Letters to the Editors

An overlooked entity in rheumatology practice: passive transfer of anti-HBc after intravenous immunoglobulin infusion

Sirs,

Hepatitis B virus (HBV) reactivation may develop in rheumatic patients especially in those receiving some immunosuppressive agents and well-identified biologic drugs. The risk varies particularly depending on previous hepatitis B serology and the type of immunosuppression. Thus, high-risk population for reactivation should be screened with full serology including HBsAg, anti-HBs and anti-HBc. Antiviral prophylaxis is also recommended for patients with negative HBsAg and positive anti-HBc panel, similar to occult HBV protocols in prophylaxis (1).

Intravenous immunoglobulin (IVIG), a fractionated blood product including concentrated immunoglobulin, primarily immunoglobulin G (IgG), is basically derived from human plasma in pools of 3000 to 10,000 plus donors. Besides its licensed indications, off label use for various immunological disorders and neurological diseases have been exponentially increased within recent years. IVIG typically has a plasma half-life of more than 3 weeks (2). Most common reported IVIG related adverse events are mild (3). Risks of infectious complications associated with IVIG are extremely infrequent due to strict screening protocols during donors' selections and extensive investigations for communicable infectious diseases (2). Passive transfer of anti-HBc after IVIG infusion is a theoretical problem but a less known phenomenon in clinical practice, rarely published in the form of case reports and not well known in rheumatology (4-6).

We present three cases of IVIG-associated anti-HBc transference in order to draw attention to this unusual entity and to make some practical recommendations.

Case 1: A 22-year-old man with a diagnosis of neuro-Behçet's was hospitalised for the development of transverse myelitis. The hepatitis panel before the administration of pulsed methylprednisolone (1 gram per day) was positive for anti-HBs and negative for anti-HBc. During follow-up, a diagnosis of macrophage activation syndrome (MAS) was made because of fever, hyperferritinaemia, hyperbilirubinaemia, and hypofibrinogenemia. During the administration of IVIG for MAS, retesting for viral hepatitis was recommended by the gastroenterology clinic because of hyperbilirubinaemia. On day 4 of IVIG treatment, elevated titres of anti-HBs and positivity of anti-HBc were detected.

Case 2: A 47-year-old woman with myelofibrosis manifested by fever, pancytopenia, hyperbilirubinaemia, and hyperferritinaemia was diagnosed as MAS. Serum anti-HBc and anti-HBs titres were negative before she was treated with high-dose methylprednisolone and IVIG. Hepatitis serology examined after completion of IVIG showed positive anti-HBc and anti-HBs.

Case 3: A 29-year-old woman was diagnosed with systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), and immune thrombocytopenic purpura (ITP). She was hospitalised for a refractory course of ITP on mycophenolate mofetil (MMF) and low-dose prednisone. An escalation of steroid dose and the introduction of oral cyclophosphamide instead of MMF were decided. Hepatitis serology before immunosuppression was remarkable for positive anti-HBs and negative anti-HBc. On the basis of the above clinical observations, re-examination on the day after IVIG treatment showed an increase in the titres of anti-HBs and positivity of anti-HBc. The hepatitis serologies examined before and after IVIG administration are summarised in Table I.

IVIG treatment may cause transient positivity in some serologic tests due to passive transfer of donor antibodies. This phenomenon is considered a theoretical possibility but is usually underestimated by clinicians in practice. Case reports of passive transfer of anti-HBc by IVIG administration have been described in the literature, but are rare (4-6). In a study of 199 cancer patients, the rate of anti-HBc positivity was estimated to be 34% 1 week after infusion and 4% 12 weeks later (7). This study demonstrated that the transition of anti-HBc from negative to positive is not as uncommon as thought and that the decline is gradual depending on the half-life of the IVIG.

In all cases, the previously negative anti-HBc became positive on day 4 or the day after completion of IVIG administration. After IVIG administration, an increase in anti-HBs titre was observed in 2 cases compared with the pre-infusion period. A change from a previously negative titre to

Table I. Characteristic features of patients that passive transference was detected following IVIG infusion.

	Gender/age	Primary diagnosis	IVIG indication	Treatment(s)	Hepatitis panel	Hepatitis panel before IVIG	Hepatitis panel after IVIG
Case 1	22/Male	Neuro-Behçet's disease	MAS	1 g/day methyl-prednisolone IVIG 400 mg/kg/day 5 days	HBsAg	Negative	At day 4 of IVIG Negative
					Anti-HBc	Negative	*Positive (7.04) (0.99-1)*
					Anti-HBs	Positive (13.87) (9.99-10)	Positive (797.54) (9.99-10)
					Anti-HBc IgM	-	Negative
					Anti-HCV	Negative	Negative
					HBV-DNA	-	Negative
Case 2	47/Female	Myelofibrosis	MAS	100 mg/day methyl-prednisolone IVIG 400 mg/kg/day 5 days	HBsAg	Negative	The day after IVIG completion Negative
					Anti-HBc	Negative	*Positive (390.2) (0.99-1)*
					Anti-HBs	Negative	*Positive (5.1) (9.99-10)*
					Anti-HBc IgM	-	Negative
					Anti-HCV	Negative	Negative
					HBV-DNA	-	Negative
Case 3	29/Female	SLE, APS, ITP	ITP	32 mg/day methyl-prednisolone Cyclophosphamide 50 mg/day IVIG 400 mg/kg/day 5 days	HBsAg	Negative	The day after IVIG completion Negative
					Anti-HBc	Negative	*Positive (9.47) (0.99-1)*
					Anti-HBs	Positive (98.06) (9.99-10)	Positive (>1000) (9.99-10)
					Anti-HBc IgM	-	Negative
					Anti-HCV	Negative	Negative
					HBV-DNA	-	Negative

APS: antiphospholipid syndrome; ITP: immune thrombocytopenic purpura; IVIG: intravenous immunoglobulin; MAS: macrophage activation syndrome; SLE: systemic lupus erythematosus.

a positive titre was observed in 1 patient, indicating passive transfer of anti-HBs.

In conclusion, we would like to remind clinicians who use IVIG as a therapeutic option in their routine practice, including rheumatologists and gastroenterologists, who are the key decision makers for antiviral prophylaxis, of this overlooked and/or underappreciated phenomenon called "passive transmission".

In light of the information obtained from our cases and the literature, we would like to make some useful practical recommendations for rheumatologists and other clinicians (4, 6, 8):

1. Positivity of anti-HBc after IVIG treatment is referred to as *passive transfer of anti-HBc* or *false positive anti-HBc serology*.
2. In patients with a positive anti-HBc test but no history of hepatitis B infection, inquire whether IVIG has been administered within the past 4 months.
3. Similar to the recommendations for immunosuppression, hepatitis B serology should be investigated before IVIG treatment.
4. In the case of a positive anti-HBc titre, the clinician should also investigate whether the patient has received IVIG in the past few months. This clinical condition should be classified as IVIG-associated *passive anti-HBc transfer* rather than reactivation.
5. Increased awareness of passive transfer will avoid unnecessary antiviral prophylaxis and prevent possible delay of immunosuppression.

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