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CASE REPORT

Reversible ileitis secondary to high dose intravenous immunoglobulin in adult kidney transplant patient treated for acute humoral rejection

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Summary

Use of high dose intravenous immunoglobulin (IVIg) has been associated with necrotizing enterocolitis in late-preterm and term infants treated for severe isoimmune hemolytic jaundice. We present the first adult case of reversible ileitis related to high dose IVIg that occurred during the treatment of acute humoral rejection in a kidney transplant recipient (original nephropathy: lupus). At the third of the 5 days of a 0.4 g/kg/day IVIg infusion, he had periumbilical pain and nausea. Non-iodine injected abdominal computed tomography (CT) demonstrated a major proximal ileitis that was absent 1 month earlier on a previous CT. After the fourth injection, IVIg therapy was discontinued. Clinical and radiological signs disappeared, respectively, 5 and 7 days after IVIg discontinuation. No other causes of ileitis were diagnosed (especially infectious, vascular, or lupus-related bowel disease causes). Usual abdominal pain and nausea during IVIg therapy may be related to sub-clinical ileitis and/or enteritis. As in newborn, such complication has to be diagnosed and IVIg infusion discontinued because of potential evolution to intestinal necrosis.

Introduction

Acute humoral rejection (AHR) is the major immunological complication of allograft kidney transplantation [1]. Diagnosis relies on the presence of acute kidney graft dysfunction, typical histopathology findings with C4d deposition in peritubular capillaries and the detection of donor specific antibodies (DSA) [2]. Therapeutic strategies commonly include the combination of plasmapheresis, intravenous immunoglobulin (IVIg) and intense immunosuppression (generally the association of corticosteroid pulses, rituximab, tacrolimus and mycophenolate mofetil) [1].

The main IVIg side effects are mild and transient including headaches, flushing fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia [3]. Late adverse events are rare and include acute renal failure and thromboembolic events [3].

The use of high dose IVIg has been associated with necrotizing enterocolitis in late-preterm and term infants treated for severe isoimmune hemolytic jaundice [4,5]. Microscopic examination of the resected intestine revealed the presence of disseminated thrombi obstructing multiple minor vessels of the mesenteric circulation. [4].

To the best of our knowledge, we present here the first adult case of enteritis related to high dose IVIg as treatment of AHR.

Case history

A 36-year-old North-African male patient received cadaveric kidney transplantation in December 2008. He began hemodialysis in February 2005 for end-stage renal disease secondary to lupus nephritis. There was no other organ symptoms related to systemic lupus erythematosus, especially no antiphospholipid syndrome. He had previously received cyclcophosphamide and plasmapheresis for lupus treatment. He did not previously receive IVIg. He had no other comorbidity. His father and his brother had type 1 diabetes.

His blood group was O positive and his HLA typing was HLA-A34, 68; B8, 39; DR13, 15; DQ5, 6. He was cytomegalovirus (CMV) negative. Class I and class II human leukocyte antigen (HLA) panel reactive antibodies (PRA) were negative prior to transplantation.

He received a kidney from a 28-year-old deceased donor (blood group O positive; HLA-A11, 34; B39, 44; DR8, 15; DQ4, 6; CMV negative). There were one HLA-A, one HLA-B, one HLA-DR and one HLA-DQ loci mismatches. The induction immunosuppressive therapy included thymoglobulin and steroid intravenous bolus (methylprednisolone) and maintenance immunosuppression regimen included cyclosporine, mycophenolate and prednisone.

Short-term evolution was excellent. At month 3, serum creatinine was 100 μmol/l and proteinuria was null. At month 4, maintenance immunosuppression was converted to calcineurin-free regimen, including everolimus, mycophenolate mofetil and low dose prednisone. At month 12, PRA were for the first time detected, with the presence of DSA (anti-DR8 and anti-DQ4). Serum creatinine was 103 μmol/l and the proteinuria was null. From month 12 to 18, blood pressure was uncontrolled (>130/80 mmHg), and ramipril and amlodipine were progressively added to the previous antihypertensive regimen using nebivolol. Secondary hypertension was diagnosed. Indeed, serum noradrenaline was fourfold higher than normal range and a computed tomography (CT) localized a 50 × 40 mm tumor in the right adrenal gland. A surgery for pheochromocytoma was scheduled.

At the same time, a rise in serum creatinine was noted. At month 19, serum creatinine was 175 μmol/l and proteinuria was 0.5 g/day. A percutaneous kidney graft biopsy demonstrated Banff grade II AHR (v0, cv0, ah1, cpt2, C4d3). The treatment of AHR was scheduled as following: intravenous methylprednisolone bolus (500 mg/day from day 1 for three consecutive days, and thereafter prednisolone 1 mg/kg), IVIg (KIOVIG©: 0.4 g/kg from day 1 for five consecutive days, maximum infusion speed: 4 ml/kg/h, osmolality 240 to 320 mOsm/l), plasmapheresis at day 1, 3, 4, 5, 7, 8 and 10), rituximab at day 5 and 12. IVIg and Rituximab were given right after plasmapheresis session if any on the same day. Moreover, everolimus was stopped and switched to tacrolimus.

At day 3 of this treatment, the patient had periumbilical abdominal pain (degree 7 on a 0–10 scale) and nausea, without vomiting or diarrhea. Blood pressure was 140/80 mmHg. Patient's medication at time of abdominal pain was: tacrolimus: 3 mg × 2/day, mycophenolate mofetil: 1000 mg × 2/day, methylprednisolone: 500 mg/day, nebivolol 5 mg/day, ramipril 2.5 mg/day, amlodipine 10 mg/day, esomeprazole 40 mg/day, epoetin beta 10000 IU × 3/week. Hepatic (ASAT: 36 IU/l, Normal range (N): 10–46; ALAT: 49, N: 10–65; LDH: 263, N: 200–450; gamma-GT: 22, N: 5–65) and pancreatic serum enzymes (lipase: 30, N: 7–60) were normal, as well as the abdominal echography. Protidemia remained between normal ranges over the AHR treatment period (min: 61 g/l; max: 67 g/l).

The day after, a noninjected CT demonstrated a major proximal ileitis: mild thickening of the proximal ileum (12 mm) which was symmetric and segmental (10–30 cm, e.g. nonfocal or diffuse) associated with minim peritoneal effusion (Fig. 1). Of note, the previous CT performed few weeks before for the diagnosis of pheochromocytoma was normal regarding small intestine. There was no argument for infectious cause (no fever, no diarrhea, C-reactive protein: 3 mg/l, neutrophil polynuclear leukocytes: 6.5 Giga/l, stool cultures: negative, special stool cultures (yersinia, campylobacter): negative, blood and urine microbiological cultures: negative), lupus-related bowel disease (antinuclear autoantibody: null; anti-C1q autoantibody: null; anti-double stranded DNA autoantibody: null), or coagulopathy (the day after a plasma exchange session, just before next session, fibrinogen: 1.9 g/l, n = 2–4 g/l; international normalized ratio: 1.1; platelet count: 250 Giga/l, N: 150–450; no clinical bleeding). Cytomegalovirus, Epstein-Barr virus, BK virus and JC virus blood viral load were null (polymerase chain reaction). There was no hypereosinophilic syndrome.

By analogy to enterocolitis observed in new-born with high dose IVIg, we discontinued IVIg treatment. The patient had received 4 days of this therapy, i.e. 1.6 g/kg overall. Two days later, abdominal pain and nausea progressively disappeared and the patient was asymptomatic 5 days later. Other therapies to cure AHR were continued as scheduled; especially, mycophenolate mofetil dose was not changed over this period. A CT was performed 1 week after the last IVIg injection. It was normal regard-

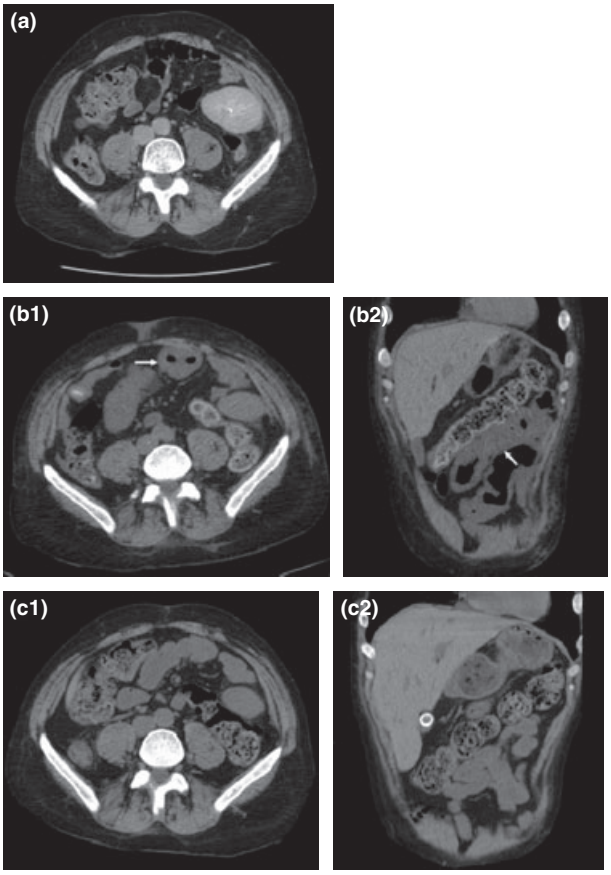

Figure 1 (a) Iodine injected computed tomography 1 month prior to AHR treatment; (b) noniodine injected computed tomography showed proximal ileitis (white arrows; b1: cross section; b2: frontal section): marked thickening of the ileum wall, peritoneal effusion; (c): noniodine injected computed tomography 1 week later IVIg discontinuation showed no ileitis (c1: cross section; c2: frontal section). AHR, acute humoral rejection; IVIg, intravenous immunoglobulin.

ing ileum and other parts of the intestine. The peritoneum was dry (Fig. 1) and the superior mesenteric artery was free of calcification, as other abdominal arteries.

At month 20 (i.e. 1 month after the beginning of the AHR treatment), clinical examination was normal in this patient. A percutaneous kidney graft biopsy at month 21 demonstrated Banff grade II AHR (no histological change compared with previous biopsy). Anti-DR8 DSA disappeared from blood stream. Patient was treated with Bortezomib as rescue therapy (1.3 mg/m^2 at day 1, 4, 8 and 11). Surgery for right adrenal gland ablation was performed at month 22. Pathology examination confirmed pheochromocytoma. At month 22, serum creatinine was 124 μmol/l; proteinuria was 0.5 g/24 h. A percutaneous kidney graft biopsy was performed that revealed chronic allograft nephropathy without peritubular C4d deposit.

Discussion

We reported the case of an acute proximal ileitis in the context of high dose IVIg infusion in a kidney transplant adult treated for AHR. Nephrologist's usual complication of high dose IVIg remains acute renal failure that occurs with sucrose-stabilized formulation [3,6]. This has been related to tubular damage induced by sucrose in the IVIg preparation [3,6]. IVIg without sucrose was used in this patients (KIOVIG©). Other serious side effects are severe deep vein and arterial thromboses [3,7,8]. Thromboses were related to rapid increase in plasma IgG concentration, immune complex formation and increased platelet aggregation that increased blood viscosity after IVIg infusion [7,8].

Rational for use of IVIg in the setting of AHR is sustained by various actions that have specific relevance to alloantibody-mediated acute rejection of transplanted allografts [9,10]. These include neutralization of autoantibodies, inhibition of activation of endothelial cells, down-regulation of antibody synthesis as a result of inhibition of B- and T-cell proliferation, and increased apoptosis of B cells [9,10]. These properties of IVIg may explain its role as a helpful adjunct in the treatment of AHR [9,10].

Our patient was treated with the usual protocol of our department in case of AHR, using Bortezomib as rescue therapy [11]. Regarding IVIg infusion, we used high dose (0.4 g/kg/day for five consecutive days) of KIOVIG© preparation. In our patient, the daily dosage was 32 g, i.e. 320 ml of reconstituted KIOVIG© solution. As recommended, the first intravenous injection was slow (0.5 ml/kg/h. i.e. 40 ml/h in this patient) for 1 h and thereafter hourly incremental increase in flow up to 4 ml/kg/h when maximum recommended was 6 ml/kg/h. We used the native arteriovenous fistula as injection site.

Because abdominal symptoms that revealed enteritis began at the 3rd day of IVIg injection and because they disappeared after IVIg discontinuation without any other change in patient's treatment and without any other enteritis cause diagnosis, we hypothesize that this ileitis was a side effect of IVIg injection. Because of the good evolution after IVIg discontinuation, we did not perform a fibroscopy and a histopathology analysis of the patient's small bowel. But importantly, consecutive abdominal CT showed that ileitis was absent 1 month before IVIg infusion and completely regressed 1 week later the ileitis diagnosis. In patients with pheochromocytoma, abdominal pain may occur in rare case of ischemic colitis and associated perforation of the colon [12]. Such pheochromocytoma complication was not related to our patient's abdominal pain. In our patient, ileitis CT scan characteristics we observed were common in infection, ischemia or

Crohn's disease, but not in lymphoma or systemic lupus erythematosus [13,14]. We did not find evidence for infection or Crohn's disease, as well as cause of transient and reversible ileitis, or drug induced ileitis cause [13,14].

In newborns treated with IVIg who had necrotizing enterocolitis [4,5], symptoms began from 2 h to 96 h after IVIg infusion start, as in our patient. We can hypothesize that ileitis was resulting from microthrombi in mesenteric capillaries. This could be attributed to an increase in plasma viscosity [15,16] or to vasoconstriction [17]. Alteration of vascular tone associated with increased viscosity may have led to transient mesenteric ischemia. We can hypothesize as well that usual and minor IVIg side effects as nausea [3] may be explained by such modifications of intestinal blood perfusion because of modification of blood viscosity during IVIg therapy.

In conclusion, we reported here a new side effect of IVIg in a kidney transplant adult treated for AHR. Abdominal pain and nausea in the course of IVIg therapy may be related to ileitis and/or enteritis. Such complication has to be diagnosed and IVIg infusion discontinued because of potential evolution to intestinal necrosis.

Authorship

SIG, JB, CPN and EV: designed research, performed research, collected data, analyzed data and wrote the paper. ACDB, CG, RC, FD: analyzed data and wrote the paper.

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