ACUTE MYOCARDITIS DUE TO LEPTOSPIRA ICTEROHAEMORRHAGIAE - CASE REPORT

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Introduction

Leptospirosis, a ubiquitous zoonosis transmitted to humans through water contaminated with animal feces, in a relevant context (professional exposure or history of aquatic sports in the open air), is relatively rare in Romania. Still, this disease may have a severe evolution, particularly that of icterohemorrhagic leptospirosis (Weil's disease) which is most frequently generated by *Leptospira icterohaemorrhagiae* and which is characterized through scleral-tegumentary jaundice, hemorrhagic syndrome, acute renal failure and meningeal irritation syndrome. It can also associate acute myocarditis and various types of pulmonary involvement. Myocarditis is an underestimated complication of leptospirosis due to the fact that it is frequently asymptomatic. Its main outline includes arrhythmias, conductivity impairment and nonspecific terminal phase abnormalities, with a reduced clinical expression. Leptospiral myocarditis can have a severe evolution, at times even fatal. It is therefore necessary to diagnose leptospirosis and acute leptospiral myocarditis as early as possible and, at times, in unusual circumstances, in order to start an efficacious treatment.

Case presentation

Twenty-nine year-old patient, R.I., was admitted in August 2006 for fever (38.5°C), scleral-
tegumentary jaundice, hemorrhagic syndrome and oliguria. The onset of the illness had taken place 7 days earlier, with headache, myalgia and alteration of the clinical status, followed by nausea, vomiting, inappetence, epigastralgia, epistaxis, serohemorrhagic cough and conjunctival hemorrhage.

The patient presented no personal pathologic antecedents other than history of contact with non-potable sweet water prior to disease onset.

The objective clinical examination upon admittance showed: altered clinical status, labial herpes, icteric skin and mucosa, purpura on the anterior thorax, conjunctival hemorrhage, serohemorrhagic cough, accentuated vesicular murmur, respiratory frequency of 16/min, without initial cardiovascular altering, HR = 100 bpm, regulate rhythm, BP = 110/80 mmHg, without orthostatic hypotension, with abdomen painful to palpation in the epigastric region, without signs of peritoneal irritation; stool with normal aspect, hyperchrome urine, oligoanuria, meningeal irritation syndrome (positive sensitive Kernig's sign), bradypsychia, bradydalia.

The laboratory tests upon admittance showed: leukocytosis (16.700/μl) with neutrophilia (90.3%) and thrombocytopenia (16.000/μl), biologic inflammatory syndrome (fibrinogen = 1.228mg/dl, positive procalcitonin), increased myocytolysis enzymes (CK = 1.065U/l, CK-MB = 50U/l, TGO = 58U/l, LDH = 630U/l) displaying descending dynamics, cholestasis (TB = 15.7mg/dl, DB = 15.1mg/dl) and azoth retention (urea = 254mg/dl, creatinine = 9.1mg/dl) with initially ascending and eventually descending trends.

At 15 days from the clinical onset of the disease, the serologic test for confirmation, represented by the microagglutination reaction, was positive for *Leptospira icterohaemorrhagiae*: 1/1.600.

Cardiopulmonary radioscopy revealed fibrocalcaneous hila, right hiliobasally accentuated pulmonary markings; heart within normal radioscopic limits.

After 3 days of hospitalization, the patient presented HR = 120 bpm, regulated rhythm and BP = 90/60 mmHg. An ECG (figure 1,2,3,4) revealed an atrial flutter with variable block. The epidemiologic, clinic and electrocardiographic data generated the suspicion of acute leptospiral myocarditis.

A cardiologic consult was requested; this underlined the absence of cardiac personal pathologic antecedents and the presence of variable block atrial flutter, with uncertain onset; the objective clinical examination revealed absence of circulatory congestion signs and of cardiac murmurs. Given: (a) the

**Figure 1, 2, 3, 4.** An ECG performed at 3 days after admittance revealed a variable block atrial flutter.
uncertain onset of the atrial flutter, (b) the contraindications of anticoagulation (thrombocytopenia and acute renal failure) and (c) the fact that the patient did not represent, at that time, an emergency for electrical conversion of the atrial flutter, being hemodynamically stable, the cardiologist did not consider electrical conversion as being opportune and recommended: a) an echocardiography; b) a calcium channel blocker (diltiazem 30 mg x 3/day, per os and, according to BP and HR, if the dose is well tolerated, an increase to doses of 60 mg x 3/day); c) cardiologic reassessment after 24 hours.

The echocardiography revealed: LVTD = 34 mm, LVTS = 25 mm, IVS = 13.5 mm, PWLV = 13 mm, global hyperkinesia, EF = 38%, moderately altered systolic CF (contractile function). Conclusions: (1) moderate LV hypertrophy; (2) moderate systolic dysfunction.

This echocardiographic data, together with the positive serology test, confirmed the diagnosis of acute leptospiral myocarditis.

One day after diagnosis of the atrial flutter, the patient presented a lipothimic episode upon changing the clinostatic position for an orthostatic one, secondary to orthostatic hypotension.

The myocarditis presented a favorable evolution under diltiazem treatment, with normalization to sinus rhythm after 4 days of treatment. The therapy over the duration of hospitalization, apart for diltiazem, consisted of:

- **diuretics**: manitol 20% in EVP (also with role of cerebral deplention) – one 250ml vial of manitol 20% solution with a rhythm of 28 drops/min, kept for 3 hours, respectively a total of 50g of manitol; furosemide 2 vials IV during the first day;
- **dopamine** in EVP, a dose of 5μg/kg/min (50mg dopamine, respectively 2.5ml out of a vial with the concentration of 20mg/ml, diluted in 250ml glucose solution 5%, with a rhythm of 40 drops/min), kept up to normalization of diuresis, for 4 hours (a total of 2 x 250 ml of solution);
- **corticotherapy**: dexamethasone IV 1 vial x 2/day, 7 days, then 1 vial/day for another 3 days, followed by prednisone in doses equivalent to 30mg/day, for 2 days, doses which were rapidly lowered to 20mg/day for 2 days and respectively to 10mg/day for another 2 days;
- **antibiotic**: ceftriaxone, slow IV 4g/day, 18 days;
- **antiemetic**: metoclopramide;
- **antisecretory drug**: ranitidine;
- **vitamins B1 and B6**;
- **thrombocyte concentrate**.

The evolution was slowly favorable, with full recovery of the patient, including that of the cardiologic parameters. The patient returned to his professional activity, respecting the medical indications (avoiding over stressing physical activity). The medical follow-ups (the most recent dating back to November 2009) did not reveal any cardiac pathologic signs.

Still, the patient shall be long-term cardiology monitored in order to detect an eventual postmyocarditic dilated cardiomyopathy.

### Discussions

Leptospirosis is endemic in South-Eastern Asia, where a lot of regions register the highest worldwide incidence of human leptospirosis. The epidemics in this area, together with those in South and North America, have contributed to considering leptospirosis a reemerging infectious disease [1]. The incidence of leptospirosis in Romania in 2007 was of 1.4 to 100.000 inhabitants [2], while in France for example, the incidence was registered to be 0.53 to 100.000 inhabitants for metropolitan France and between 5.48 and 22.85 (except for Futuna with 1100) to 100.000 inhabitants in the French islands [3].

Leptospirosis can occur at any time during the year, with a peak incidence during summer and autumn [2,3]. The median incubation period is 14 days, for our patient, the interval having been 11 days. Being aerobic bacteria responsible for ubiquitous zoonoses (rats, birds, amphibians), the Leptospira spirochetes can survive, after urinary excretion, for
up to 9 months in their natural reservoir, sweet water. Most frequently, the human transmission occurs indirectly, transcutaneous or transmucosal; in the case we have reported, the probable transmission was transcutaneous. The risk groups are farmers, drainage workers, veterinarians and individuals who practice aquatic sports in the open air.

After the incubation period of 7 to 15 days, an inaugural flu-like syndrome occurs. The state phase is represented by septicemia with endotoxinemia and multiple visceral involvements (hemorrhaging syndrome through endothelial involvement – capillary vasculitis, jaundice secondary to hepatocellular dysfunction, acute renal failure, variable pulmonary involvement, cardiac affliction – myocarditis, pericarditis, asceptic meningitis, uveitis and myalgias). Five prognostic factors are independently associated to an increased mortality: dyspnea, oliguria, leukocytosis > 12,900/mm³, terminal phase abnormalities on ECG and alveolar infiltrates on the chest X-ray [4]. Our patient presented oliguria and leukocytosis = 16,700/mm³, but the acute renal failure was moderate and rapidly reversible, without need for dialysis. A recent study has revealed independent prognostic factors associated with a severe evolution: jaundice and clinical or ECG manifestation of cardiac involvement [5]. In our patient’s case, the jaundice was intense and the cardiac involvement was represented by an acute myocarditis which appeared 10 days after the onset of leptospirosis and was clinically manifested through HR = 120/min, irregular heartbeat and BP = 90/60 mmHg; the ECG revealed an atrial flutter with variable block. Another particularity of this case was the fact that the cardiologist did not consider the electrical conversion of the flutter as being opportune, due to the uncertain onset of the flutter, due to the presence of anticoagulation contraindications (thrombocytopenia and acute renal failure) and due to the fact that the flutter was well tolerated hemodymanically, not representing a conversion emergency. Therefore, the cardiologist recommended treatment with diltiazem. As for the lipothimic episode, it most probably occurred in the context of orthostatic hypotension.

5-10% of the total number of cases of leptospirosis develop a severe icteric outline with variable degrees of multiple organ failure and 16-40% of these cases develop acute renal failure. The rate of mortality in leptospirosis can reach 20% in the cases with jaundice and renal involvement (Weil’s disease). Some other frequently described complications are necrosing pancreatitis, respiratory distress, myocarditis and uveitis. The severe jaundice outlines require secondary and tertiary therapy: admittance of the patient to the intensive care unit with supportive treatment, including dialysis and/or circulation support [1]. Fortunately, in our patient, the myocarditis and the acute renal failure had a benign evolution, without requiring circulation assistance or dialysis.

Myocarditis is an underestimated complication of leptospirosis due to the fact that it is frequently asymptomatic, its main features (arrhythmias, conductivity impairment and nonspecific terminal phase abnormalities) manifesting a reduced clinical expression.

In the course of leptospirosis, congestive heart failure appears rarely, while nonspecific ECG changes are more frequent. Up to 1/5 of the patients with cardiac monitoring present arrhythmias: atrial fibrillation, atrial flutter (present in our reported case), sinus tachycardia discordant to the feverish episode, premature ventricular contractions and ventricular tachycardia. Cardiovascular collapse can rapidly develop and, in the absence of circulation support, it can be fatal. Several patients with severe systemic involvement (Weil’s disease) frequently present 1st degree atrioventricular block and nonspecific transient ST segment and T wave abnormalities or, seldom, bradycardia discordant to the feverish episodes, ventricular extrasystoles, congestive heart failure and pericarditis. 50-100% of the deceased patients presented cardiac involvement [6].

Radiologically, the heart can display a normal aspect or it can be suggestive of cardiomegaly. The echocardiography is the imagistic investigation which can provide data on the morphology and function of the heart, indispensable for a correct differential diagnosis and an adequate treatment of myocarditis. In a study quoted by Dixon [6], echocardiography revealed cardiomegaly in 9% of cases, out of which 50% with biventricular dilation and 50% with left ventricle dilation. In 3 of 4 patients, the heart returned to its normal sizes; in the 4th patient, the dilation persisted. The same author cites a similar study which described 80 cases of Weil’s disease, out of which 8 had presented a symptomatic heart affliction, and out of these, 2 displayed radiological cardiomegaly and clinical manifestations of congestive heart failure [6]. Another clinical and radiological outline is acute pulmonary edema (APE), both cardiogenic and non-
cardiogenic (acute respiratory distress syndrome – ARDS), the differential diagnosis between these two entities and hemorrhagic pneumonia being possible through hemodynamic measurements or through echocardiography. In the course of leptospirosis, cardiogenic APE is more frequent than ARDS.

Generally, the ECG and rhythm abnormalities display an early remission in the course of the disease, but at times, myocarditis can progress, being even fatal (in 25% of cases of fatal leptospirosis [6]), but it is reversible under adequate antibiotic therapy and circulation assistance during the phase of severe cardiac failure. It is therefore necessary to suspect a diagnosis of leptospirosis and also of acute leptospiral myocarditis as early as possible and sometimes even under unusual circumstances, in order to be able to provide a treatment which would definitely be more efficient when started earlier, as was the case with our patient and also, with the case reported by Dixon [6] and with another more severe case with cardiogenic shock, which required insertion of an intra-aortic balloon counterpulsation, but which eventually displayed a favorable evolution [7].

In the field literature on leptospirosis, fever is described in 95-100% of cases, headache in 61%, and vomiting in 33-83% of cases [5,8], all these symptoms being also present in the case we have reported.

The pulmonary involvement is variable, present in 20 to 70% of cases, being frequently eclipsed by jaundice (present in 39-83% of cases), renal involvement (45-55%) or meningeal pathology [5,8,9], while the cardiac affliction (myocarditis or pericarditis) is reported in 9.7 to over 10% of cases [5,6]. Clinically, the pulmonary involvement manifests through cough, hemoptysis and dyspnea. The severe pulmonary involvement is rare, expressed through massive hemoptysis, hemorrhagic pneumopathy (as in the case we have reported), pulmonary edema and, rarely, through ARDS.

Biologically, the present case is particular through the moderate character of the acute renal failure accompanied by intense jaundice.

Bacteriologically, isolating *Leptospira* is difficult since their growth is slow and demanding, requiring special media. Thus, the etiologic diagnosis is most frequently performed through the serologic method of Martin and Petit (identification of antibodies through microagglutination), with a cut-off value of 1/100 (in our case 1/1,600). These antibodies generally appear between 12 and 15 days from the illness’ onset, which explains the initial negative serologic test, when performed in the asymptomatic phase. Frequently, we can identify immunity towards multiple *Leptospira* serogroups. A differential diagnosis is required for the fever caused by hantaviruses, which is more and more common worldwide and which needs to be considered in the case of negative leptospirosis serology [10].

The evolution of leptospirosis is frequently towards spontaneous healing. The indication for antibiotic therapy is controversial, several protocols being available: penicillin G 6 million IU/day, aminopenicillin 1 g 4 times per day or doxycycline 100 mg bid. It seems that antibiotic therapy is efficient only when started early in the disease evolution, up to 4 days after inoculation; this is quite difficult to achieve since this time span corresponds to the incubation period, when the patient is still asymptomatic and thus does not address a doctor. Antibiotherapy is currently allowed due to the fact that it reduces the duration of fever and that of the renal failure [11]. In the immunologic phase, late in the disease’s development, certain authors recommend the treatment with penicillin G 100,000 IU/kg/day for 7 days [11]. The association of a corticoid bolus, suggested by certain authors for the severe visceral afflictions, might diminish mortality [12].

Certain cases of Herxheimer reaction to penicillin have been described; this may question the indication of antibiotic therapy in mild outlines of the disease.

In the case we have reported, ceftriaxone was administered through slow IV 4g/day, 18 days, associated with corticotherapy (dexamethasone 10 days, followed by prednisone 6 days). For the acute renal failure, diuretics were administered: mannitol 20% in EVP (with role of cerebral depletion, as well) – for 3 hours, a total of 50g; furosemide 2 vials IV in the first day and dopamine in EVP 5μg/kg/min, kept up to normalization of diuresis, respectively for 4 hours (a total of 2 x 250ml solution); symptomatic treatment with antiemetic and antisecretory drugs; thrombocyte concentrate and vitamins B1 and B6.

Vaccination is mandatory for the individuals professionally exposed to potentially contaminated waters.

In the reported case, the contamination circumstances as well as the clinical presentation of leptospirosis underline the importance of considering this diagnosis with potential severity when faced with any feverish icteric syndrome, particularly if the patient associates a hemorrhagic syndrome,
in the context of contact with sweet, calm water, even in the distant history, (within an interval of 15 days).

Conclusions

Severe leptospirosis may present a large variety of clinical outlines. Mortality in these cases, which frequently associate jaundice and azotemia, varies between 15 and 40% [1,6]. Even if there is a cardiac involvement (in over 10% of cases), a fatal outcome is frequently the result of renal or hepatic impairment, while the cardiac involvement appears to be the cause of exitus in only 25% of the fatal cases [6]. Still, patients with severe leptospirosis need to be carefully monitored because they can develop a cardiac pathology. Echocardiography or invasive hemodynamic monitoring can be extremely useful for the differential diagnosis and the efficient treatment of cardiomegaly and of diffuse pulmonary infiltrates. It is believed that immediate initiation of IV penicillin therapy can be efficacious even when started late in the development of the disease, by significantly reducing the high mortality of the cases of severe leptospirosis [6,11].

References