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SEROLOGICAL INTERFERENCE RELATED TO INTRAVENOUS IMMUNOGLOBULINS: A CASE OF FALSE IMMUNIZATION AGAINST HEPATITIS B VIRUS

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ABSTRACT

Introduction: Intravenous immunoglobulins (IVIG) are derived from pooled plasma obtained from thousands of donors and are widely used in the treatment of inflammatory, infectious, and immunodeficiency disorders. Due to their origin, these preparations may contain antibodies directed against various infectious agents. Their administration can therefore result in passive transfer of antibodies, potentially interfering with the interpretation of certain serological tests.

Case description: We report a case of false-positive anti-HBs antibodies observed following IVIG administration in a patient with no prior history of vaccination, who was being followed for polyarteritis nodosa with resistance to first- and second-line therapies.

Serological testing was performed as part of a pre-therapeutic workup prior to initiation of tocilizumab. Subsequent follow-up tests demonstrated a progressive decline in antibody titres, consistent with the clearance of passively transferred immunoglobulins.

Discussion: Passive transfer of anti-HBs and anti-HBc antibodies, as well as other antibodies targeting infectious agents or autoimmune antigens following IVIG administration, has been previously described in the literature. This situation is of particular clinical relevance in patients who are candidates for immunosuppressive therapy, which may induce reactivation of certain pathogens. Misinterpretation of these results may lead either to unnecessary prophylactic treatment or to inappropriate modification or delay of essential immunosuppressive therapy. To avoid misleading results, it is recommended to perform baseline serological screening prior to IVIG initiation, to store a reference serum sample for potential retrospective analysis, and, in patients receiving high doses, to avoid IgG-based serological assays in favour of diagnostic methods such as polymerase chain reaction.

Conclusion: Increased awareness among clinicians and laboratory specialists is essential to prevent unnecessary investigations and delays in appropriate patient management.

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KEYWORDS

Intravenous immunoglobulin, serological interference, false-positive serology, passive antibody transfer, diagnostic challenge

LEARNING POINTS

- False-positive serological results following intravenous immunoglobulin (IVIG) therapy, may lead to diagnostic confusion and unnecessary investigations.
- Internists should consider recent IVIG administration when interpreting serological tests, to avoid misdiagnosis and inappropriate management.
- Careful timing and interpretation of serological tests in patients receiving IVIG is essential.

INTRODUCTION

Intravenous immunoglobulins (IVIG), composed primarily of immunoglobulin G (IgG), are widely used in the treatment of numerous inflammatory, infectious, hematologic conditions and immunodeficiency disorders[1]. They are produced from plasma pools collected from several thousand donors and purified through processes that remove most IgM and IgA fractions, resulting in a preparation predominantly composed of IgG[2].

Many laboratory investigations, particularly in infectious diseases and autoimmunity, rely on the detection of antigen-specific IgG. In patients receiving IVIG, these assays may therefore reflect both administered antibodies and those synthesized by the host[3]. However, this possibility remains insufficiently considered when interpreting serologic results.

We report the case of a patient with polyarteritis nodosa who developed false-positive hepatitis B virus (HBV) serology after IVIG administration, in order to raise awareness of the diagnostic pitfalls associated with this phenomenon.

CASE DESCRIPTION

A 24-year-old female, followed since childhood for histologically confirmed polyarteritis nodosa, was being managed in a context of resistance to first- and second-line therapies, including corticosteroids, azathioprine, methotrexate, and anti-TNF agents. She was admitted to the internal medicine department for an active flare of her disease and received a course of intravenous immunoglobulins (IVIG) during hospitalization.

Given the persistence of disease activity, initiation of tocilizumab therapy at a dose of 400 mg administered as a monthly infusion was decided. A pre-treatment evaluation was therefore performed, including HBV serology using a chemiluminescent microparticle immunoassay on an Abbott Architect ci4100 analyzer. Previous HBV serological tests had been negative. The results obtained are presented in *Table 1*.

The report concluded that the "serological profile was consistent with post-vaccination immunization," an unexpected finding in this patient with no history of hepatitis B vaccination. Subsequent follow-up testing demonstrated a progressive decline in antibody titers, supporting the exogenous origin of the detected antibodies. This evolution suggested the hypothesis of passive antibody transfer following IVIG administration *(Fig. 1)*.

DISCUSSION

Pooled human immunoglobulin preparations contain hepatitis B surface antibodies (anti-HBs) derived from donors who were previously vaccinated or recovered from HBV infection. Passive transfer of anti-HBV antibodies after IVIG administration has already been described[3].

This situation is of particular clinical importance in patients who are candidates for immunosuppressive therapy, which may induce HBV reactivation, as misinterpretation may lead either to unnecessary antiviral prophylaxis or inappropriate modification of essential immunosuppressive treatment.

To reduce the risk of infectious transmission, plasma donations undergo rigorous screening in accordance with international quality standards. Detection of anti-HBs or hepatitis B core antibody (anti-HBc) in IVIG preparations

Parameter	Normal values (unit)	Pre-IVIG	Post-IVIG
Hepatitis B surface antigen (HBs Ag)	<1 (sample/cutoff ratio)	Not detected	Not detected
Anti-HBs antibodies (mIU/ml)	<1	3.28 (Negative)	29.28 (Positive)
Anti-HBc antibodies	<1 (sample/cutoff ratio)	0.08 (Negative)	0.50 (Negative)

Table 1. *Evolution of HBV serologic profile before and after IVIG administration.*
Abbreviations: HBV, hepatitis B virus; IVIG, intravenous immunoglobulin.

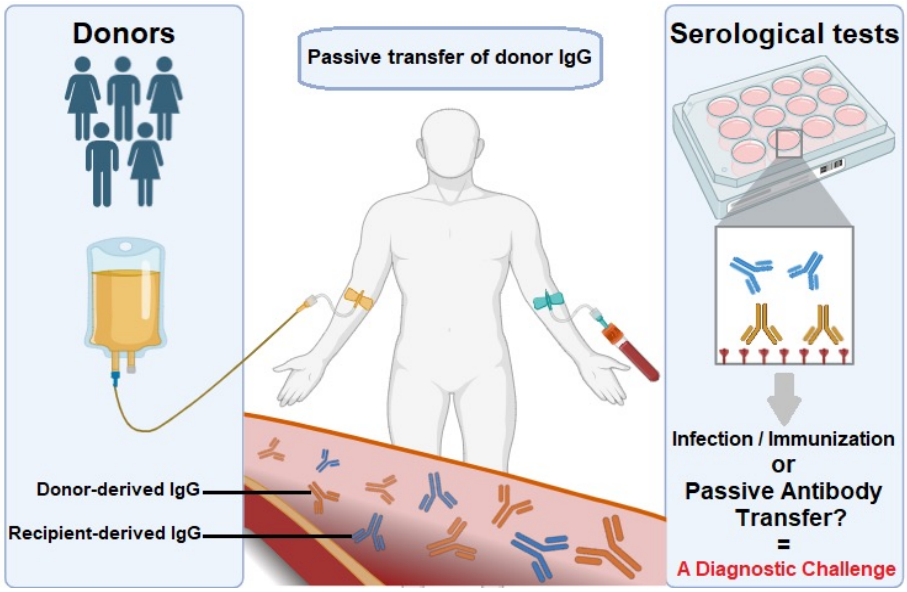


Figure 1. Passive antibody transfer after IVIG administration. Abbrevations: IVIG, intravenous immunoglobulin.

may be tolerated provided that active viral infection in donors has been excluded[4].

Bright et al.[3] evaluated several commercial IgG preparations for infectious serologic markers (HBV, syphilis, human immunodeficiency virus, human T-cell lymphotropic virus) and selected autoimmune markers (antineutrophil cytoplasmic antibodies ANCA, antinuclear antibodies, anticardiolipin IgG/IgM, anti–double-stranded deoxyribonucleic acid [DNA]). All tested preparations were positive for anti-HBc at neat concentration, and most remained positive after dilution; anti-HBs were strongly positive, while HBs antigen (HBsAg) remained negative.

Other passively transmitted antibodies have been reported, including those directed against *Toxoplasma gondii*[5], rubella virus, cytomegalovirus, hepatitis A and E viruses, varicella-zoster virus, and severe acute respiratory syndrome coronavirus 2[6].

IVIG may also contain red blood cell alloantibodies leading to ABO discrepancies and incompatible crossmatches[7]. The galactomannan assay used in invasive fungal infection diagnosis may also be affected[8].

The probability of detecting HBV serologic markers after IVIG decreases exponentially over time due to antibody clearance. In our case, anti-HBs titres declined within 1 month, consistent with the IgG half-life of 21–24 days. However, passive anti-HBc antibodies may remain detectable for up to 4 months, and the mean half-life of passively transferred anti-HBs antibodies is approximately 17.7 days[9].

Features suggestive of passive antibody transfer include absence of clinical signs of infection, recent IVIG administration, presence of antibodies without detectable viral antigen or DNA, isolated anti-HBc IgG without IgM anti-HBc, and progressive decline in antibody titres. To avoid misleading results, hepatitis screening prior to IVIG initiation is recommended, along with storage of a baseline serum sample for retrospective analysis. In patients receiving high-dose IVIG, IgG-dependent assays should be avoided when possible, and molecular methods such as polymerase chain reaction should be preferred[10].

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