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Hepatitis E Virus Cross-Reactivity and False-Seropositivity: Challenges to Diagnosis

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Hepatitis E Virus (HEV) infection is generally manifested by a self-limiting acute hepatitis E and in some cases, by fulminant hepatic failure [1]. Hepatitis E may be symptomatic or asymptomatic with an overall fatality rate of about 2% worldwide [2]. HEV is an emerging pathogen that has recently evolved to cause chronic liver infections as well as neurologic signs and symptoms [3,4]. Recently, an interesting case of acute hepatitis E, concomitant with rash and arthralgia has been reported, too [5]. Post-viral rashes, arthralgias or Adult-Onset Still's Disease (AOSD) are known to be triggered by many herpes viruses, adenoviruses, enteroviruses, retroviruses, paramyxoviruses, including rubella and hepatitis viruses (HAV, HBV and HCV) [6]. Previously, an association of acute polyarthritis with hepatitis E has shown evidence for past immunization against herpes viruses, like Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) [7].

The proper and timely diagnosis of hepatitis E is technically very challenging. In the absence of an approved algorithm, the consistency of serological tests and viral load (HEV RNA) quantification in terms of sensitivity and specificity are the limiting factors. In acute hepatitis E, HEV-IgM and -IgG rise simultaneously in the narrow window of detectable viraemia. Furthermore, HEV-IgM false-positive reactions against EBV and CMV have been shown previously [7]. Very recently, a retrospective analysis of HEV serology of 1423 samples has shown a high degree of EBV and CMV cross-reactivity where approximately 33.3% and 24.2% of HEV-IgM positive samples were also positive for EBV- and CMV-IgM, respectively [8]. Of these, while only four HEV-IgM positive sera showed HEV RNA, indicating true positivity, three demonstrated cross-reactivity against EBV. Only 13.3% of samples with HEV-IgMseropositivity were HEV RNA positive that highlighted a low positive predictive value of serological testings.

Notably, in the recent report by Al-Shukri et al. [5], though the patient's serology has revealed markers of past infections with CMV and EBV, neither the age of herpes infection nor the history of high fever, rash, arthralgia or AOSD-like symptoms, if any, were mentioned. While the time-related occurring and simultaneous recovery of the two illnesses did indicate a unique manifestation of HEV, a fortuitous or indirect association of rash and arthralgia with post-herpes infection in the patient could not be ruled out. It might be very possible that the clinically silent or asymptomatic illness that was actually initiated by CMV or EBV in the past was reactivated by HEV later.

In sum, ample of HEV false-positive results due to EBV- and/or CMV-IgM cross-reactivity has indicated that serology is unreliable in the diagnosis of acute hepatitis E. Therefore, the diagnosis of HEV infection should be based on clinical presentations raised liver transaminases, serology, as well as confirmatory viral RNA testing.

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