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Case Report

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A Positive Complement Dependent Cytotoxicity Immunoglobulin G Cross Match Due to Autoantibodies Developed After Hepatitis B Virus Infection with a Negative Luminex Bead Assays in a Renal Transplant Recipient

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Abstract

Human leucocyte antigen (HLA) alloimmunisation is considered a major histocompatibility barrier to successful organ transplantation, and a positive complement-dependent cytotoxicity crossmatch (CDC-XM) has historically been considered an absolute contraindication for kidney transplantation without desensitisation. Ongoing infections can also give rise to complement activating immunoglobulin (IgG) autoantibodies in blood, which can be detected by CDC-XM assay, but these autoantibodies do not confer additional risk to renal transplantation. Clinically inappropriate decisions, such as transplant denial, may be made if a false-positive CDC-XM is not interpreted correctly. We describe a patient who contracted hepatitis B virus infection just prior to his kidney transplant surgery from a living donor, which turned his previously negative CDC-XM result positive, resulting in the deferral of his transplant surgery. Proper correlation with solid phase (Luminex bead) assays helped him to undergo successful kidney transplantation without prior desensitisation.

Keywords: Case Report, CDC-XM, Hepatitis B, Single Antigen Bead, Luminex, Autoantibodies

Introduction

Pretransplant screening consisting exclusively of testing based on complement-dependent cytotoxicity (CDC)-based techniques is associated with several drawbacks, such as detection only of complement activating antibodies, reduced sensitivity compared to solid phase assays and false positivity.[1] False positivity in CDC crossmatches (CDC-XMs) have been noted in patients with autoimmune disorders, such as systemic lupus erythematosus (SLE), or who receive drugs such as rituximab, antithymocyte globulin (ATG) or intravenous immunoglobulin (IVIg)[, or who have IgG autoantibodies that may be of infectious origin [1-3]. We describe a patient with end-stage renal disease awaiting kidney transplant who developed positive CDC-XM after contracting hepatitis B virus (HBV) infection from his dialysis unit. However, careful interpretation using solid-phase assays and their clinical correlation established that the result was a false positive and thus prevented denial of his transplant.

Case Report

A young end-stage renal disease patient on maintenance haemodialysis was being worked up for kidney transplantation; his mother, being a good immunological match, was serving as the donor (Tables 1 and 2)

Table 1: Hla Dna Typing (A, B, DR)

	HLA - A	HLA - B	HLA -DR
RECIPIENT	A*11 A*11	B*35 B*51	DR B1*15, DR B1*15
DONOR	A*11 A*11	B*35 B*35	DR B1*11, DR B1*15

Table 2: Immunological Work Up Before Hbv Infection

INVESTIGATION	RESULT
CDC HLA T&B CELL CROSS MATCH	T CELL –Negative; B CELL - Negative
FLOW CYTOMETRY HLA T&B CELL CROSS MATCH	T CELL –Negative; B CELL - Negative
SINGLE ANTIGEN BEAD ASSAY [SAB] CLASS I & II	No positive antibody identified against Class I (A, B, C) and Class II Loci (DP, DQ, DR) (in the cocktail of antigens present in the assay)

Two weeks prior to his scheduled transplant surgery, he contracted HBV, likely from his dialysis unit. Transplant surgery was postponed and treatment for HBV infection with entecavir was started. When his HBV DNA levels became undetectable in serum after about 6 weeks of antiviral treatment, his transplant surgery was rescheduled. Fibro Scan was negative for liver cirrhosis but his CDC-XM, which was negative before he contracted HBV, was positive for B cells [Table 2] and remained persistently positive for B cells when checked again after two weeks. However, his repeat single antigen bead (SAB) test did not identify any donor specific antibodies (DSA). Considering the development of IgG autoantibodies due to HBV infection as the cause of positive CDC-XM, the transplant surgery was conducted successfully without prior desensitisation. ATG was used as the induction agent and entecavir was continued after transplant, along with three immunosuppressant drugs (tacrolimus, mycophenolate mofetil and prednisolone). A renal biopsy done three months post-transplant showed no features of rejection.

Discussion

False positivity in CDC-XMs has been noted in patients with autoimmune disorders, such as SLE, or who receive drugs such as rituximab, ATG or IVIg, or who have IgG autoantibodies that may be of infectious origin, as in our case [1-3]. Such antibodies confer no additional risk to kidney transplantation and are an inappropriate reason for transplant denial or pretransplant desensitisation. False positivity in CDC-XM due to IgM-type autoantibodies can be avoided by treating the serum with dithiothreitol (DTT) [4]. CDC-based assay results depend strongly on the vitality of the donor lymphocytes, highlighting another major limitation of this assay [5]. The use of highly sensitive Luminex technology, along with CDC-XMs to assess the immunologic risk of renal transplant candidates, has greatly enhanced the ability to categorise patients and has paved the way to avoiding hyperacute antibody-mediated rejection and checking the false positivity and false negativity of test results.

Because Class I antigens are present on both T and B cells and Class II antigens are present only on B cells, CDC-XM results should be interpreted carefully [Table 3].

Table 3: Interpretation of Cdc Xm

T Cell Xm	B Cell Xm	Interpretation
Negative	Negative	• No Donor specific antibody • Non Complement binding • Antibody titer too low
Positive	Positive	• Donor specific antibody to Class I • Donor specific antibody to Class I + II
Negative	Positive	• Donor specific antibody to Class II • Low level of Class I • False positive “sticky B Cell”
Positive	Negative	• Technical error [possibly due to B cell viability]

Development of complement-activating IgG antibodies due to ongoing infection (e.g. HBV), leading to positive CDC-XM, can be explained by the underlying physiological mechanisms. There is a spectrum of auto-reactivity in serum antibodies ranging from the innately produced, poly-reactive IgMs that clear the tissues of post-apoptotic debris to the pathological IgGs that are associated with autoimmune diseases. The former represent ‘‘natural’’ antibodies produced by a unique population of B-1 cells from birth in an apparent default pattern without the need for antigen presentation. However, research has shown that IgG autoantibodies are abundant and ubiquitous in the serum of all immunocompetent humans and are consistently present in individuals over time [3].

The presence of self-reactive IgG autoantibodies in human serum is not always an indicator of central tolerance breakdown, as seen in autoimmune diseases, but may represent an adaptive mechanism to clear intercellular debris arising from disease-induced tissue damage. This increased autoantibody production is appropriate to the clean-up of that debris. Considering the complexity of follicular B-2 cell activation, and the adaptive nature of the antibody response, IgG autoantibodies are perfectly suited to clear the debris from situation-specific events such as infections or trauma. On the other hand, the limited, pre-programmed innate natural IgM panel is incapable of this kind of tailored response [3]. When unexpected results are encountered during pre-transplant screening, as in our case, causes of false positivity of tests, such as ongoing infections, should be sought before

transplantation denial. Testing for non-HLA antibodies when a CDC-XM is positive despite negative solid phase assays, without any other identifiable cause, should also be considered [6].

Conclusion

Clinically inappropriate decisions may be made if false-positive pre-transplant screening test results are not interpreted correctly. This may unnecessarily limit patients' access to transplantation or result in the administration of unnecessary and costly desensitisation treatment, which is associated with the potential adverse effects of enhanced immunosuppression. There is no single perfect test till date, providing the desirable accuracy, quantitation, sensitivity and specificity to determine the immunological risk for a particular transplant recipient, so multiple imperfect assays should be used to determine true antibodies. This necessitates a personalised decision-making process for each transplant recipient with inputs from the clinicians and HLA laboratories.

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