

## Antithymocyte globulin-induced refractory hypotension in renal transplantation recipient

Sir,

A 43-year-old man, known case of end-stage renal disease (ESRD), scheduled for renal retransplantation after having the first transplantation 15 years back. He was on regular immunosuppressant and follow-up. Since last 3 months, his urine output decreased and creatinine level rose, labeled as ESRD again, and was on hemodialysis. His wife as living-related ABO incompatible was accepted as donor. Thorough workup of recipient was normal as per the institute protocol. As per the institutional protocol for ABO incompatible transplantation, immunosuppressant agents tacrolimus, mycophenolate, steroid, and rituximab were given and plasmapheresis for 5 cycles was done on alternate day to reach the desired antibody titer of < 1:8.

A day before transplantation, ultrasonography-guided left intrajugular central venous triple lumen catheter was placed. On the morning of surgery, 75 mg of antithymocyte globulin (ATG) was given through central line at 4 am over a period of 6 h. In the operation theater, blood pressure (BP) was 128/80 mmHg, heart rate 120/min, and SaO<sub>2</sub> 98% on room air. The balanced general anesthesia was given as per the institute protocol. After induction, the patient was hemodynamically normal with invasive arterial blood pressure and CVP monitoring. After 30 min post induction, BP decreased to 90/60 mmHg and managed with fluids.

Thereafter, noradrenaline (NE) was started at 3 µg/min. Metabolic acidosis increased over the time and inotropic support was gradually increased. Refractory hypotension was managed as shown in Table 1. Intravenous methylprednisolone 500 mg was given before anastomosis as part of immunosuppression. After anastomosis of artery, vein, and ureter, 200 ml urine output came in for 30 min and after that anuria occurred. There was diffuse oozing after the anastomosis, with a total blood loss of 1.5 L. Thromboelastography was done and on that basis fresh frozen plasma and platelets were transfused. The hemoglobin dropped from 9 to 5 g/dL, so 2 units of packed red blood cells were transfused. It was decided not to extubate, so the patient was shifted to the ICU for mechanical ventilation. noradrenaline and vasopressin were continued in increasing doses. Echocardiography in postoperative period was within normal functions. Immediately in the postoperative ICU, the patient was scheduled for hemodialysis. Sustained low-efficiency dialysis was started, but the patient could not tolerate, so switched to continuous renal replacement therapy. The patient condition worsened with no improvement in acidosis and hypotension even after all the possible resuscitative measures and the patient expired after 24 h period.

ATG is indicated as initial immunosuppressant in renal transplant recipients and for treatment of acute rejection.<sup>[1]</sup> This patient was going for retransplantation with ABO incompatible graft, so ATG was given. The coagulopathy may be attributed to ATG.<sup>[2]</sup> The patient developed refractory hypotension intraoperatively which is a reported adverse effect. The possibility of hyperacute rejection of graft ruled out by immediate postoperative biopsy that showed no features of hyperacute rejection.

Serious immune-mediated reactions due to ATG include anaphylaxis or severe cytokine release syndrome (CRS). It

**Table 1: Serial arterial blood gas, lactate, hemodynamic, and resuscitative measures**

Time	pH	HCO <sub>3</sub>	Base excess	Lactate (mg/dl)	Invasive arterial blood pressure (mmHg)	Heart rate (/min)	Remark
After induction	7.4	19.1	-6.7	10.2	110/74	100	
Vascular clamp in	7.3	16	-10	18	108/78	104	Norad (NE) at 20 µg/min
Vascular clamp out	7.2	17.2	-11	22	104/68	108	NE at 20 µg/min
Skin closure	7.2	17.1	-12	29	114/72	115	NE at 30 µg/min
Postoperative (h)							
1	7.2	10.2	-16	65	104/66	124	NE at 40 µg/min and vasopressin 2.4 U/h
2	7.2	14.4	-12	54	110/71	128	NE at 40 µg/min and vasopressin, dialysis
4	7.2	12.4	-13	67	112/74	132	NE at 50 µg/min and vasopressin, dialysis
8	7.2	15.3	--10	69	100/56	136	NE at 60 µg/min and vasopressin, dialysis
12	7.3	12.4	-14	56	90/65	142	NE at 60 µg/min and vasopressin, dialysis
16	7.2	10.3	-13.3	71	88/54	143	NE at 60 µg/min vasopressin and adrenaline
20	7.1	9.4	-14	75	78/45	152	Vasopressin and adrenaline
24	7.1	8.4	-16	78	66/43	156	NE at 80 µg/min, vasopressin and adrenaline

can cause serious cardiac or respiratory complications, or in certain cases, mortality. CRS is a form of SIRS, result in severe hypotension that is unresponsive to treatment with conventional vasopressors leading to vasodilatory shock or vasoplegic syndrome that is refractory to high-dose NE. Various factors include endothelial injury and depletion of endogenous AVP with release of multiple neurohumoral and inflammatory mediators such as prostaglandin I<sub>2</sub>, bradykinin, interleukin (IL)-1 $\beta$ , and atrial natriuretic peptide.<sup>[3]</sup> In the case of refractory vasoplegia, high levels of IL-1 $\beta$ , IL-6, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , platelet-activating factor, and adenosine result in the substantial induction of endothelial inducible NO synthase (iNOS). The resulting high levels of nitric oxide (NO) and cGMP within the vascular myocytes cause changes at the subcellular level, which directly give rise to the vasoplegic state. This leads to induction of endothelial iNOS, unregulated NO synthesis, and widespread activation of guanylate cyclase in vascular smooth muscle relaxation. It presents as severe decreased SVR and vasomotor hyporeactivity that persists despite a high cardiac output, high-volume resuscitation, and high-dose NE administration.<sup>[4]</sup> The tocilizumab (humanized, immunoglobulin G1 $\kappa$  antihuman IL-6 receptor monoclonal antibody) is an effective treatment for severe or life-threatening CRS. The arginine vasopressin and its derivatives, methylene blue, and diaspirin cross-linked hemoglobin had been proven effective for treatment of vasoplegia due to CRS.<sup>[5]</sup>

There are reported cases of fatal intraoperative anaphylactic shock and severe cardiovascular reaction with acute renal failure due to prolonged infusion of ATG during adult orthotopic liver transplantation<sup>[6]</sup> and in a pediatric renal transplant recipient.<sup>[7]</sup>

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### Conflicts of interest

There are no conflicts of interest.

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