

Leptospirosis Mimicking Collagen Vascular Disease in a Thirteen-Year-Old Iranian Girl

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A thirteen-year-old girl from Dezfoul, Iran was referred to our hospital with a history of eight days of high fever, headache, odynophagia, diffuse abdominal and body pain especially limb pain. She then developed conjunctival erythema, transient maculopapular rash on the trunk and also diplopia. No obvious or specific point was shown in the history. In the lab studies, she had very high sedimentation rate (ESR), bandemia and leukocytosis and thrombocytosis with negative results for an array of infectious diseases. Before making a vasculitis diagnosis a microscopic agglutination test for leptospira and then PCR test in blood and stool were requested and revealed to be positive for leptospira. She responded to doxycycline and remained well after one year of follow-up. Leptospirosis should be considered in differential diagnosis of vasculitic syndromes in Iran even for patients from seemingly non-enzootic areas.

Keywords: Leptospirosis; Iran; Vasculitis; Child

1. Introduction

A variety of infectious diseases presented as undifferentiated febrile syndromes can mimic leptospirosis (1). It appears that this disease is not that common in kids in Iran, however unnecessary diagnostic and therapeutic steps may be taken if the possibility is neglected. Here, we introduce a case which could be wrongly diagnosed as systemic vasculitis with no obvious source of contamination.

2. Case Presentation

A thirteen-year-old girl from Dezfoul, Iran was referred to our hospital with history of eight days of high fever, headache, odynophagia, and diffuse abdominal and body pain especially limb pain. She had received one shot of benzathine penicillin without any improvement. After 4 days, she developed conjunctival congestion, lip desquamation and also erythematous rash on the cheeks, neck and upper parts of her chest. Physical exam on admission revealed an ill appearance with vital signs as follows: blood pressure = 80/50 mmHg, pulse rate = 118/min, respiratory rate = 30/min and temperature = 39°C. There was bilateral non-purulent conjunctivitis, pharyn-

geal erythema without exudation, small red papules on the cheeks, neck and upper chest with sparing the nasolabial folds. A 2/6 systolic murmur was also evident. The rest of the examination was normal, except for bilateral mild edema on the lower legs. No history of travel from her city, swimming or animal contact or consumption of raw dairy product was present. She was a smart student with no previous history of any significant medical problem. In addition, there was no history of weight loss, drug exposure or rheumatologic diseases in her family. To rule out viral and bacterial causes of such a picture some preliminary investigations were done. The results are shown in Table 1.

Blood, urine, and stool cultures were negative. On day four of admission, she developed a temporary diplopia and dizziness which improved after 48 hours without any specific intervention. A cardiac consult was requested in which there was just mild mitral regurgitation but no evidence of pericardial effusion, coronary involvement or vegetation were noted. PPD test was non-reactive; chest X-ray was normal. On the 6th day of admission, she was still febrile, anorexic and pale with severe limb pain and inability to walking; It appeared that collagen vascular diseases were worked up while results were

Implication for health policy/practice/research/medical education:

Leptospirosis can be manifested like a systemic illness especially collagen vascular diseases and should be considered even for cases with low prevalence of disease in Iran.

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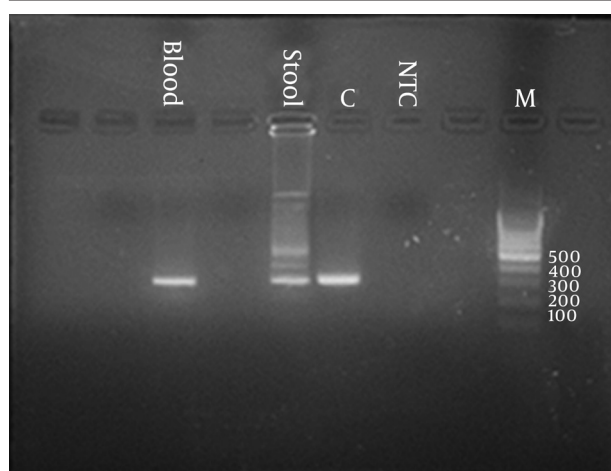
negative for ANA, anti-ds DNA, anti-GBM antibody, and circulatory immune complex (CIC). Complement levels were also normal. Ophthalmologic consult findings were not compatible with an active rheumatologic disease. A microscopic agglutination test for *Leptospira* spp. was requested which revealed to be positive. Hence, a PCR test on peripheral blood and stool samples for leptospira was performed and both were positive. Materials and methods for PCR were as follows:

Master Mix Taq DNA poly: 1U
 dNTP (dCTP, dGTP, dTTP): 250 μ m, TrisHCl (pH= 10mM, KCl: 30mM, MgCl₂: 1.5mM, tEmplate DNA: 20ng, primer F, R: 10 pmol, H₂O up to 20 λ)
 Thermal cycler ABI 2720

Table 1. Results of Laboratory Tests

Requested tests	Results
CBC	WBC=11.9 \times 10 ³ (segmented: 69%, band: 18%, lymphocyte: 10%, monocyte: 3%)
Sedimentation rate	94 mm/1th hour
Platelet count	238,000/mm ³ on first exam, then increased to 640,000/mm ³
Biochemistry	Na, K, Ca, urinary creatinin and calcium as well as 24 hours urinary protein were normal
Renal function tests	BUN and creatinin were normal. Urinalysis was normal except for microscopic hematuria and 1+ protein
Liver function tests	ALT, AST, alkaline phosphatase and GGT were normal. LDH mildly increased; total protein and albumin were decreased significantly
Serologic tests	ASO titer, Wright, 2ME, Coomb's Wright, and Widal tests all were negative

Figure 1. Results of PCR



From Left to Right: Blood, Stool, Positive Control, NTC, Marker

2.1. Test Procedure

For each patient 0.25 μ L of primer F and 0.25 μ L of primer R and 9.5 μ L of H₂O and 10 μ L of extracted DNA is added to lyophilized tube with usual temperature profile tubes is placed on the thermal cycler. Electrophoresis of the PCR product on 2% agarose v gel containing Rima SI g ht in TBE buffer at voltage 80-100 v for 30 minute. The gel is evaluated with UV transluminator. For each test one positive control; one NTC and one DNA marker are evaluated simultaneously on the same gel. The gel is shown in Figure 1.

Doxycycline was started after which fever subsides gradually. Her complaints all resolved after 10 days. Her CBC and platelet counts were normal and sedimentation rate dropped to 13 mm/1th hour after 3 weeks of treatment. After 1 year follow-up, she was quite normal in terms of clinical and laboratory findings.

3. Conclusions

Leptospirosis is a zoonotic disease of global importance, caused by spirochetes of the genus *Leptospira*. Based on antigenic relatedness, human pathogenic *Leptospira* interrogans strains have been differentiated into > 200 serovars, classified into 24 serogroups (1). A variety of wild and domestic animals form the natural reservoir for pathogenic leptospire. Transmission to humans results from exposure to the urine of infected animals either by direct contact or through contaminated soil or water (2). Recent surveillance data indicate an increase in disease incidence in some countries; for example in Germany the incidence has increased to 0.06 per 100,000 from 1998 to 2003 (2).

Leptospirosis is present in almost all world areas except poles; China, India and Brazil are among the most contaminated areas (3). Although most cases in Iran have been reported from northern parts of the country with 192 cases from Gilan province in 1997, but serologic investigation of cattle in some central provinces like Arak and Qom has shown considerable positivity indicative of spreading status of the disease in the country (3). South-western part of Iran is also probably contaminated as in a study in Ahvaz in 2003, 15% of samples from sheep were positive for *Leptospira* spp; some of them had positivity for more than one species (4). Some serovars like pomona followed by canicola, icterohaemorrhagiae, grippityphosawere more prevalent in this study; but icterohaemorrhagiae was the most common serovar from northern part of the country (3). Although serologic investigation of human Leptospirosis in tribal areas of central west provinces has also shown strong positivity (48.5%) at a minimum titer of 1/100 especially to serovarhardjo, Dezful has not been recognized as an enzootic focus in Iran. So this case shows that other parts of country might be contaminated now and this diagnosis should be in mind for every case with compatible clinical picture.

Clinical presentation of Leptospirosis is quite mislead-

ing and it is simply overlooked even in countries with high grade of endemicity. In a study in Turkey, The most frequent initial symptoms and findings were fever, fatigue, headache, nausea and vomiting and increased muscle sensitivity which all can be misdiagnosed by a viral infection (5). Kawasaki disease in children and other collagen vascular diseases might also be confused with Leptospirosis as in our case there was severe body pain and conjunctival involvement. In the absence of hepatic and renal involvement and with high rate of erythrocyte sedimentation rate this case could be potentially diagnosed as a nonspecific vasculitis and become a candidate for taking IVIG or corticosteroids, probably both with no result; these treatments might increase the diagnostic problem as checking antibodies could be potentially affected by former and a nonspecific anti-inflammatory action of corticosteroids may affect the acute phase reactant indicators. Therefore, it is very important to diagnose cases with Leptospirosis properly. The employment of Warthin-Starry silver staining, polymerase chain reaction, and immunofluorescent, immunohistochemical methods and microscopic agglutination test can be useful for diagnosis, each with its benefits and limitations (6). In Iran, the microscopic agglutination test is being used for years with good results, but for more than one decade the usage of different types of primers for PCR methods have been encouraging (6-8). Early diagnosis with PCR methods can potentially permit the physicians to start treatment on time as for most serologic tests including microscopic agglutination test it may need more than 10 days to become diagnostic and there are some evidence that delayed treatment might not be effective for patients (6). Presentation of this case with nonspecific severe constitutional signs and symptoms and compatible sex and age for collagen vascular diseases especially with high sedimentation rate could be misleading, especially when she comes from non-endemic area for leptospirosis, so given the spreading areas of such a zoonotic disease in Iran it is very important to consider leptospirosis as an important differential diagnosis of vasculitis syndromes even in patients from apparently non-infected areas.

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Authors' Contribution

Alireza Nateghian wrote the discussion and diagnosed the case. Dr Amin Lavasani: wrote the manuscript and followed up the case. Dr Soudabeh Hoseini took the lab tests and performed the interpretation of laboratory data.

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