

Letter to the Editor

Successful cure of C1q deficiency in human subjects treated with hematopoietic stem cell transplantation*To the Editor:*

Hematopoietic stem cell transplantation (HSCT) is used to cure a number of primary immunodeficiency diseases but has never been attempted for patients with complement deficiencies because most complement factors are produced in the liver rather than the bone marrow. Inherited deficiency of the C1q component of the classical complement pathway is a severe autosomal recessive immunodeficiency disease associated with a high risk of death from either fulminant bacterial infections or systemic lupus erythematosus–like autoimmunity.¹ Indeed, C1q deficiency is the strongest disease susceptibility gene for the development of severe systemic lupus erythematosus in human subjects, with a 90% risk of skin disease and a 50% risk of renal disease.² C1q is unusual in that it is synthesized by bone marrow–derived monocytes.^{3,4} Studies in mice suggest that C1q deficiency might be amenable to treatment with HSCT.^{5,6}

We have previously reported on a consanguineous Pakistani family in which the father and 5 of 6 sons were affected by C1q deficiency.¹ The father died of chronic glomerulonephritis at 38 years of age, and one of his sons died at 17 months of *Streptococcus pneumoniae*–induced meningitis. Since publishing this report in 2007, another son had an acute central nervous system vasculopathy at 17 years of age and remains in a “locked in syndrome” 18 months after the acute event. A third son who is now 17 years old survived *S pneumoniae*–induced meningitis at the age of 3 years and an acute central nervous system vasculopathy at age 10 years, which was successfully treated with high-dose prednisone and intravenous cyclophosphamide pulse therapy. After completing a 2-year course of intravenous cyclophosphamide pulse therapy (monthly for 6 months and then every 3 months for a further 18 months), his disease was kept under control with rituximab, although he had a persistent lupus-like rash on his cheeks and ears (Fig 1, A) and increased SS-A60 and anti-cardiolipin autoantibody levels. Double-stranded DNA autoantibody levels were negative. He was attending mainstream school but required additional teaching support.

In view of the family history, incomplete control of the patient’s autoimmune disease, and risk of further exacerbations and overwhelming infection, at age 16 years, the patient underwent HSCT from his healthy HLA-matched brother by using a reduced-toxicity conditioning with fludarabine (40 mg/m²), treosulfan (42 mg/m²), thiotepa (10 mg/kg), and alemtuzumab (0.3 mg/kg). Graft-versus-host disease (GvHD) prophylaxis was given in the form of alemtuzumab before transplantation and prednisolone, cyclosporine, and mycophenolate after transplantation because of the previous and ongoing autoimmune disease and thus perceived increased risk of this posttransplantation complication. No GvHD was observed. Two months after HSCT, he had a sub-clinical EBV viremia that was successfully treated with rituximab. Six months after transplantation, his B-cell numbers remain suppressed by the rituximab, but otherwise, the patient has full donor chimerism and is off all anti-GvHD prophylaxis. Restoration of hematopoiesis, myelopoiesis, and platelet production, as well as normal complement function (CH50 and serum C1q), was

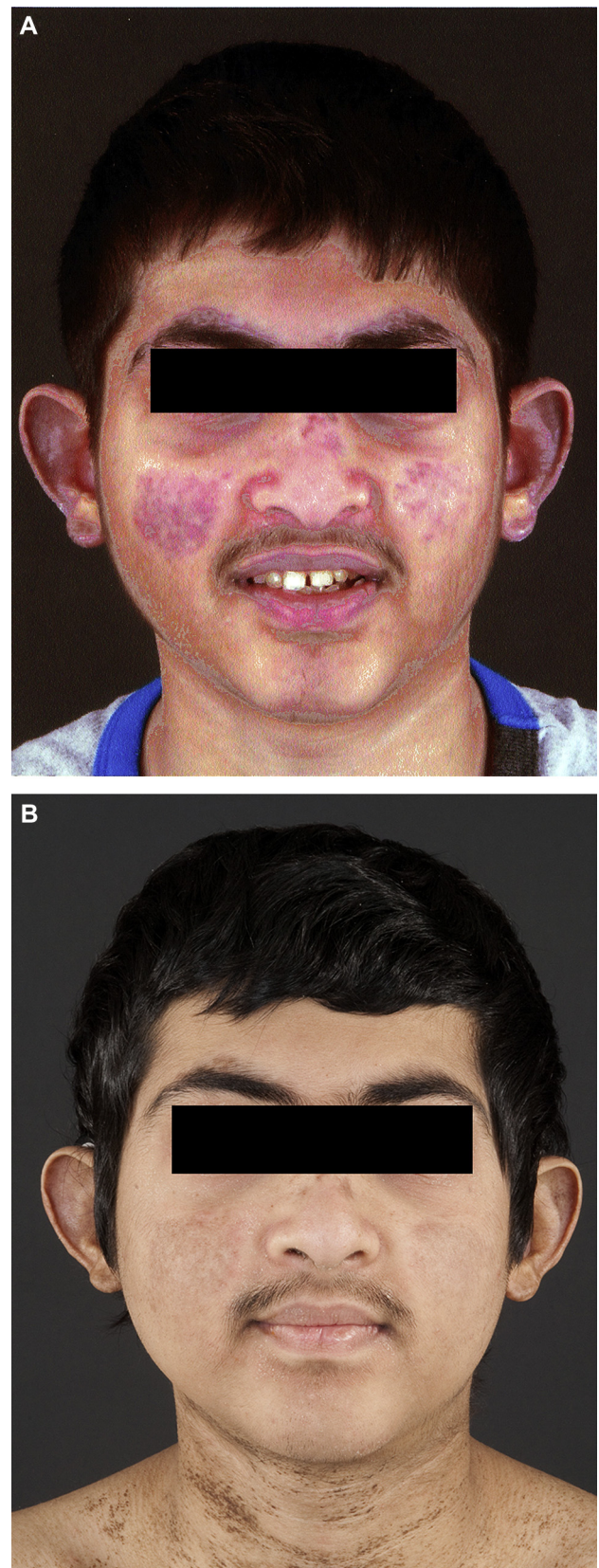


FIG 1. Facial rash before (A) and after (B) HSCT.

TABLE I. Changes in complement and autoantibody titers after matched sibling bone marrow transplantation for C1q deficiency

Parameter	Normal range	Before BMT	Weeks after BMT						
			1	2	4	6	12	16	24
Leukocyte engraftment									
Neutrophils (× 10 ⁹ /L)	1.50-6.00	1.50	0.05	1.18	3.58	5.15	3.09	1.01	3.20
Lymphocytes (× 10 ⁹ /L)	1.50-4.50	1.62	0.07	0.25	0.40	0.12	0.29	0.46	0.30
Monocytes (× 10 ⁹ /L)	0.10-1.50	0.20	0.54	0.65	0.36	0.36	0.21	0.23	0.22
CD3 (× 10 ⁶ /L)	622-2402	761				32	36	233	96
Complement									
CH50 (U/mL)	392-1019	<275	<275	588	838	967		978	659
C1q (mg/L)	70-140	<10	<10	<0	75	70		69	76
Autoantibodies									
SS-A60 (Ro) AI	0-0.9	>8.0	>8.0	>8.0	>8.0	>8.0	5.2	4.0	3.3
SS-B (La) AI	0-0.9	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
dsDNA (IU/mL)	0-0.9	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Anti-cardiolipin IgG (GPLU)	0-5.7	18.0	18.0	18.0	18.0	18.0	12.0	6.9	5.3

BMT, Bone marrow transplantation; dsDNA, double-stranded DNA; GPLU, IgG phospholipid units; SS-A60, Sjögren syndrome A 60-kDa protein autoantibody (equivalent to anti-Ro).

observed from 2 to 4 weeks after transplantation, and levels have remained stable and within the normal range over the last 5 months (Table I). The facial lupus rash has resolved (Fig 1, B), and the previously increased SS-A60 and anti-cardiolipin autoantibody levels, which did not decrease before transplantation after treatment with either intravenous infusions of cyclophosphamide or rituximab, were observed to decrease from 3 months. The patient and his family provided written consent to publish their case.

This is the first report of successful treatment of a complement immunodeficiency with HSCT. In view of the high risk of morbidity and mortality of C1q immunodeficiency, HSCT might be considered a treatment option for other patients with this complement immunodeficiency.

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