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Letter to the Editor

A Case of Methotrexate Intoxication Misdiagnosed as Crimean-Congo Hemorrhagic Fever

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Crimean-Congo hemorrhagic fever (CCHF) is a fatal zoonotic disease caused by a *Nairovirus* belonging to *Bunyaviridae* family [1]. Main routes of transmission to human are infected tick bites and direct exposure to blood and tissues of infected animals or other patients. After an incubation period of 1 to 7 days, a flu-like illness accompanying non-specific symptoms such as fever, chill, headache, myalgia, and digestive problems occurs. In severe cases, the primary symptoms followed by hemorrhagic manifestations including petechiae, ecchymosis, hematuria, and melena. Thrombocytopenia, leukopenia and elevated transaminase levels are the most frequent abnormal laboratory findings in CCHF patients [2].

Similar to other infectious diseases, early diagnosis of CCHF is an essential step in the prevention of further spread of infection and adoption of appropriate patient management strategies. Nevertheless, due to lack of pathognomonic features of CCHF and non-specific symptoms or signs particularly in the early stages of the infection, the disease may be misdiagnosed as other conditions with a similar clinical presentation such as malaria, yellow fever, dengue, meningococcemia and several non-infectious diseases including cirrhosis, malignancies, hematological diseases and collagen tissue disorders [3, 4]. Here we report a case of methotrexate toxicity in a rheumatoid arthritis patient misdiagnosed as CCHF.

In July 2016, a 56-year-old unemployed CCHF suspected man was admitted to Sassan hospital in Tehran, Iran. His symptoms and signs included fever, myalgia, dizziness, severe retropharyngeal hematoma, inflation, petechiae, hemoptysis, and gastrointestinal (GI) bleeding. Severe thrombocytopenia (Platelets=6000/µL), low hemoglobin level (6.5 g/L) and leukopenia (WBC<4000/ µL) were observed in his laboratory findings.

According to the clinical symptoms, laboratory findings and the history of travel to a village in the north of Iran, the patient was considered as a CCHF probable case. Based on the protocol of National Committee on Viral Hemorrhagic Fevers (NEC), the patient was isolated, ribavirin therapy was initiated, and his serum sample was delivered to the Department of Arboviruses and Viral Hemorrhagic Fevers, Pasteur Institute of Iran (National Reference Laboratory) for molecular and serological diagnosis of CCHF.

To confirm CCHF virus infection laboratory analyses including RT-PCR and IgM ELISA were carried out [5] for three blood samples (0, 5 and 10 days post onset of symptoms). Following the negative laboratory results for CCHF infection, clinicians investigated patient's medical history thoroughly, and it was revealed that he had rheumatoid arthritis and was under methotrexate therapy. Following these findings, the treatment with methotrexate was immediately discontinued and 7 days later the patient was fully recovered.

Due to the non-specific symptoms of CCHF, especially in its early stages, differential diagnosis of the disease is crucial [6]. Although, most important differential diagnoses of CCHF include malaria, rickettsia, leptospirosis, borreliosis and also other viral hemorrhagic fevers, some non-infectious diseases and medical conditions that are associated with fever and severe thrombocytopenia can also be misdiagnosed as CCHF [7-9].

There are small data on non-infectious medical conditions that overlap sign and symptoms of CCHF. A recent study conducted in Turkey on the etiology of PCR-negative suspected CCHF patients indicated that from 76 cases with a non-CCHF diagnosis, 45 (59.2%) had other infectious diseases, while the remaining 31 cases (40.8%) had non-infectious conditions among which isolated thrombocytopenia and toxic hepatitis were the most frequent ones [8].

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In this report, we described a methotrexate toxicity mimicking CCHF signs and symptoms. High dose methotrexate is used for the treatment of cancer. FDA also approved this drug for treatment of rheumatic diseases with a lower dose compared to cancer therapy in 1988. Some side effects of methotrexate including fever, gastrointestinal problems, rash, thrombocytopenia, leukopenia and elevated transaminase are among the most common symptoms and signs of CCHF [10, 11].

In such cases, the epidemiological background such as the history of travel to endemic areas, history of tick bite, and direct contact with blood, tissues and body fluids of the infected animal or human as well as a careful examination of patient records should be brought into consideration to reach the most accurate clinical diagnosis.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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