LETTER TO THE EDITOR

Rituximab therapy for cytomegalovirus-associated auto-immune hemolytic anemia in a liver-transplant recipient

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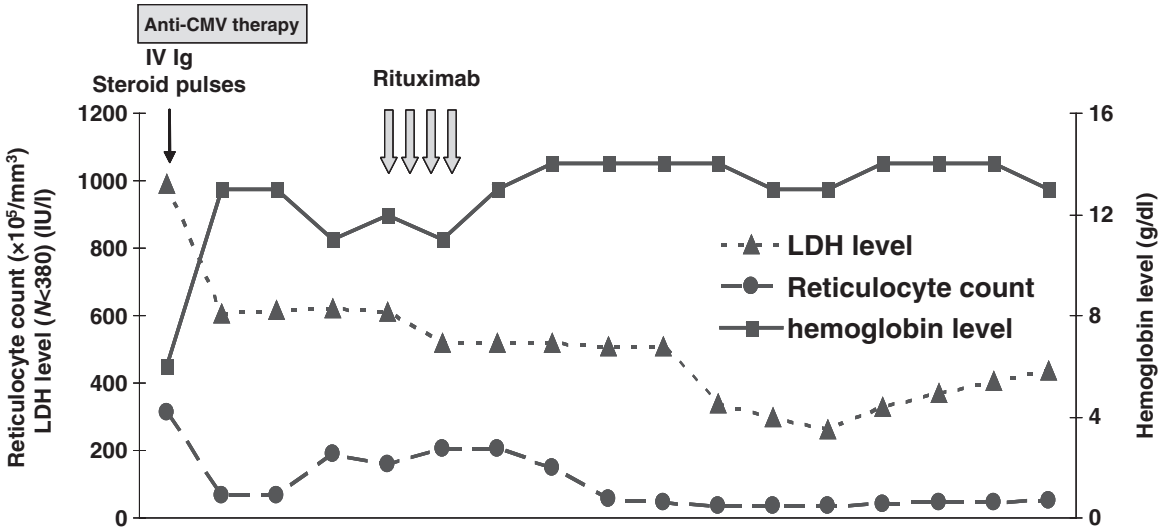
Cytomegalovirus (CMV)-associated auto-immune hemolytic anemia (AIHA) occurs mostly in infants [1] and in HIV-infected adults [2]. We herein report the first case to occur in a solid-organ-transplant recipient.

A CMV seronegative liver-transplant (LT) recipient was referred to our unit 1 year post-transplantation with fatigue, dyspnea, and icterus. Immunosuppression relied on tacrolimus/mycophenolate mofetil/prednisone. He received valganciclovir prophylaxis until 2 months before admission (CMV seropositive donor). Physical examination showed pallor and conjunctival icterus. Blood samples revealed acute anemia (hemoglobin 6 g/dl), thrombopenia (120 000/mm^3), hepatitis with slight cytolysis (transaminase levels 1.5 N), and cholestasis (γ-glutamyl transferase 4 N). Total/unconjugated bilirubin levels were 78/53 μmol/l. Reticulocyte count (311 000/mm^3), elevated lacto-dehydrogenase (LDH; 4 N), and low haptoglobin (<0.06 g/l) levels defined hemolytic anemia. Toxic or



	Baseline	1	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Months																		
Darbpoeitin α (μg/week)	0	200	100	100	100	100	100	100	50	50	50	25	25	25	0	0	0	
Tacrolimus C0	14.4	9.8	7.8	9.4	9.4	7.2	6.1	8.9	ND	ND	ND	5.4	7.8	6.5	5.7	5.4	5.4	
MMF dose (g)	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Steroids (mg)	5	40	10	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
CMV DNAemia (Log copies/ml)	5.07	2.83	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
CMV Ig M	0	22.2	30.2	-	21.1	10.3	13.6	-	-	-	-	-	-	-	-	-	-	
CMV Ig G	0	2	1.6	-	1.8	3.4	2.7	-	-	-	-	-	-	-	-	-	-	

Figure 1 Outcome of hemoglobin and lacto-dehydrogenase (LDH) levels, as well as reticulocyte count after cytomegalovirus-associated auto-immune hemolytic anemia.

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immuno-allergic hemolytic anemia was excluded (sole co-medication: insulin). Blood smears showed no morphological abnormalities in erythrocytes, with absence of schistocytes. Identification of cold agglutinins and a positive Coombs' test for complement fraction C3d (titer > 1/8) made the diagnosis of AIHA in a setting of primary CMV-infection (CMV DNAemia: 5.07 log/ml whole blood; CMV antibody [IgM]). Other virological tests, including HIV, human Herpes viruses 6 and 8, Epstein–Barr virus, and hepatitis A, B, C, and E viruses, were all negative. Immunological testing showed low titers of antinuclear antibodies (1/160) and rheumatoid factor (100 UI/ml). There was no evidence of monoclonal proliferation nor of cryoglobulinemia.

Antiviral treatment was 3 weeks of intravenous ganciclovir (10 mg/kg/day) followed by oral valganciclovir (900 mg/day) for another 3 months. Under this treatment, CMV DNAemia and CMV IgM antibodies became negative within 2 and 4 weeks, respectively and remained so until last follow-up. Anti-CMV IgG became positive 21 days after starting ganciclovir at high titer which remained elevated until last follow-up. AIHA was treated by three pulses of methylprednisolone (2 mg/kg/day), followed by oral prednisolone (1 mg/kg/day) for a month, before steroids were progressively tapered. Concomitantly, he received 0.5 g/kg/day of intravenous immunoglobulins (IVIg) for the first 4 days, a blood transfusion, and darbopoietin-α (200 μg/week). Nevertheless, the hemolytic process continued; thus, at 6 months after initial AIHA diagnosis, 100 μg/week of darbopoietin-α was still necessary to maintain stable hemoglobin levels. Therefore, we implemented rituximab therapy (four weekly courses of 375 mg/m^2 each). Three months after the last rituximab infusion, although haptoglobin levels remained low, LDH and reticulocytes were markedly reduced and hemoglobin was stable. Cold agglutinins were hardly positive at last follow-up. Darbopoetin-α was progressively stopped. Complete remission of AIHA has been maintained after 1 year follow-up (Fig. 1).

The pathophysiology of CMV-associated AIHA remains unclear [3]. CMV infection might result in auto-reactive B-lymphocyte clones. Cross-reactivity between viral epitopes and erythrocytic antigens is also possible [4].

Conventional treatment of AIHA relies on immunosuppression (steroids and/or IVIg) with or without splenectomy [5]. However, recently, rituximab has been used with good results in some cases [6]. In CMV-related AIHA, patients have been additionally treated with ganciclovir, or with anti-CMV globulins.

In conclusion, we report the first case of CMV-associated AIHA in a LT patient. Complete remission was obtained with rituximab infusions.

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