

A Mystery Unsolved:

41 year-old male in good health with sudden onset of high fever for a week.

C.C. (Chief Complaint)

Fever for one week

H.P.I (History of Present Illness)

A 41-year-old male with hypothyroidism and gastroesophageal reflux disease presented to the Massachusetts General Hospital on October 14th, 2015 due to high fever for a week.

This patient was in his usual state of health until 8 days ago when he had a fever of 38.3°C with noticeable dull lower back pain, neck stiffness, night sweats, light sensitivity and myalgias. He had taken ibuprofen and acetaminophen around the clock which he thought it was the usual flu symptoms. However, fever persisted. He began to notice eye pain with injected conjunctivae and found that his left eye had some haziness and blurry vision. He denied of double vision, floaters, discharge or tearing. He had no feelings of nausea or vomiting but slightly decreased appetite.

It was not until 2 days ago when his fever spiked to 40°C and he went to Newton-Wellesley Hospital for assistance. Rapid flu test was negative and electrolytes and chest x-ray appeared to be normal. The patient was told he had a viral illness but they did not think it was meningitis and he was therefore discharged the next day. Shortness of breath was felt the day before admission and darker than usual urine (orange) was noticed. In addition, he found erythematous maculopapular rash across his chest, back, and face. Therefore, he presented to the MGH ED for further assistance and management.

P.M.H. (Past Medical History):

1. Hypothyroidism due to Hasimoto's thyroiditis
2. Gastroesophageal reflux disease
3. Attention deficit hyperactivity disorder

F.H. (Family History)

Father with congestive heart failure, hypertension, prostate cancer and kidney problems

Mother with psoriasis

Grandmother with rheumatoid arthritis

Sister with attention deficit hyperactivity and bipolar

Social History

Smoking- denied

Alcohol- social drinker, 1-2 beers a week

Illicit Drug- denied

Occupation- works in finance

Married with 2 daughters with age 2 and 8; sexual active with wife only.

Travel History

Lennox, MA 3 weeks ago (western MA wooded area) for a tour camp with his daughter outside Cape Code and Tanglewood for the past month

Allergy

None

Medications

1. Omeprazole (Prilosec) 20mg capsule
2. Levothyroxine 100mcg tablet

R.O.S (Review of Systems)

Constitutional: fever, fatigue, malaise, night sweats, chills and decreased appetite

Head/Eyes: Blurred vision over left eye but improved

ENT/Neck: neck stiffness

Chest/Respiratory: slight shortness of breath

Cardiovascular: slight shortness of breath

GI/Abdominal: nil

GU/Flank/CVA/Pelvic: nil

Musculoskel/Extr/Back: lower back pain

Skin: erythematous maculopapular rash across his chest, back, and face

Neuro: nil

Psych: nil

Heme/Lymph/Imm: nil

Endo: nil

P.E. (Physical Examination)

Vitals: Temp 10.7 | P 73| BP 117/60| RR 20| spO2 94 Room Air, Input/output:1800/150

General: The patient is awake and alert and oriented to persons, place, and time. Slightly distressed in bed

Skin: scattered erythematous, blanching maculopapular rash across chest and back

HEENT: Pupils is equal in sized and reactive to light

Sclera: anicteric ; conjunctiva: not pale

Neck: supple, no carotid bruits, no lymphadenopathy

Heart: Regular rate and rhythm without murmur. S1 and S2 heard. No gallops

Lungs: Clear to auscultation bilaterally

Abdominal: soft, nontender and nondistended. No splenomegaly or hepatomegaly

Extremities: Normal range of motion for all limbs and joints

Neurologic: Cranial nerves II through XII are grossly intact

Lab data**Lab Profile 10/14/2015**

WBC	4.40	Na	136	ALT	117	IGG	917
RBC	4.87	K	4.3	AST	85	IGA	181
HGB	14.2	CL	96	ALKP	89	IGM	115
HCT	41.7	CO2	27	CRP	147.8	SPEP	Pend
MCV	85.6	BUN	21			ANA	Neg
MCH	29.2	CRE	1.73	TSH	0.5		
MCHC	34.1	EGFR	44	Free-T4	1.2		
PLT	139	GLUC	115				
MPV	10.1	Anion	13	PT	12.8		
RDW	12.4	Ca	9.1	PT-INR	1.0		
%Neutro	69.3	Phos	3.6				
%Lymph	16.8	Mg	2.3				
%Mono	13.0	T-Bili	0.7				
%EOS	0.2	D-Bili	0.2				
%BASO	0.5	TP	7.4				
NRBC%	0	ALB	4.1				
ANEUT	3.05	GLOB	3.3				
ALYMP	0.74	LDH	222				
AMONS	0.57	LACT	1.3				
AEOSN	0.01	LIPS	55				
ABASOP	0.02	CK	59				

Urinalysis

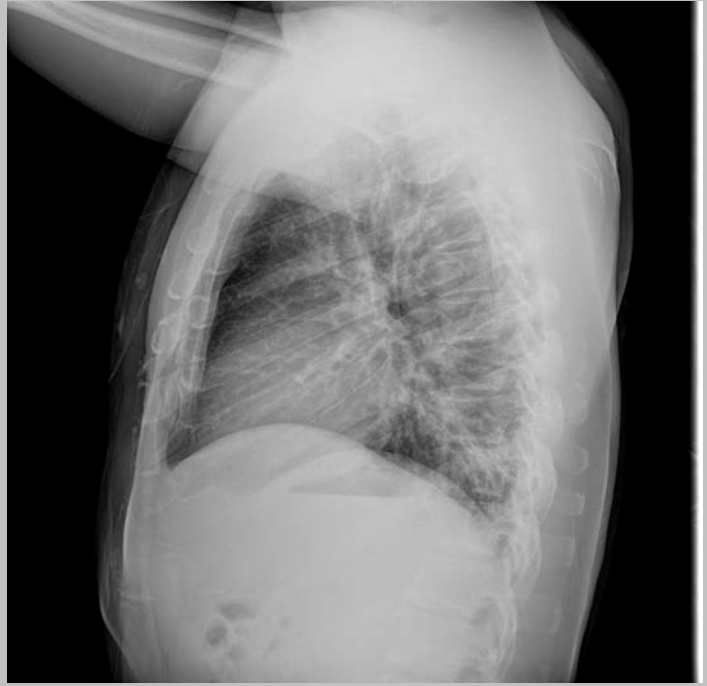
UA-color	Amber	UAS-RBC	3-5
UA-Clarity	Cloudy	UAS-WBC	5-10
UA-GLUC	Neg	UAS-BACT	1+
UA-Bili	Neg	UAS-SQHI	Present
UA-Ket	Neg	HCAST	3-5
UA-SPGR	1.024	GCAST	3-5
UA-BLD	Neg	UAS-MUC	Present
UA-pH	5.0		
UA-Protein	2+		
UA-UROBI	1+		
UA-NIT	Neg		
Leuk-EST	Neg		

Image

1. Chest X-ray

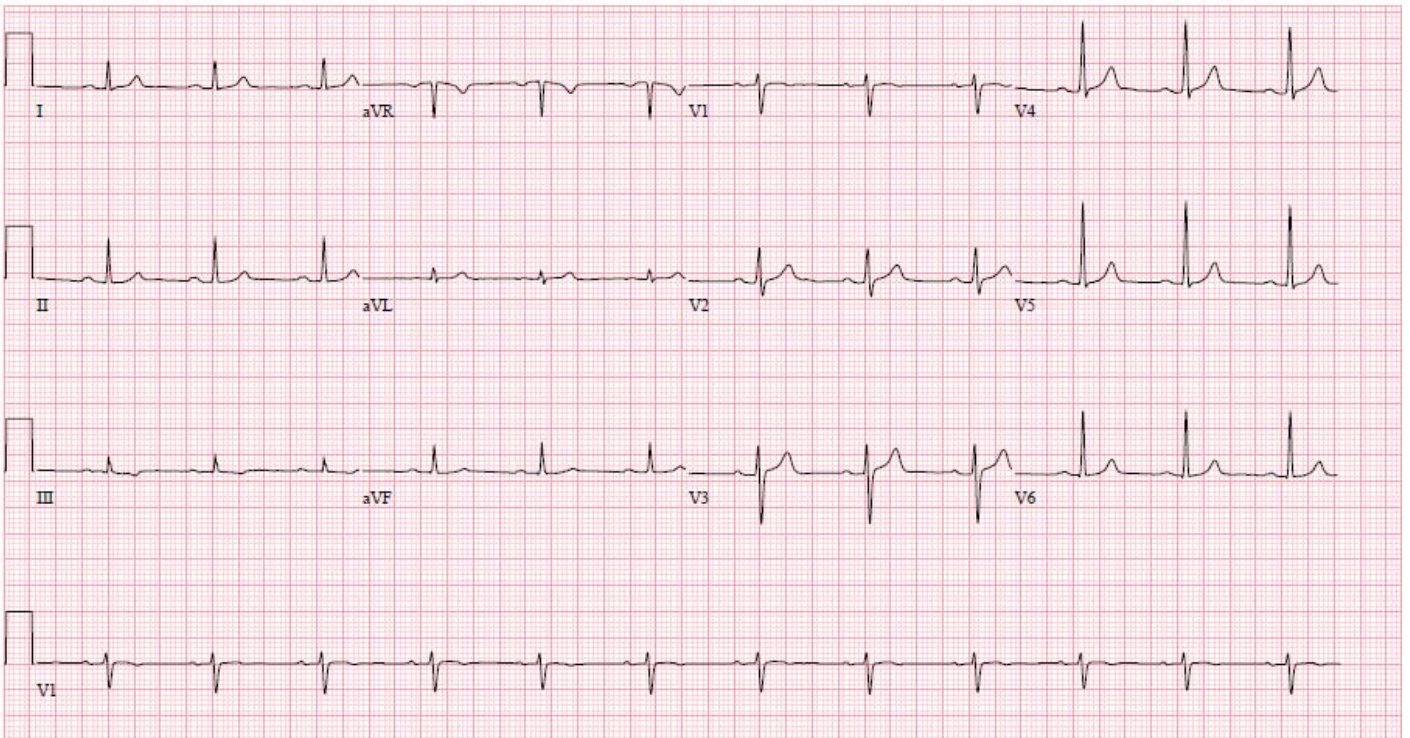
Admission Day AP view

Admission Day lateral view

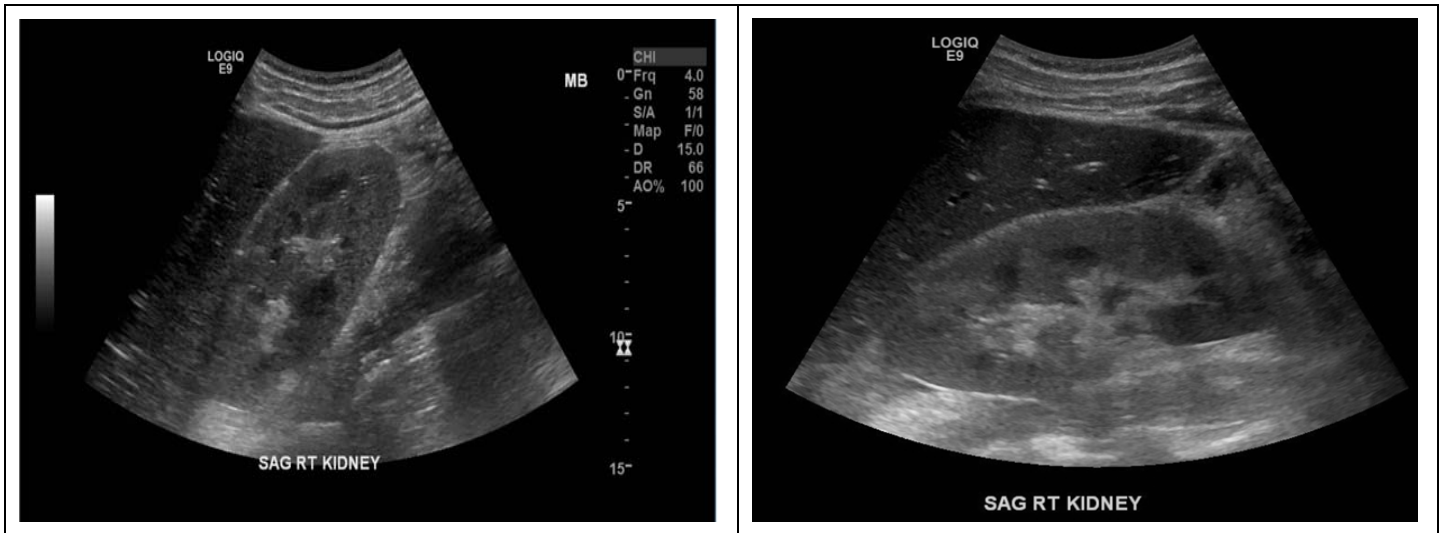


2. EKG (Admission Day)

Normal Sinus Rhythm with rate of 73BPM



3. Ultrasound of the Kidney



Assessment

This patient is a 41-year-old man with history of hypothyroidism and GERD that presents with 1 week of fever, rash, and conjunctiva redness. His lab data revealed acute kidney injury and transaminitis concerning for leptospirosis due to his exposure history.

D.D. (Differential Diagnosis)

1) Fever and Rash:

Differential for fever and rash is extensive but this case is likely due to an infectious cause given acute onset and high grade fevers. Since the patient had traveled to rural areas with exposures to mosquitoes, tick borne and mosquitoes borne illness is a high concern (Leptospirosis, ehrlichia, Lyme disease and anaplasma). Acute HIV can also present with rash, retro-orbital pain and photophobia. This could also be an atypical severe infectious mononucleosis with symptom signs of fever, rash, fatigue, malaise, and back pains and this patient had mononucleosis before. Secondary syphilis with fever, rash, proteinuria and abnormal liver function tests also cannot be ruled out. Suspicion of aseptic meningitis given neck stiffness but this symptom had subsided. Elevated CRP and ESR, thrombocytopenia and mild leukopenia suggest rheumatologic illness. Malignancy is possible at this point as well but infectious cause will be focus first.

2) Acute Kidney Injury

His creatinine baseline is 1 and had increased to 1.7. The most likely explanation could be intravascular volume depletion due to his large volume fluid loss from fevers and night sweats which he was unable to adequately compensate with his PO intake. He had been taking large quantity of NSAID which may further impaired renal perfusion. Given his eye findings, renal failure and transaminitis, leptospirosis was the leading differential but not yet proven. There are case series that describes Leptospira on kidney which includes AIN, ATN and vasculitis. AIN is likely as there are WBCs in the sediment; ATN is also possible with muddy brown casts seen and vasculitis may be a possibility with RBCs in the sediment.

Hospital Course

After admission, he was given empiric doxycycline, ceftriaxone, and methylprednisolone after consulting infectious department and rehydrated with intravenous fluid therapy (1L NS on mIVF at 150cc/hr overnight). After receiving pain medication of acetaminophen, he felt better but fever and chills still persisted. Ultrasound of the kidney revealed trace fluid around bilateral kidneys and head CT without IV contrast showed no acute intracranial abnormality. After admission to the floor, he noticed he had minimal urine output and began to have shortness of breath which required O2 supplementation. Initially, 1L NC was given and the patient was doing well in addition with 20 mg IV lasix. Subsequently in the afternoon, an increasing amount (6L NC was placed on NRB satting 100%) was given. At this point, 120 mg IV lasix was administered and chest X-ray revealed persistent dense retrocardiac opacity, small left pleural effusion, and patchy right basilar opacities with persistent airspace opacities. Creatinine went up to 7.75 from 1.73 on admission. A renal biopsy was suggested but was unable to perform with patient at this state. This patient was deemed to require a higher level of care and was transferred to the intensive care unit.

Upon arrival at the MICU, the patient's saturation was in the 80s with 10 LPM NC. Blood pressure was 140/90 and HR was 80. Shortness of breath with diffuse abdominal pain was noted. The main concern was his worsening hypoxemia and respiratory failure. Continuous veno-venous hemofiltration (CVVH) was initiated due to volume overload. After about 3 days in MICU, his rapid recovery with creatinine dropped back to 1.3 allowed him to be transferred back to the floor. With his exceedingly impressive resolution, he had no more fever, rash, and dyspnea and was discharged after 6 days stayed in the hospital.

Throughout the hospital course, he was tested for:

Lab Tests			
legionella Ag	Negative	Ehrl EwingII/Canis	Negative
MRSA nasal culture	Negative for MRSA	Anaplasma Phagocyto	Negative
VRE rectal culture	Negative for VRE	Ehrlichia chaffeens	Negative
CMV IgG Ab	Positive	Lyme	Negative
CMV IgM Ab	Negative	Ehrl muris-like	Negative
Anti-dsDNA Ab	Not available	PARASITE THK SMEAR,B	No parasites seen
Leptospira Ab	Negative	PARASITE THIN SMEAR,B	No parasites seen
Meptapneumovirus Ag	Negative	HIV-1 RNA PCR	Not detected
Adenovirus Ag	Not available		
Parainfluenza 1-3 Ag	Not available		
RSV Ag	Negative		
Babesiosis AB Intrap	Not Detected		
Babesia Microti IgM and IgG	<1:20 and <1:64 respectively		
Heterophile Ab	Negative		
Antinuclear Ab	Not available		
Rheumatoid Factor	<30		

Discussion

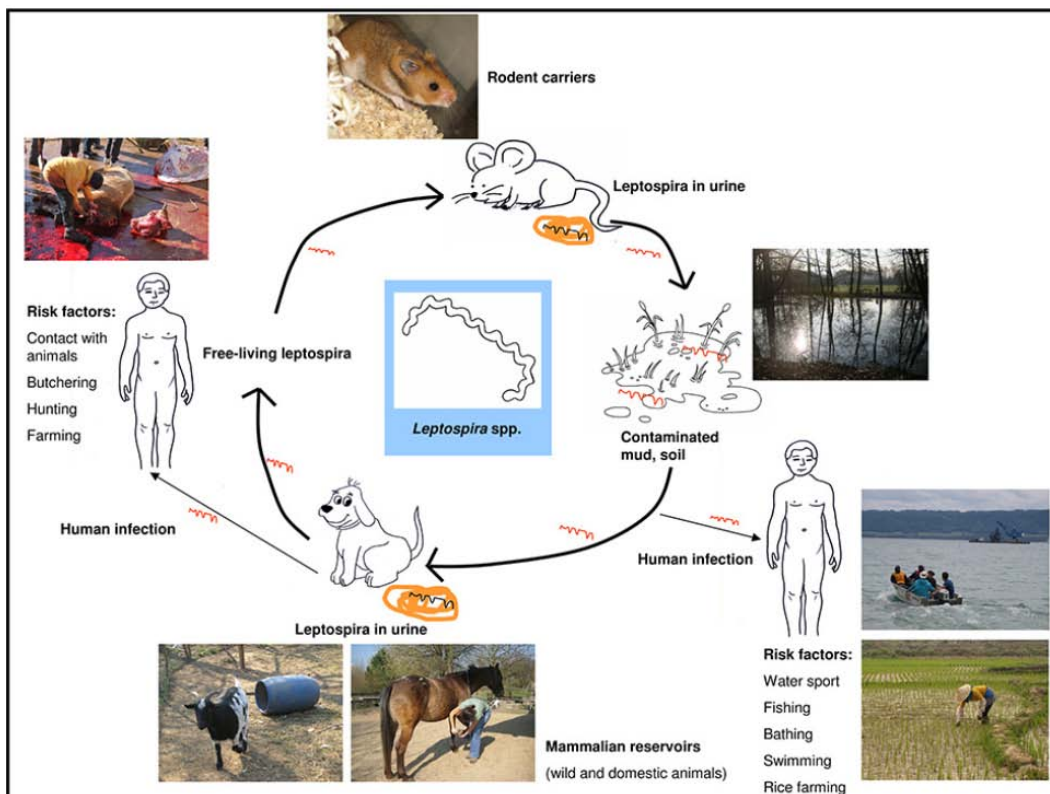
Why did you choose the case?

This case was mysterious at the beginning because of its wide range of possibilities from his differential diagnosis. Being on the consultation team of the renal department and comparing with the most acute kidney injury being consulted, the course of this case was unique in that his renal function worsened extremely fast but also recovered in an impressive short amount of time. This was quite a rare phenomenon. Even though this case led many to believe that the most leading etiology for this patient was leptospirosis due to his symptom and signs of fever, myalgias, and conjunctival suffusion; however, data after his discharge revealed otherwise. He was tested negative for leptospira antibody. Therefore, this case remains unclear and mysterious of its diagnosis. Difficulty in ascertaining the cause for the patient is quite common in the medical field and definitely an interesting case to be discussed.

What's new in the literature reading to your case, such as diagnostic aids, treatment or any other aspects?

When a patient presents with fever and rash, it always poses an urgent diagnostic and therapeutic dilemma for clinician because of its broad differential diagnosis. Some of these patients might be in a life-threatening condition as with our case [1]. Tabak et al., 2012 looked at 100 adult patients who had fever and rash in any part of the body and found that the most common causes of maculopapular rash and fever were measles, cutaneous drug reactions, varicella, adult-onset Still's disease (ASD) and rickettsial disease. Our patient's endorsed acute onset of high fever for a week which seemed to be an infectious cause. One of the unique symptoms that our patient endorsed was conjunctivitis which along with his travel history of outdoors gave us an impression of leptospirosis.

Leptospirosis is a prevalent disease most commonly found in temperate and tropical regions [2]. It is a zoonosis that is caused by the pathogen spirochetes of the genus *Leptospira*. The incidence is relatively low in the United States but human infection is usually due to exposure to environmental sources such as animal



urine, contaminated water and soil, or infected animal tissue [2]. Rodents are the most important reservoirs with transmission in most settings. The life cycle of the *Leptospira* spp can be seen in Figure 1 [6]. With our case, his wife did mention seeing a rodent passing by near where they traveled. In 75-100% of patients, leptospirosis generally cause acute onset of fever, rigors, mylagias and headache.

Figure 1. Life cycle of pathogenic *Leptospira* spp. [6]

The incubation period can be from 2 days to 26 days with an average of 10 days [2]. Since the patient with his family went out camping three weeks ago, it was still within the incubation period. Conjunctival suffusion is a clinical sign but occurs in about 55% of the patients [2].

A case-control study in Taiwan that looked into 22 confirmed cases after a typhoon outbreak identified the following symptoms that were more associated with these confirmed cases: hemorrhagic diathesis, myalgias, bilateral enlarged kidneys, sterile pyuria, hypokalemia, and thrombocytopenia [3]. In laboratory studies and imaging, white blood cells are generally less than 10,000/microL, and the patient may endorsed thrombocytopenia and hyponatremia. Urinalysis often exhibit proteinuria, pyuria, granular castas and sometimes hematuria. Elevated creatine kinase and elevated hepatic transaminases are often seen [2]. Our patient did experienced myalgias, pyuria, hematuria and proteinuria. His potassium level was within the normal range (4.1-4.6); however, on the day with his sever dyspnea, his sodium dropped to 133. He also endorsed thrombocytopenia. With these symptoms, it correlated well with leptospirosis.

Other differential diagnosis such as dengue fever, scrub typhus, ehrlichiosis, other rickettsial diseases, and viral diseases such as Hantavirus cannot be excluded. Viral or bacterial meningitis could also be the cause. These were all tested during his hospital stay but some results came out negative and some were still pending.

The incidence of acute kidney injury in leptospirosis varies from 10% to 60% depending on the disease and age in endemic tropical countries [5]. The pathophysiology of renal impairment due to leptospira is shown in figure 2 [5]. The main factors are direct nephrotoxic action of leptospira and toxin-induced response. Studies in rats found that leptospira adhered to the epithelial surface of the renal tubules in the first week and then into the tubular lumen in the second week [5].

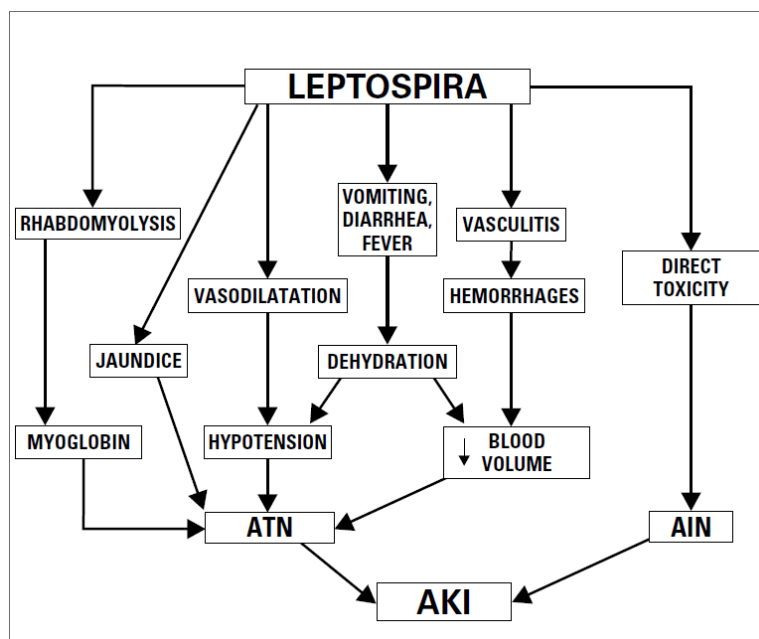


Figure 2. Pathophysiology of renal impairment caused by leptospira

Most cases of leptospirosis are self-limited without antimicrobial therapy; however, if complications pose significant life-threatening situations, antibiotics should be used [4]. For hospitalized adults with severe disease, penicillin, doxycycline, ceftriaxone, or cefotaxmine are usually used with duration of seven days [4]. Our patient was given doxycycline and ceftriaxone.

In summary, our patient had many symptoms, lab studies that correlated well with leptospirosis. Since leptospirosis is a rare case seen in non-endemic areas, it is still very interesting to see the whole part of this infectious disease and how it affects the renal function. Even though the antibody for leptospira came out negative in the end, and the diagnosis remains unknown, this case was still very interesting in its diagnosis process and its course.

References

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Contact Information

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Dates of rotation: September 30, 2015 – October 25, 2015

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