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Prikaz bolesnika | Case report

Adjunctive treatment of leptospirosis with corticosteroids: a case report

Liječenje leptospiroze kortikosteroidima: prikaz bolesnika

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Summary

Leptospirosis is one of the most globally widespread zoonosis caused by pathogenic spirochetes from genus Leptospira spp. Icteric leptospirosis is a severe form of the disease which affects 5-15% of patients with leptospirosis, is often rapidly progressive and has a high mortality rate. Early diagnosis of leptospirosis is crucial for initiation of adequate antimicrobial therapy in order to prevent the advent of complications and reduce mortality. Literature offers an increasing amount of evidence that early application of corticosteroids affects the course of the disease, prevents the onset of multiorgan failure, reduces mortality and reduces the duration of hospitalization. This paper is a case report of a patient with severe icteric leptospirosis who was treated with antimicrobial and corticosteroid therapy. The patient recovered fully, with no remaining morbidity after the severe disease.

Sažetak

Leptospiroza je jedna od globalno najraširenijih zoonoza, uzrokovana patogenim spiralnim bakterijama iz roda Leptospira spp. Ikterična leptospiroza je teški oblik bolesti koji se javlja kod 5-15 % bolesnika i često ima brzu progresiju i visoku smrtnost. Pravovremena sumnja i dokaz leptospiroze ključni su za početak adekvatne terapije kako bi se spriječio razvoj teškog oblika bolesti i smanjila smrtnost. U dostupnoj literaturi sve je više dokaza kako rana primjena kortikosteroida kod teških kliničkih oblika utječe na tijek bolesti, sprječava razvoj multiorganskog zatajenja organa, smanjuje smrtnost i skraćuje vrijeme hospitalizacije. Ovo je prikaz bolesnika s teškom ikteričnom leptospirozom koji je liječen antimikrobnom i kortikosteroidnom terapijom. Bolesnik se u potpunosti oporavio bez zaostalih posljedica teške bolesti.

Introduction

Leptospirosis, caused by pathogenic spirochetes from the genus *Leptospira spp* is one of the most widespread zoonoses worldwide[1]. According to the World Health Organization and The International Leptospirosis Society data, it is estimated that about 350.000 to 500.000 people are affected by leptospirosis each year[2]. Croatia is 13th most affected country in the world and the 1st in Europe, with 17.3 patients with leptospirosis reported per 1.000.000 people[3]. The course of infection in humans is usually mild („flu-like") and the disease often remains unrecognized and undiagnosed[4]. A more severe form of the disease affects 10% of patients, out of which 30 to 60% have an unfavourable outcome[5]. Severe disease is defined as fever associated with two or more of the following features: icterus (bilirubin > 51.3 µmol/ L), oliguria (diuresis < 400 ml/24 hours, creatinine > 133 µmol/ L or urea >25.5 mmol/ L) or organ failure (ARDS, pulmonary haemorrhage, acute insufficiency or renal failure, acute liver lesion, melena, hematemesis or multiorgan failure)[6]. This paper is a case report of a patient with severe icteric leptospirosis treated in Slavonski Brod General Hospital in October 2017.

Case Report

A 59-year-old male patient was admitted to the Infectious Diseases ward with fever and icterus. The symptoms started 10 days prior to admission with mild respiratory symptoms and general weakness, which were followed by nausea, vomiting, diarrhoea, febrility, intensive stomach pain, and calf myalgia. The patient noticed reduced urine output, but was not dysuric. On the day of admission, the patient noticed the yellowing of his skin. Epidemiological history revealed that the patient lives in a rural area, works in the field

of agriculture and keeps pigs. His disease was sporadic. The patient did not travel outside of Croatian borders. Two weeks prior to symptom onset, the patient had cleaned the pigsty. His past medical history was unremarkable and he did not take any medication. He admitted to daily consumption of alcohol and smoking of cigarettes.

On admission the patient was of clear consciousness, febrile, mildly dyspnoeic, tachycardic, dehydrated, he was shivering and his vital parameters were stable (SpO_2 95%, RR 115/70 mmHg, c/p 100/min, RF 22/min, GCS 15). His skin and visible mucosa were icteric, with no rash or petechiae. His stomach was above the level of his chest, diffusely painful to palpation, but with no abdominal guarding. There was meteorism, peristalsis was clearly audible, his liver was enlarged up to 8 cm, and the edge of spleen was palpable. The remainder of his physical examination was unremarkable.

Initial laboratory workup revealed leukocytosis with predominant neutrophilia, thrombocytopenia, increased inflammation markers and liver function tests, lowered electrolytes and hypoalbuminemia, albuminuria and erythrocyturia, with a normal coagulation panel (Table 1). Markers of viral hepatitis A, B, C, and E were negative, as was stool microbiological analysis. The patient's urine and blood cultures remained sterile. Abdominal ultrasound and CT were performed, revealing a small amount of free fluid in his pelvis, an enlarged liver, a left suprarenal gland adenoma, an enlarged gallbladder with wall thickening, but no gallstones. Chest X-ray was unremarkable. Due to suspicion of leptospirosis, serology and PCR were performed in blood and urine samples. Antimicrobial treatment was started with ceftriaxone (2g q. d. i. v.), along with parenteral rehydration with crystalloid solutions, gastroprotection, and electrolyte disorder correction.

Table 1. Laboratory findings

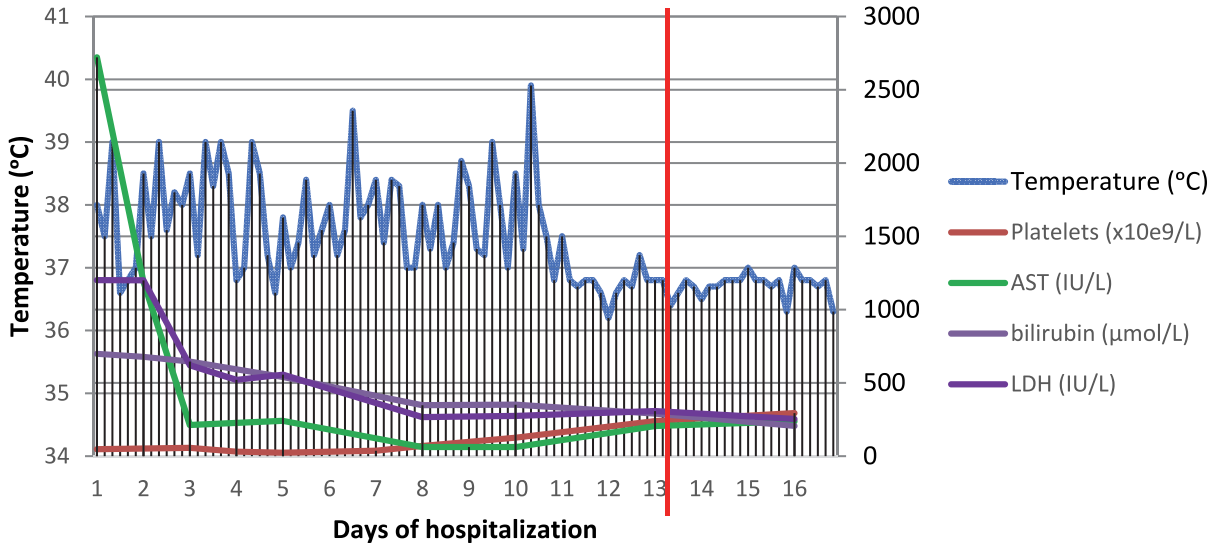
	Day 1	Day 10	Day 20	Day 28	Reference value
L eukocytes (cells x10*9/L)	**35,16**	**17,9**	**13,8**	**14,65**	3,4 - 9,7
Neutrophils (%)	**94,5**	**92,4**	63	47	44 - 72
Erythrocytes (x10*12/L)	**3,76**	**3,34**	**3,03**	**3,46**	4,34 - 5,72
Hemoglobin (g/L)	**132**	**113**	**103**	**112**	138 - 175
Platelets (cells x10*9/L)	**47**	**23**	404	338	158 - 424
Urea (mmol/L)	**10**	**10,4**	4,4	2,3	2,8 - 8,3
Creatinine (μmol/L)	**122**	**100**	41	39	64 - 104
Na+ (mmol/L)	**130**	**122**	130	136	137 - 146
K+ (mmol/L)	**3,0**	**2,1**	4,9	4,6	3,9 - 5,1
Total bilirubin (μmol/L)	**698,7**	**540,2**	**127**	**58**	3 - 20
Aspartate aminotransferase (IU/L)	**2721**	**241**	**94**	**57**	11 - 38
Alanine aminotransferase (IU/L)	**1748**	**333**	**295**	**119**	12 - 48
Glutamyl transferase (IU/L)	**158**	**35**	**320**	**293**	11 - 55
Alkaline phosphatase (IU/L)	**196**	**67**	**251**	**203**	20 - 142
Lactate dehydrogenase (IU/L)	**1199**	**556**	**253**	187	< 241
Creatine kinase (IU/L)	140	77		10	< 177
Albumin (g/L)	**21**				40,6 - 51,4
Prothrombin index (%)	**64**	**41,8**	71	73	70 - 120
C- reactive protein (mg/L)	**55,9**	**36**	4,7	**22,8**	< 5

Despite the initiated therapy, the patient remained febrile up to 39°C every day. On the third day of hospitalization, a confluent macular rash appeared all over the patient's skin, most prominently in the stomach and shin area. The rash initially appeared macular and blanching, but became evidently haemorrhagic the next day, with ecchymosis appearing on the patient's shins. The fifth day of hospitalization the patient complained of sudden onset of dyspnoea, chest pain, and dry cough. The rash progressed to purpura on the same

day and spread to the entire area of legs, arms, and stomach. Laboratory workup revealed a further drop in platelet count (23 x 10^9/L) with the sudden appearance of anaemia (erythrocytes 3.34 x 10^{12}/L, haemoglobin 113 g/L), acute respiratory insufficiency and coagulopathy (PV 42 %, INR 1.71). ECG and chest X-ray served to exclude acute coronary syndrome and haemorrhagic pneumonitis. Leptospirosis was confirmed by PCR in patient's serum. Diuresis was normal throughout hospital stay.

Since the patient remained hyperpyretic with the progression of purpura and clinical and laboratory deterioration, despite adequate antimicrobial therapy, corticosteroids were introduced (methylprednisolone 1g q. d. i. v.). The patient promptly became afebrile, the skin purpura gradually receded and laboratory findings normalized (Figure 1). Corticosteroid treatment was continued for 14 days with gradual de-escalation of dose. The patient was discharged after 30 days of hospital stay, in a good general state. Serology results

Figure 1. Dynamic of the patient's temperature and laboratory findings before and after corticosteroid therapy (red vertical line)



available after discharge confirmed the presumed diagnosis (*L. interrogans sv. Autumnalis* 1: 2000, *sv. Patoc* 1:2000, *sv. Poi* 1:1000...).

Discussion

This patient presented with acute icteric leptospirosis. Icteric leptospirosis affects 5- 15 % of patients, often progresses rapidly and has a high mortality rate[7]. The patient's history of alcohol abuse likely contributed to faster deterioration and a more severe presentation of the disease. A search of the literature yielded only two other reports discussing the clinical course of leptospirosis in patients with alcoholism as a comorbidity, with this report being the first one in Croatia[8]. It has been observed that, in patients with concurrent alcoholism, bilirubin is frequently high and may persist for several weeks, but transaminases and alkaline phosphatase are usually moderately elevated[8]. This patient also presented with high bilirubin and slightly elevated alkaline phosphatase levels, with the distinction that transaminases were also extremely elevated. In leptospirosis, thrombocytopenia is correlated with a worse outcome[9]. This patient presented with severe thrombocytopenia, predicting a potentially severe disease course.

The range of differential diagnoses in this patient was wide, including viral or alcohol-induced hepatitides, but his epidemiological history necessitated a high degree of suspicion of leptospirosis. Correspondingly, empirical treatment for leptospirosis was started immediately. Early recognition and diagnosis of leptospirosis are crucial for adequate initiation of treatment. It is generally believed that antimicrobial treatment should be started as early as possible (before the 5th day of illness) in order to reduce the likelihood of a severe disease course[10]. A major complicating factor with this patient was that, by the time he sought med-

ical attention, the disease had been active for 10 days, with daily high fevers despite antibiotic treatment.

The decision to introduce corticosteroids was influenced, along with a progressive deterioration in the patient's general state, thrombocytopenia, and anaemia, by the appearance of respiratory symptoms. Pulmonary involvement is a known complication of leptospirosis with a mortality rate as high as 30 to 60%[5]. While pulmonary haemorrhage was not proven in this patient, the clinical suspicion inspired a new therapeutic approach.

Five studies[11,12,13,14,15] on patients with a severe form of leptospirosis treated with corticosteroids have been published to date (mostly concerning patients with pulmonary haemorrhage and multiorgan failure). These patients were treated with corticosteroids in the first 12 hours since the onset of respiratory symptoms (tachypnea >30/min, dry cough, dyspnoea or haemoptysis). An effective dose of methylprednisolone is stated to be 1g parenterally for three days, followed by de-escalation throughout minimally seven days. One study warns that the use of corticosteroids may increase the risk of nosocomial infections[15].

This patient experienced no further progression of respiratory symptoms and was ultimately discharged in good health and with no repercussions. It could be theorized that the favourable outcome was largely due to the timely administration of corticosteroids.

This work has contributed to the recent evidence that corticosteroids positively affect the outcome of a severe form of leptospirosis. Despite clinical publications up to date, no clear guidelines on corticosteroid treatment in a severe form of leptospirosis exist and further research in this area is needed.

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