Methotrexate as a rescue therapy for persistent cellular rejection and donor specific antibody reduction

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Foundation:

Regardless immunosuppression, allograft rejection persist as a morbidity cause of heart transplant. In this situation more intensive immunosuppression is indicated. Low cost efficient strategies are necessary in this scenario.

Case Report

Male, 21 years-old, dilated cardiomiopathy with negative panel reactive antibodies (PRA) was submitted to heart transplantation, with negative real crossmatch by complement dependent lymphocyte, receiving a donor organ of 41 years-old, with HLA profile A2, B35, B51, Cw04, Cw15, DR14, DQ5.

Two years and 7 months after transplantation, the patient was admitted to the emergency room with signs of heart failure (HF). At that time, he was taking mycophenolate sodium and tacrolimus with a good serum level. Endomyocardial biopsy (EMB) revealed moderate cellular rejection (2R), without histological or immunohistological signs (c4d) of antibody-mediated rejection (AMR)-(pAMR 0).

The patient was treated with methylprednisolone and thymoglobulin.

The PRA requested at hospital admission showed donor specific antibody (DSA): B35 (5008 mfi mean intensity fluorescence), B51 (10,334 mfi,) Cw15 (13,739 mfi), Cw4 (11,431 mfi) and DQ5 (9,028 mfi). The second EMB showed persistence of 2R(cell rejection) and pAMR 0, despite the patient's clinical improvement. New treatment with methylprednisolone in high dose associated with methotrexate was then performed.

After that, the BEM control showed no rejection (0R e pAMR0). New PRA revealed negativity of B35, B51, Cw4 antibodies, with decrease of DQ5 (2431 mfi) and Cw15 (3042 mfi) and *de novo* DR14 (2185 mfi).

There was an improvement in ventricular function and the patient was discharged with 4 immunosuppressants (prednisone, tacrolimus, mycophenolate and methotrexate). After 3 months there was a negative PRA.

Table - DSA before the use of methotrexate (MTX)

DSA	B35	B51	Cw15	Cw4	DQ5
Pre-MTX	5008 mfi	10334 mfi	13739 mfi	11431 mfi	9028 mfi

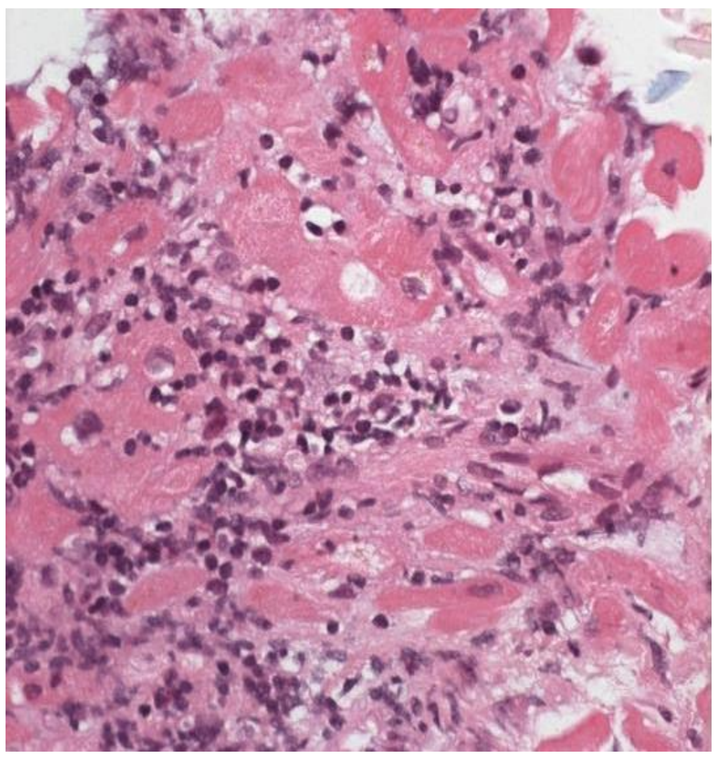

Fig - Endomyocardial biopsy: Acute grade 2R (moderate, intermediate grade) rejection, with a focus of aggression on cardiomyocytes by inflammatory lymphomononuclear infiltrates

Discussion

In this case, the association of methotrexate as the fourth immunosuppressive drug, has been shown to be an interesting strategy in the treatment of persistent ACR and, moreover, in the reduction of DSA, known trigger for the development of AMR.