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Case Report

IgA-mediated autoimmune haemolytic anaemia in a 9-year renal transplanted patient

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Introduction

Haemolysis of multiple aetiologies may occur in solid organ transplant patients. Microangiopathic haemolytic anaemia is a rare complication of anti-calcineurin agents. In ABO-compatible but ABO-non-identical solid organ transplantation, acute haemolysis has also been related to allo-antibodies (Abs) derived from donor B lymphocytes. Drug-induced haemolysis [1], lymphoproliferative and infectious complications must also be considered. In rare cases, a secondary aetiology cannot be found. In cases with positive direct antiglobulin test (DAT), idiopathic autoimmune haemolytic anaemia (AIHA) is diagnosed.

Autoimmune diseases (AID) under immunosuppressive treatments are rare [2–5] and appear paradoxical. In the general population, less than 2.5% of AIHA are mediated by IgA [6]. We report here the first case of IgA-mediated AIHA (IgA AIHA) in a renal transplant patient.

Case report

A 43-year-old woman with a polycystic kidney disease and with no history of AID began haemodialysis in 1995. She had a renal transplant from a deceased donor in 1997. Blood group of recipient and donor was O rhesus +. HLA typing of recipient was A11 A25 B35 B44 DR01 DR15 DQ05 DQ06 and of donor was A26 A33 B14 B51 DR01 DQ05. Initial immunosuppressive therapy consisted of prednisolone, tacrolimus and azathioprine. She had never had an episode of acute rejection.

During the transplant course, the patient had the following comorbidities: (1) major obesity leading to steroid withdrawal in 2001; (2) hypertension early after transplantation (the last treatment consisted of ramipril and irbesartan); (3) baso- and spino-cellular skin carcinoma in March 2004, leading to a progressive azathioprine withdrawal which was complete in April 2005; (4) diabetes mellitus in 2004 (she was initially treated with metformin; then insulin glargine and repaglinid were added).

Since April 2005, her immunosuppressive regimen had consisted of tacrolimus monotherapy. Serum creatinine was 69 μmol/L, and inulin clearance was 109 mL/min/1.73 m^2.

The patient was hospitalized in emergency in April 2006, with dyspnoea and severe anaemia [haemoglobin (Hb): 4.7 g/dL]. She received a transfusion of 2 units of red blood cells (RBC). Laboratory analysis revealed haematocrit 14%, reticulocytes 516 Giga/L, LDH 3000 UI/L, serum bilirubin 61 μmol/L and haptoglobin <0.1 g/L. Platelet count was 128 Giga/L. Peripheral blood smear was normal. Renal function remained stable.

One week before this hospitalization, moderate anaemia was noted in a routine blood sample, with Hb 9.7 g/L, elevated LDH and haptoglobin <0.1 g/L. The patient was asymptomatic. AHAI was suspected, but routine DAT and the indirect antiglobulin test (IAT) were negative.

On the day of hospitalization, weak reaction for IgG (+) and strong reaction for IgA (+++) were observed on the DAT. Neither bound nor unbound anti-platelet Abs was found.

Medication that had been recently introduced or that was known to induce haemolysis was discontinued: ramipril, irbesartan, metformin, insulin glargine and repaglinid.

On the 2nd day of hospitalization, intravenous corticosteroid (Methylpredisone), at a dose of 2 mg/kg daily, was started. No improvement of laboratory results was noted.

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The patient had to be transfused with 2 more units of RBC on the 5th day. On the 6th day, intravenous polyvalent immunoglobulin (poly-Ig), at a dose of 0.4 g/kg daily for 5 days, was started. On the 12th day, the Hb level began to increase (6.6 and 7.5 g/L on the 12th and 14th day respectively).

Viral infections, lymphoproliferative disorders or AID, were excluded by serological investigation, normal bone marrow aspirate, normal computerized tomography scan, normal serum protein electrophoresis and negative autoAbs. The serum of the patient did not react with normal RBC in the presence of metformin.

We concluded with a diagnosis of idiopathic IgA AIHA.

One and six months after hospitalization discharge, the Hb level was 10.8 and 14.0 g/L, respectively. Corticosteroid therapy was discontinued. One year later, no recurrence was observed and specific anti-IgA DAT was negative.

Discussion

In the general population, most reported IgA AIHA presents initially as severe haemolytic anaemia with negative DAT [6]. Routine DAT includes anti-IgG and anti-C3d. When such DAT is negative and AIHA is suspected, a second DAT using monospecific anti-human IgA Abs must be performed [6].

AIHA is a rare cause of haemolytic anaemia in transplant patients [4]. It typically occurs late after solid organ transplantation [4]. The development of autoAbs under immunosuppressive therapy [2–5] is still incompletely understood. It may involve unbalanced B/T cell regulation. Anti-calcineurin agents act by inhibiting activation of the IL-2 gene and clonal expansion of T-cells. They suppress the primary immune response, but spare B-cell activity. In human AIHA, there is a B-cell activation with an increased number of circulating cells expressing PCA1, a marker of B-cell differentiation [7]. It may also involve unbalanced Th1/Th2 cytokine or IL-12/IL-10 regulation. In mice and human AIHA, Th2 cytokines levels such as IL-4 and IL-10 are increased [7]. On the other hand, IFNγ and IL-12 levels are decreased [7]. In a model of mercury-induced AID in rodents, Mellergård *et al.* showed that low doses of tacrolimus could selectively down-regulate Th1 cells [8]. In a murine chronic graft-versus-host disease (GVHD) that was previously described as a Th2-like response [9], Bundick *et al.* showed that low doses of anti-calcineurin agents markedly increased the GVHD before exhibiting an inhibitory effect on GVHD at higher doses [9].

Our patient was under tacrolimus monotherapy. We think that it could have allowed a subtype of autoreactive B-cells to proliferate, especially after withdrawal of the anti-proliferative azathioprine treatment.

Moreover, we cannot exclude metformin [10] or other drug-induced autoimmune haemolysis [1] despite negative immunological tests. A drug could have acted as a trigger in this particular immunologic environment. The best way to assess this hypothesis would be to reintroduce the treatment. Because of the severity of initial presentation, we avoided this option.

In summary, we described a severe IgA-AIHA occurring in a 9-year renal transplant patient on tacrolimus monotherapy. This case suggests that IgA monospecific DAT needs to be performed in cases of negative routine DAT in patients with haemolytic anaemia. Low dose tacrolimus monotherapy could be implicated in the physiopathology of this AID, by disturbing lymphocytes B/T balance. Metformin or another treatment may also be the trigger of this autoimmune cytopenia.

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Conflict of interest statement. None declared.

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