptospira while swimming in his trip at the same area, as reported by a Japanese group (14). Furthermore, during the summer of 2015 a Swiss family was diagnosed with leptospirosis after rafting in Mae Taeng (tributary of the Ping River) (15), a zone next to Mae Taman (the spot where one of our travelers swam in the river).

Our patients presented with normal or slightly elevated WBC, lymphopenia and low platelets which could suggest leptospirosis undifferentiated fever over other diagnosis such as dengue or typhoid fever which typically present with low WBC, after ruling out them as well as malaria. This is consistent with an observational prospective study, the authors found that thrombocytopenia without leukocytosis or leukopenia were prominent features amongst leptospira infections(16). Moreover, a noticeable leukocytosis is associated with severe forms of the disease and poorer prognosis(16),(17).

These cases highlight the importance of an accurate travel advice to travelers going to
North Thailand: avoid swimming or wading in potentially contaminated soils or waters, avoid contact with flooding, avoid contact with rodents (18) and take precautions with other mammals able to shed leptospires such as elephants (19).

Moreover, since leptospirosis may be a common diagnosis among travelers and routine serological tests are not enough sensitive (20), Leptospira spp. PCR and MAT should be considered as a reliable tests to diagnose the disease among the suspected cases. Nevertheless, in our report, one patient was PCR negative and one serovar was not identifiable, PCR should be made at correct timing to be positive, from 0-7 days in serum and up to 21 days in urine, and also MAT need to be performed with a representative panel of serovars from the acquisition of leptospira to be positive. (20)

In conclusion, since travelers are increasingly visiting Thailand, undifferentiated, non-malaric, fever cases with normal WBC and low platelets, after ruling out diseases such as typhoid fever, scrub typhus or dengue should be considered as possible leptospirosis cases; especially those with a history of contact with water, flooding, animals or moist soils, particularly if they are coming from a tropical country, such as. Thailand after rainy season (from May/June to October/November); even from regions with moderate leptospirosis incidence rate.

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