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Case report

To B or not to B: how the hepatitis B surveillance case definition can misdirect public health actions

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Abstract

Surveillance case definitions are utilised to understand the epidemiology of communicable diseases and to inform public health actions. We report a case of hepatitis B infection that meets the case definition for newly acquired infection. However, further investigation revealed that this was most likely past resolved hepatitis B infection with subsequent reactivation secondary to immunosuppression, rather than a newly acquired infection. This case highlights the importance of thorough case and clinician interviews, in combination with detailed assessment of pathology results in collaboration with treating clinicians, to determine the most appropriate public health actions.

Keywords: Hepatitis B; surveillance; case definition; transmission; reactivation

Introduction

The hepatitis B virus (HBV) is transmitted via percutaneous or mucosal exposure to blood or bodily fluids from an infected person. Transmission has been confirmed to occur from mother to child; via non-sexual household contact; sexual contact; needle sharing; and occupational exposures in the healthcare setting.[1]

Surveillance case definitions are utilised to understand the epidemiology of communicable diseases and to inform public health actions. The Communicable Disease Network Australia (CDNA) has two surveillance case definitions for confirmed cases of hepatitis B – one for newly acquired cases (Box 1) and one for unspecified cases.[2]

Case history

In May 2023, the South East Public Health Unit (SEPHU) in Melbourne, Victoria received a laboratory notification of hepatitis B infection for further investigation. The case was a woman in her seventies who was tested for hepatitis B in April 2023 as a potential source for a needlestick injury. She was in hospital following surgery performed on 3 April 2023 and required a blood transfusion on 8 April 2023. The case had negative hepatitis B serology in February 2022, thus meeting the hepatitis B newly acquired case definition (Table 1).

The case has a history of chronic lymphocytic leukaemia (CLL) and was treated with ibrutinib between 2015 and 2021. Due to disease relapse, she was switched to venetoclax and rituximab in February 2022. Hepatitis B serology was repeated in February 2022 as baseline screening prior to commencing rituximab.

The case was born in Greece and emigrated to Australia in 1970. She has no record of ever being vaccinated for hepatitis B.

Box 1: Hepatitis B (newly acquired) CDNA surveillance case definition[a]

A confirmed case requires **laboratory definitive evidence** only.

Laboratory definitive evidence

Detection of hepatitis B surface antigen (HBsAg) in a patient shown to be negative within the last 24 months

OR

Detection of HBsAg and immunoglobulin M (IgM) to hepatitis B core antigen, except where there is prior evidence of hepatitis B infection

OR

Detection of hepatitis B virus by nucleic acid testing, and IgM to hepatitis B core antigen, except where there is prior evidence of hepatitis B infection

a Source: reference 2.

Table 1: Hepatitis B test results at different timepoints

	Timepoint			
Test	**8 July 2014**	**18 February 2022**	**23 April 2023**	**25 April 2023**
Hepatitis B surface antigen (HBsAg)	Negative	Negative	Positive	Positive
Hepatitis B core antibody – total [anti-HBc (Total)]		Negative	Negative	Negative
Hepatitis B core antibody – IgM [anti-HBc (IgM)]			Negative	
Hepatitis B surface antibody (anti-HBs)[a]				0 mIU/ml
Hepatitis B e antigen (HBeAg)				Positive
Anti-HBe (Hepatitis B antibody)				Negative
HBV viral load[a]			639 $X10^6$ IU/ml	827 x 10^6 IU/ml

a IU: infectious units.

Exposure investigation

The public health actions for a newly acquired case of hepatitis B include an investigation to determine the likely exposure source for the case, in order to identify other potential exposures and opportunities to interrupt further transmission.[2] Traceback should be up to six months before the most recent negative test result.

Interviews conducted with the case's general practitioner and next of kin did not identify any clear sources of infection. Testing hepatitis B serology on other family members, including siblings in Greece, was recommended but no results were available.

The case's family believed she acquired the infection from the blood transfusion, but a thorough investigation by Lifeblood quickly excluded this. The recent hip surgery was also most unlikely as a source of infection: transmission from healthcare workers in Australia is rare, and the incubation period for detection of HBsAg in the blood following exposure is usually 4–10 weeks.[3,4]

Discussion

This case raises several issues pertaining to diagnosis, clinical management and public health follow-up of newly diagnosed hepatitis B infection in an immunocompromised host.

From a clinical perspective, there was no evidence that the case had a history of hepatitis B infection. HBsAg was negative in 2014 prior to commencing immunosuppressive therapy with ibrutinib for CLL, and again in February 2022 prior to switching to rituximab for CLL. Despite recommendations that HBsAg, anti-HBc and anti-HBs are all performed when testing for hepatitis B infection, it is unclear why the patient was only tested for anti-HBc in 2022 and anti-HBs testing was never performed.[5]

Rituximab, a monoclonal anti-CD20 antibody, is associated with high risk of hepatitis B reactivation and the US Food and Drug Administration has issued a boxed warning regarding increased risk of hepatitis B reactivation in patients with positive anti-HBs or anti-HBc.[6,7] It is recommended that such patients receive preventive antiviral therapy with tenofovir or entecavir.[5,8] Based on the February 2022 serology result, there was no indication to commence antiviral therapy. The patient's last dose of rituximab was in July 2022 and liver function tests remained normal throughout this time. Testing as the source of a healthcare worker needlestick injury likely aided early diagnosis of hepatitis B reactivation.

There are several reasons to suggest that it is much more likely that this case had past resolved hepatitis B infection with subsequent reactivation secondary to immunosuppression, rather than a newly acquired infection. Firstly, no clear exposure sources were identified. In addition, the case was born prior to the introduction of hepatitis B immune globulin (HBIG) and HBV vaccination. Endemic rates of hepatitis B infection in the case's birthplace, Greece, are known to be high: prevalence of HBV infection was reported at over 18% in Greek army recruits in 1973, and 44% of patients admitted to a cancer unit in Greece during 1986–1995 had at least one HBV marker positive.[9,10] The case had also been on B cell depleting therapy for many years, supporting the hypothesis that the 2022 results could represent a false negative core antibody result.

Notwithstanding the above, this case does meet the surveillance case definition criteria for a newly acquired hepatitis B infection. While brief consideration was given to the blood transfusion as a potential exposure source, this was considered highly unlikely as all blood products in Australia are screened for hepatitis B with nucleic acid testing (NAT). Since this was instituted in 2010, there has only been one case of probable transmission of hepatitis B via blood transfusion in Australia, and the risk of transmission is estimated to be less than one in one million units transfused.[11] Likewise, the recent hip surgery is an unlikely source given the timeframe and the rarity of transmission of hepatitis B from healthcare workers to patients in Australia.[12] It should be noted that although there is no mandated testing of healthcare workers in Australia for eligibility to work, it is necessary to comply with the CDNA National Guidelines for healthcare workers living with blood borne viruses.[13]

Although we cannot prove that this case did have past hepatitis B infection, the combination of her epidemiological risk, her clinical history that includes haematological malignancy, immunosuppressive therapy and hypogammaglobulinaemia, and the lack of a likely exposure source all suggest that this is most likely reactivation rather than a newly acquired case. This is further supported by the fact the anti-HBc (both total and IgM) remained negative on the most recent testing.

There are several issues that stem from this case. Firstly, it is critical to assess prior HBV exposure with all three markers: HBsAg, anti-HBc and anti-HBs (the latter is an important additional marker in non-immunised individuals). It also highlights the issues with screening and testing of immunocompromised patients who may have low or absent antibody levels. And finally, it raises the question of the need for ongoing follow-up and potential regular screening for HBV reactivation in patients on rituximab with negative hepatitis B serology who are from a country with a high prevalence of hepatitis B. If all three serological markers were not tested prior to the development of immunosuppression, then monitoring with liver function tests, HBV DNA and HBsAg every 1–3 months, as recommended for those with resolved infection not on prophylaxis, may be considered.[14] An alternative approach would be to simply monitor liver function tests and consider hepatitis B infection if there is an unexplained rise in alanine aminotransferase (ALT).[5]

Conclusion

The current surveillance case definition for acute hepatitis B has limitations and may incorrectly include people with HBV reactivation. This is of particular relevance in the setting of immunosuppression, and if prior HBV exposure is not assessed with all three markers (HBsAg, anti-HBc and anti-HBs). This case meets the surveillance case definition for newly acquired hepatitis B; however, their clinical and public health management were both based on an assessment that this is likely reactivation rather than a true new infection.

While consistent and strict application of surveillance case definitions is appropriate to ensure trend data is accurate at a population level, public health practitioners should be alert to the possibility that some confirmed cases of newly acquired hepatitis B may not represent a recent transmission event. Thorough case and clinician interviews, in combination with detailed assessment of pathology results in collaboration with treating clinicians, are essential to determine the most appropriate public health actions.

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