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Dengue virus infection in a course of typhoid fever

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Abstract

Dengue is a mosquito-borne viral infection caused by dengue virus (DENV) belonging to a group of Flaviviridae. Disease is widely spread in tropical and subtropical regions of Southeast Asia, Africa and the Americas. DENV infection causes a spectrum of illness including flu-like syndrome and potentially life-threatening dengue hemorrhagic fever. Confirmation of DENV infection requires serological serum tests or detection of viral genetic material in a serum sample. There no specific treatment for dengue but symptomatic therapy should be implemented in all cases. Recently there are two modern DENV vaccines available for the people living in the countries at a risk of infection. Efficiency and safety profile of both vaccines are debatable. Dengue symptoms may imitate clinical picture of other diseases that are typical for endemic DENV regions. We present a case of 22-year-old Indonesian woman treated originally due to typhoid fever who develop the symptoms of DENV infection.

Introduction

Dengue is mosquito-borne tropical disease caused by dengue virus (DENV) belonging to a family of Flaviviridae (the same as Yellow fever virus, Zika virus, West Nile Virus). Vectors of the disease are mosquito mainly of the species *Aedes aegypti* and *Aedes albopictus* which are widely spread in many tropical and subtropical regions of Africa, the Americas, the

Eastern Mediterranean, South-East Asia and the Western Pacific [1]. The global prevalence of dengue raised in recent decades which is linked to development of urban population, increase air travel and spreading habitat of *Aedes* mosquito [2]. It is estimated that 400 million people are affected by the disease yearly. Most of them are local citizens but tourists are also at a risk of infection [3]. Some popular touristic places of Southeast Asia are in a group of high prevalence especially: Philippines, Singapore and Indonesia.

Dengue virus infection causes a spectrum of illness ranging from usual flu-like syndrome to rare but potentially fatal complication called dengue hemorrhagic fever. Typically, first dengue infection is characterized by high fever, headache, muscle and joint pain, lymphadenopathy and gastrointestinal disturbances that occur after incubation period of two weeks. Severe dengue is a complication more prevalent for children that usually happen during second or next infection. It features with severe bleeding, respiratory distress and multi-organ impairment [4]. To confirm the diagnosis, serological (detection of IgG and IgM anti-DENV antibodies) or genetic (detection of DENV RNA) tests are needed. There is no specific treatment in case of dengue but symptomatic treatment including fluid replacement, analgesics and non-steroid anti-inflammatory drugs are provided. Tetravalent, live-attenuated DENV vaccine is available for local people in endemic regions (especially in Philippines) but recently it is not recommended for tourists traveling to countries with a high risk of dengue infection [5]. Due to weakening of immune system capacity in course of dengue infection the disease may be combined with other infectious diseases which are often characterized by the similar symptoms.

Typhoid fever belongs to a group of infectious diseases that can imitate first infection or relapse of DENV infection. This bacterial infection caused by gram-negative bacteria *Salmonella* Typhi usually spreads by ingestion of contaminated water or food. The disease is mainly found among children and adolescents in Eastern Asia, Latin America and the Caribbean. Initial phase of typhoid fever is characterized by high fever, headache, lymphadenopathy, abdominal pain and gastrointestinal symptoms. In late phase serious, life threatening complications as intestinal hemorrhage or intestinal perforation may occur [6]. Diagnosis in cases of suspected typhoid fever is based on typical clinical course, isolation of the pathogen by blood culture, classic serological Widal test and PCR-based identification of *Salmonella* Typhi genetic material in blood sample [7]. Specific treatment of typhoid fever with antibiotics is decisive to curing disease with minimal complications. Recommended therapy including drugs from a group of fluoroquinolones, cephalosporins or macrolides needs to be combined with symptomatic treatment. Worldwide two types of typhoid vaccine are available and used – inactivated parenteral vaccine and live-attenuated oral vaccine. Efficiency of vaccines is less than 80% (depending on source of a data) but both are recommended for people living regions endemic for typhoid and also for tourists traveling to these countries [8].

We present a case report of a patient diagnosed with typhoid fever that develops symptoms of DENV infection during a treatment of original condition.

Case report

A 22-year-old Indonesian woman was admitted to Dr Soetomo Hospital in Surabaya in Indonesia with the symptoms of mild fever (38°C), abdominal pain, nausea and vomiting. Based on blood morphology test and serological Widal test typhoid fever was confirmed.

According to guidelines doctors implement therapy with first-line antibiotic – ceftriaxone (in a dose of 2g per day). During seven days of follow-up general condition of a patient improve and she was discharged home. On the second day out of hospital patient develop rapidly increasing fever up to 41°C, severe fatigue and headache, which localized in an occipital part of a head. In the next days patient presented rash in the form of petechiae on lower limbs, back and abdomen. Blood morphology test revealed moderate lymphopenia (0,5 G/l), granulocytopenia (1,0 G/l) and severe thrombocytopenia with a platelet level dropping from 111G/l to 14 G/l. However, there were no signs of external or internal bleeding.

Due to the occurrence of the typical symptoms and DEMV infection in the medical past (at the age of four) patient was diagnosed with dengue fever. Diagnose was based mainly on a clinical picture and basic laboratory tests. Advanced diagnostic tests were not performed. Patient underwent treatment including intravenous fluid replacement therapy and high dosage of acetaminophen. Due to significant risk of massive bleeding non-steroid anti-inflammatory drugs were avoided. Two weeks of hospitalization and maintenance therapy have resulted in improvement of patient's condition and led to discharge home.

Discussion

According to World Health Organization, dengue, the dangerous flavivirus transmitted by mosquitoes, spreads with the fastest rate from all viral-borne entities [9]. Nowadays, it is estimated that around 100 countries are endemic to the virus that contributes to 40% of the world's population living in the endangered area [10]. What is more, travelers have potential to spread the disease, yet the number is still underestimated due to shortage of centers allowing proper diagnosis in countries of Europe [11]. Current studies indicate that most of infections are imported from the regions of Asia [11]. The number of infections remains high despite the common approach to various ways of prevention involving removal of mosquito habitats and using the insecticides. Despite, the attempts of scientists, the efficient and unified vaccine has not been introduced yet. The first officially licensed vaccine was introduced in 2015 [12]. It was a tetravalent recombinant, CYD-TDV vaccine (Dengvaxia) that underwent complex phase 3 clinical trial program. The trial involved 10 countries from Asia and Latin America that were endemic to dengue. The results were considered as unpredicted that qualified the vaccine as only an additional tool in prevention of the disease. According to the official study, during 25 months follow-up after first dose, in group ≥ 9 years (due to safety reasons) with confirmed dengue, the efficacy was estimated to “81.9% (95% confidence interval [CI], 67.2%–90.0%) for individuals with baseline seropositive status and 52.5% (95% CI, 5.9%–76.1%) for those who were seronegative at baseline” [12]. Such numbers indicate that a mechanism of the vaccine broadens preexisting immunity levels rather than stimulates newly developing immunity. Yet, while taking into account long term follow-up (4-5 years), it appears that the rate of hospital cases in vaccinated group (age 9-16) was significantly lower than in case of on-vaccinated teenagers. Moreover, predictions show that the number of dengue hospitalization may be minimized by 10%-30% over 30 years. The prevention of dengue is essential as it minimize the chance of life-threatening type of dengue - dengue haemorrhagic fever (DHF) and shock syndrome (DSS). These conditions could result in high mortality rate - considering patients with DSS it may reach 44%. Furthermore, both DHF and DSS are more likely to happen as secondary infection [13] as it may happen in case of patient presented in the report due to coinfection of dengue and typhi. The coinfection of dengue is an

effect of the virus on the immune system of the organisms. Most common coinfections with dengue are *Escherichia coli*, *Salmonella*, *Burkholderia pseudomallei*, herpesvirus, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis* and *Mycoplasma pneumoniae* [14]. Nevertheless, the coinfection of dengue and typhoid is rare yet still observed not only in the region of Asia, but also in India. Secondly, coinfection with the diseases may delay the process of diagnosis due to atypical manifestation. Such misinterpretation can postpone the sufficient treatment of the patient. Presented patient was not vaccinated for dengue or typhi. However, there is a great probability that this fact would not change the course of illness and would not minimize the risk of dengue reinfection. More efficient seem to be simple prevention considering usage of repellents, window protective mesh and suitable clothing. When it comes to typhi, the vaccine is effective although the protective period last around 3 years. Female patient suffered from the typical form of acute dengue fever: with sudden beginning, high body temperature up to 41 Celsius degree, headache, pain of the bones and joints and lymphadenopathy. The general signs were associated with rash in the form of petechiae on lower limbs, back and abdomen. Due to severe thrombocytopenia with a platelet level dropping there was a suspicion of dengue hemorrhagic fever but any kind of bleeding, external or internal, was not diagnosed. DHF is typical for Thailand and Philippines region and is more frequents among people reinfected with another serotype of the virus. The patient was secured against bleeding by avoidance of non-steroid anti-inflammatory drugs. The fever started to decrease after 2 days and patient has started to go into remission. Because woman manifested typical symptoms and signs of dengue disease as well as she reported this infection in her medical past, the diagnosis was fast and did not require any specific tests. The treatment was symptomatic - it supposed to prevent hemorrhage, shock and alleviate the hemorrhagic diathesis. Presented case report is not a warning for tourists. Described patient is an Indonesian female with curious coinfection of typhoid fever and second-time dengue infection. Typhoid fever can be easily avoided by vaccination which is recommended. As mentioned above, the vaccine for dengue is not as effective as it should be, that is why there are ongoing programs working on a dengue vaccine to cover all four serotypes [15]. In 2017 it was announced that the vaccine should have been used only in people who had had a previous dengue infection due to more severe course of the subsequent infections [16]. For many developing countries - like Indonesia, typhoid fever and dengue fever, endemic infections, remain as crucial public health concerns [17].

Co-infection supposed to be considered while dealing with cases of dengue or typhoid fever with or without atypical features. In order to reduce the development and negative effects of disease, along with improvement of sanitation and personal hygiene, emphasis should be given on vaccination against typhoid [18]

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