CASE REPORT

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Facing dengue fever – our first experience

Suočavanje s dengom: naše prvo iskustvo

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Abstract

Introduction. Dengue fever is a mosquito-borne disease caused by dengue virus, endemic in tropical and subtropical regions, where it is mostly imported from. The most common clinical form is classic dengue fever. We presented the first dengue case microbiologically confirmed in Serbia. **Case report**. A 34-year-old male got classic dengue fever after arrival from Cuba. The disease occurred suddenly with fever, myalgias, skin rash, hepatosplenomegaly, cytopenia, abnormal aminotransferase and creatine kinase levels. The diagnosis was confirmed with virological diagnostic methods. Significant leukopenia and thrombocytopenia as well as elevation of serum creatine kinase activity were recorded from the very beginning of hospitalization, but were gradually normalized. The whole duration of hospitalization was accompanied by laboratory signs of liver lesion. The disease had favourable outcome. At hospital discharge, the patient was afebrile, asymptomatic, with discrete erythematous rash on torso and arms, normal hemathological values and creatine kinase level and moderately elevated alanine-aminotransferase level. **Conclusion**. Considering global climate changes and growing international traffic, our health care service needs to be ready for possible massive outbreaks of dengue and other tropical infectious diseases in forthcoming years.

Key words:
dengue; diagnosis; signs and symptoms; leukopenia; thrombocytopenia; creatine kinase.

Apstrakt

Uvod. Denga je oboljenje izazvano virusom denge, endemsko u tropskom i suptropskom pojasu. Autohtoni slučajevi retki su u Evropi. Oboljenje je najčešće uvezeno iz endemskih regija sveta. Prikazan je prvi slučaj denge koji je mikrobiološki potvrđen u Srbiji. **Prikaz bolesnika**. Po povratku s Kube, 34-godišnji muškarac se razboleo naglo, s febrilnošću, mialgijama, kožnim osipom, hepatosplenomegalijom, citopenijom, patološkim nalazima aminotransferaza i kreatin kinaze. Dijagnoza denge potvrđena je metodama virusološke dijagnostike. Značajna leukopenija i trombocitopenija bile su glavne karakteristike krvne slike. Laboratorijski znaci lezije jetre registrovani su tokom cele hospitalizacije. Aktivnost kreatin-kinaze u serumu bila je povišena na prijemu u bolnicu. Uz simptomatsko lečenje, bolest je imala povoljnu evoluciju, bez komplikacija. Bolesnik je otpušten iz bolnice afebrilan, bez tegoba, s diskretnim eritemom kože trupa i ruku. Vrednosti hematoloških parametara i kreatin kinaze na otpustu bile su uredne, a aktivnost alanin aminotransferaze umereno povišena. **Zaključak**. Zdravstvena služba naše zemlje trebalo bi da, u uslovima globalnih klimatskih promena i sve razvijenijeg međunarodnog transporta, bude spremna, u organizacionom, kadrovskom i materijalno-tehničkom pogledu, da odgovori na epidemijsku pojavu denge i drugih tropskih infektivnih bolesti u predstojećem periodu.

Ključne reči:
denga; dijagnoza; znaci i simptomi; leukopenija; trombocitopenija; kreatin kinaza.

Introduction

Dengue fever is an infectious disease caused by dengue virus, Flaviviridae family. There are 4 subtypes of the virus (DEV 1-4). The disease is worldwide distributed. It is endemic in many countries throughout Africa, Asia and South America. A half of million people throughout the world is being diagnosed with dengue *per* year [1]. Most dengue cases in Europe are imported from endemic regions. A total of 1,118 confirmed cases were reported in 15/24 countries of Europian Union in 2012; 78% of them were imported from Asia, and 10% originated from South America [2]. Autochtonous dengue cases were described in Europe as well, like in Croatia [3] and France [4]. A dengue outbreak was reported in

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Madeira (Portugal) with more than 2,000 cases [5]. In urban areas, the virus maintains in life cycle between human and *Aedes aegypti* mosquito. Mosquito gets infected by feeding on viremic person and transmits the infection to a healthy person during repeated blood feeding. Viremia lasts for 4–7 days. The virus then replicates in reticuloendothelial cells [6]. Dengue is sometimes difficult to differentiate from the other vector-borne diseases: malaria, chikungunya, yellow fever, tick-born encephalitis. In these cases, virological diagnostics is necessary, like virus isolation on cell culture, viral antigen NS1 serologic tests like enzyme immunoassay (ELISA) and rapid tests [7]. Polymerase chain reaction (PCR) is used for detection of viral ribonucleic acid (RNA). Treatment of dengue is symptomatic. The vaccine for human use for protection against dengue is not licenced so far. However, ongoing phase III clinical studies of attenuated tetravalent vaccine are promising [8]. We presented the first microbiologically confirmed dengue case in Serbia.

Case report

A 34-year-old male from Novi Sad surroundings was hospitalized at the Clinic for Infectious Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia on 5 October, with the diagnosis of dengue. He has been living in Havana, Cuba, for the last three years. The disease started abruptly on 30 September; he complained of fever raising up to 39.7°C, chills, headache and myalgias. The temperature was dropping temporarily with abundant sweating and then raising again. On the third day of the disease, his general condition improved, the body temperature was normal, but he started caughing dry. From day 4 after onset of the disease, the temperature reached 39^0 C again, followed by constitutional symptoms. Laboratory findings taken just before hospital admission (Table 1) showed marked leukopenia (1.6×10^9/L) and thrombocytopenia (74×10^9/L normal range 140–400 × 10^9/L) mild elevation of creatine kinase-352 U/L (normal range 24–195 U/L), two-fold elevation of alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) level, one-third-fold elevation of alanine aminotransferase (AST) level, while the other laboratory findings were within normal limits. On hospital admission (day 6 after onset of the disease), the patient had discrete maculopapular skin rash on torso and forearms and on palpation. The serum sample was sent to Department for Virology, Institute for Public Health of Vojvodina, Novi Sad, Serbia. Real-time polymerase chain reaction (PCR) test (using reagents and protocols obtained from the Centers for Disease Control and Prevention (CDC) to dengue virus 1-4 was done; it was positive to type 3 dengue virus on day 7. In adition, indirect immunofluorescence test (IIFT) immunoglobuline (IG) M/IgG (manufacturer Euroimmun, Lübeck, Germany) against dengue virus 1-4, West Nile virus, Japanese encephalitis virus, yellow fever virus and tick-borne encephalitis virus were applied. The only positive finding was related to IgM antibodies to subtype 3 dengue virus on day 7 of the disease. The patient was isolated and rehydrated. He was permanently afebrile during the stay at hospital. His only complaint was mild dry cough with normal chest radiogram finding. The peak serum creatine kinase activity was reached on the first day of hospitalization – 975 U/L and gradually normalized to the sixth day. Moderately elevated ALT level of 221 U/L was recorded at hospital discharge. Both the white blood count and platelets were normaly on discharge (Figures 1 and 2). The patient was dismissed from the hospital on 9th day after admission afebrile, in a good general condition, with slight diffuse erythematous rash on the trunk and arms.

Discussion

Dengue is the most common arthropod-borne infection in the world. According to World Health Organisation (WHO), since seventh decade of the former century, its incidence has raised up to 50–100 millions of cases *per* year and has inc-

Table 1

Blood laboratory findings just before hospital admission

Laboratory finding	Actual values	Reference values
Erythrocyte sedimentation rate (mm/h)	5	2–6
White blood count (× 10^9/L)	1.58	4.0–10.0
neutrophils (%)	64.3	40.0–74.0
lymphocytes (%)	23.0	19.0–50.0
monocytes (%)	4.5	2.0–10.0
eosinophils (%)	2.4	0.0–7.0
Platelets (× 10^9/L)	74	140–400
Creatine kinase (U/L)	352	24–195
Total bilirubin (μmol/L)	9.8	2.0–21.0
Direct bilirubin (μmol/L)	4.2	0.0–3.4
Alanine-aminotransferase (U/L)	104	0–50
Aspartate-aminotransferase (U/L)	100	10–75
Alkaline phosphatase (U/L)	95	60–142
Gamma glutamyl transferase (U/L)	148	0–73
Urea (mmol/L)	4.3	3.2–8.2
Glucose (mmol/L)	6.7	4.1–5.9
Lactat dehydrogenase (U/L)	586.0	0.0–1327.0
C-reactive proteine (mg/L)	3.3	0.0–5.0
Potassium (mmol/L)	4.0	3.5–5.5
Sodium (mmol/L)	137	132–146

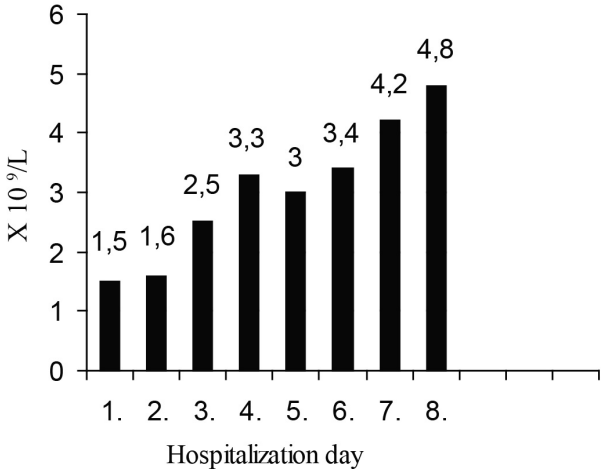

Fig. 1 – Peripheral blood leukocytes during hospitalization.

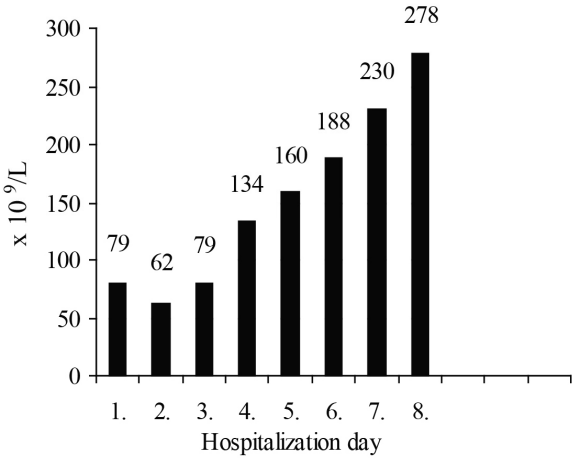

Fig. 2 – Peripheral blood platelets during hospitalization.

reased 30-fold. Great public importance of dengue is also highlighted by the fact that half of the world population lives in the areas where dengue is endemic disease. During last several years, Serbia has been affected by drastic migrations of its own people, motivated by the search for higher life standard. At the same time, our country is exposed to the flows of refugees from the Middle East, who are trying to escape the war in their own countries. This is the reason why our health system must be capable to handle the threat of tropical infectious diseases such as dengue and other haemorrhagic fevers, not only in terms of technological and material resources but in terms of medical knowledge as well. Naturally, we suppose that dengue in our patient would be recognized faster and easier in a country which is endemic for dengue.

Since 1970, the Caribbean (where Cuba is located) have been hit by frequent dengue outbreaks. Our patient aquired dengue virus infection in Cuba. In our patient IgM antibodies against dengue virus type 3 were found out by serologic method (IIFT). These antibodies are detectable in 99% cases of dengue until 10th day of disease. IgG antibodies can be detected in most cases over the first week of disease and their titer raises slowly [9]. Type 3 dengue virus infection was confirmed by real time PCR test. Mild form of disease can be explained by patient´s younger age (severe haemorrhagic form hits children in more than 90% of cases), lack of comorbidity as well as lack of secondary infections with other types of virus which predispone to severe forms of the disease. Viremic phase in dengue matches clinical presentation of the disease, lasting for 4–7 days, so in that period molecular diagnostics remains a good diagnostic tool [9]. Literature data describe "flu-like syndrome" in clinical presentation of dengue; our patient presented with the same clinical features. "Flu-like syndrome" is the consequence of inflammatory response with cytokine production. Maculopapular rash on the trunk and arms went away soon after admission, so from the second day of hospitalization only a diffuse non-itchy rash could be seen on those parts of the body. According to literature data, rash in dengue most commonly appears as morbilliform or maculopapular. Moderate splenomegaly indicated a generalised disease of viral origin. On the third day of hospitalization a short-term improvement occurred, followed by a drop in temperature to its normal values. Biphasic course of the disease is being mentioned in clinical studies of dengue as a common feature [9, 10].

Cytopenia can be expected in dengue patients because of a potential direct infection of chematopoetic cells of bone marrow in the course of early viremia [11]. Our patient had a significant leukopenia followed by a moderate thrombocytopenia which did not require substitutional therapy. During the hospitalization, gradual and complete spontaneous normalisation of white blood count and platelets was registered. Blood leukocytes tended to rise from the admission (1.5×10^9/L) to the discharge from the hospital (4.8×10^9/L). Platelets varied from 74×10^9/L on the admission to 278×10^9/L at the discharge from hospital. Normal blood coagulation tests during the whole course of hospitalization were responsible for the lack of haemorrhagic syndrome. High serum creatine kinase level was recorded several times during the hospitalization. It might be the consequence of perivascular mononuclear cell infiltration of muscles. Data describe dengue cases with myositis and rhabdomyolysis [9, 12]. Fortunately, deadly outcome due to hepatic failure is rare. AST is somewhat higher than ALT at early stage of the disease, which is supported by muscle damage due to infection. In our patient, ALT level was higher than AST level, probably because of late blood testing in relation to the beginning of the disease [9, 13].

Among the surrounding countries, the autochtonous transmission of dengue was recorded only in Croatia [14]. In this country, the presence of mosquito *Aedes albopictus* may be responsible for autochtonous appearance of dengue [15]. In Serbia there have been no conditions for autochtonous occurrence of dengue so far, because neither the suitable vector has been registered nor continuous appearance of imported

dengue cases has been occurring. Epidemiology of dengue in Serbia appeared to be slightly different in comparison to the sixties of the former century. At that time, the initial investigation on seroprevalence to dengue virus 1 and 2 has been carried out and exposure of Serbian human population to those subtypes of dengue virus has not been confirmed [16]. The presence of viremic patient and suitable vector are necessary conditions for local outbreak appearance [17]. If those conditions were fulfilled in the future, Serbia could face autochtonous dengue in the same way Croatia is facing it now.

Conclusion

Considering global climate changes and growing international traffic, our health service needs to be ready for possible massive outbreaks of dengue and other tropical infectious diseases in forthcoming years.

Patients with history of previous stay in tropical regions known for dengue appearance who have high fever, "flu-like" syndrome followed by a skin rash, hepatosplenomegaly and cytopenia, optionally, and followed by haemorrhagic syndrome should arouse the suspicion on dengue fever.

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