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Use of Bortezomib in the Treatment of C3 Glomerulonephritis Refractory to Eculizumab and Rituximab

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INTRODUCTION

C3 glomerulopathy (C3G) is a chronic kidney disease defined by the predominance of C3 deposition in the renal glomeruli.[1] C3G is caused by dysregulation of the alternative pathway of complement activation. The majority of C3G is caused by acquired factors—circulating Igs that stabilize the formation of the alternative pathway C3 convertase, C3bBb, which are referred to as C3 nephritic factor (C3NeF).[2] In a smaller subset of C3G, autoantibodies that bind to and interfere with factor H, a protein that competes with factor B for C3 binding and acts as a cofactor for factor I, are present.[3] The remaining patients have genetic dysregulation of the alternative pathway. C3G is currently treated by a combination of immunosuppression and complement pathway inhibition with mycophenolate, prednisone, eculizumab, and rituximab.[4,5] Little is known regarding treatment options for the many patients with incomplete response or unacceptable side effects with these therapies. In this report, we describe the use of bortezomib to induce factor H autoantibody remission in a patient with longstanding C3G.

CASE PRESENTATION

We report the case of a young man with refractory C3 glomerulonephritis. He initially presented with the clinical picture of postinfectious glomerulonephritis at 6 years of age. He was subsequently lost to follow up for 3 years and, when re-evaluated, was found to have persistently depressed C3 level and nephrotic-range proteinuria (Table 1). He started prednisone, and although the C3 level remained below the assay limit of detection, the proteinuria normalized. Following the discontinuation of prednisone 2 years later, the proteinuria became severe, and a renal biopsy sample showed hypercellular, lobular glomeruli consistent with membranoproliferative glomerulonephritis (Figure 1a). Additional blood studies were performed at that time: factor H autoantibody was detected by enzyme-linked immunosorbent assay, fluid-phase C3 convertase stabilization was detected by immunofixation electrophoresis, and C3 convertase stabilization assay results were positive (Iowa University Molecular Otolaryngology and Renal Research Laboratories). Sequencing alternative pathway component genes was unrevealing. The patient was treated with mycophenolate 750 mg twice daily and prednisone 20 mg every other day, and the remained stable until the age of 16 years, when he developed worsening proteinuria. At that time, mycophenolate was discontinued and eculizumab was added. He had subsequent improvement of proteinuria, normalization of his soluble membrane attack complex, and improved appearance of the glomerular basement membrane on ultrastructural examination (Figure 1b).

At 19 years of age, despite being on eculizumab, his proteinuria worsened, and he was noted to have significant T-cell lymphopenia. Four doses of rituximab were administered and prednisone was discontinued. After 4 months, there was no improvement in proteinuria, and the C3 level remained below the assay limit of detection. Prednisone was restarted. The patient subsequently received 12 sessions of plasmapheresis and 2 additional doses of rituximab. His urine demonstrated a decrease in RBC, but he continued to have significant proteinuria with low serum albumin,

Table 1. Key clinical parameters

	Age 16 yr, eculizumab Started	Age 19 yr, rituximab 4 doses	Age 20 yr, rituximab 2 doses	Age 21 yr, bortezomib started	Age 22 yr, kidney biopsy	Present day
Creatinine (mg/dl)	0.3	0.6	0.6	0.6	0.8	0.5
Albumin (g/dl)	2.2	2.6	2.5	1.7	3.2	3.5
Urine Protein/creatinine	2.41	2.55	7.82	13.05	2.82	2.37
C3 (mg/dl)	<15	<15	<15	<15	110	131
UA blood (mg/dl)	1	1	1	1	0.2	0.2

and the C3 level remained below the assay limit of detection. Mycophenolate was restarted. Despite these interventions, he deteriorated clinically and developed anasarca requiring diuretics, worsened hypertension, and grossly bloody urine. The factor H autoantibodies had declined (Figure 2) following treatment with rituximab; however, because the C3 level remained below the limit of detection, we hypothesized that autoantibody continued to dysregulate the alternative complement pathway. To further decrease autoantibody production, we decided to target plasma cells with bortezomib. Mycophenolate and prednisone were stopped, and shortly thereafter, at 21 years of age, bortezomib was started at 1.6 mg twice weekly for 2 weeks, followed by 1 week off, with dexamethasone 20 mg taken prior to each treatment. The patient quickly

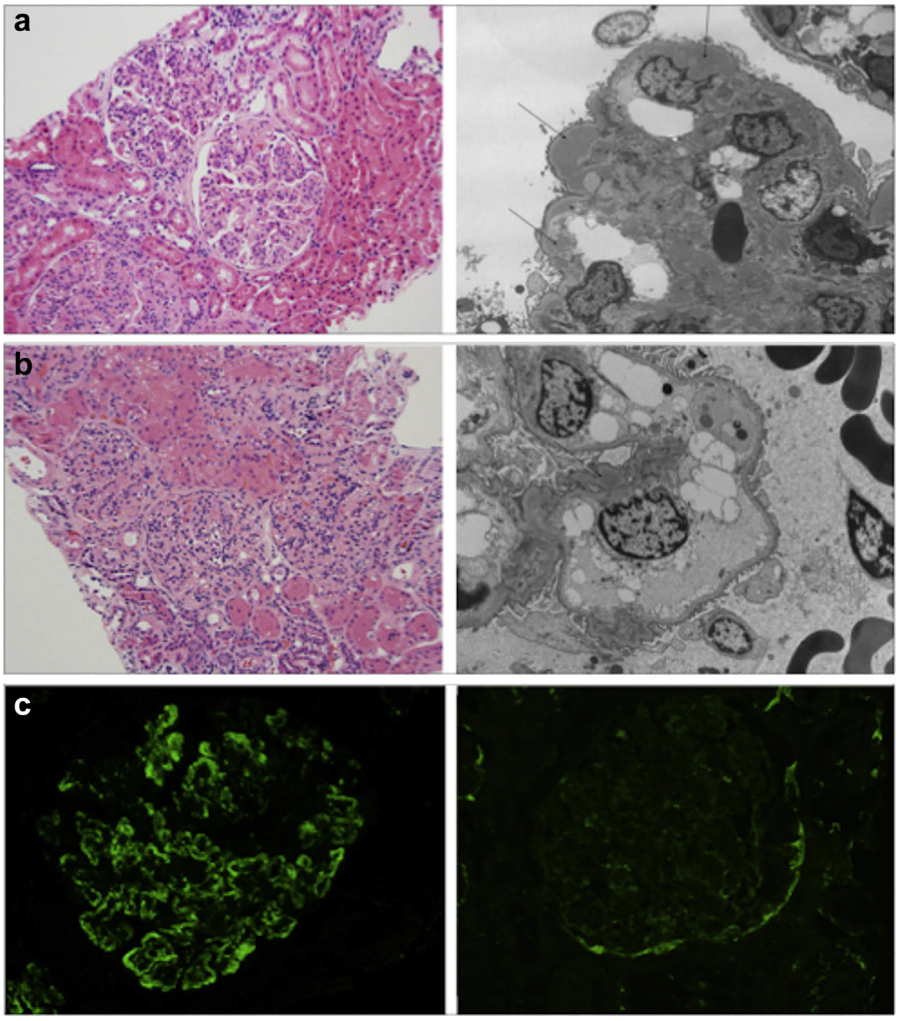

Figure 1. Renal biopsy sample images at presentation and throughout the treatment course. (a) (Left) Hematoxylin–eosin staining demonstrating hypercellular, lobular glomeruli, and (right) electron microscopy demonstrating mesangial and subendothelial deposits (arrows). (b) Persistent glomerular hypercellularity on hematoxylin–eosin staining and (right) electron microscopy with decreased deposits in the basement membrane (arrow points at persistent mesangial dense deposits). (c) Immunofluorescence microscopy showing improvement of C3 staining from (left) 2 years before, and (right) 1 year after, starting bortezomib.

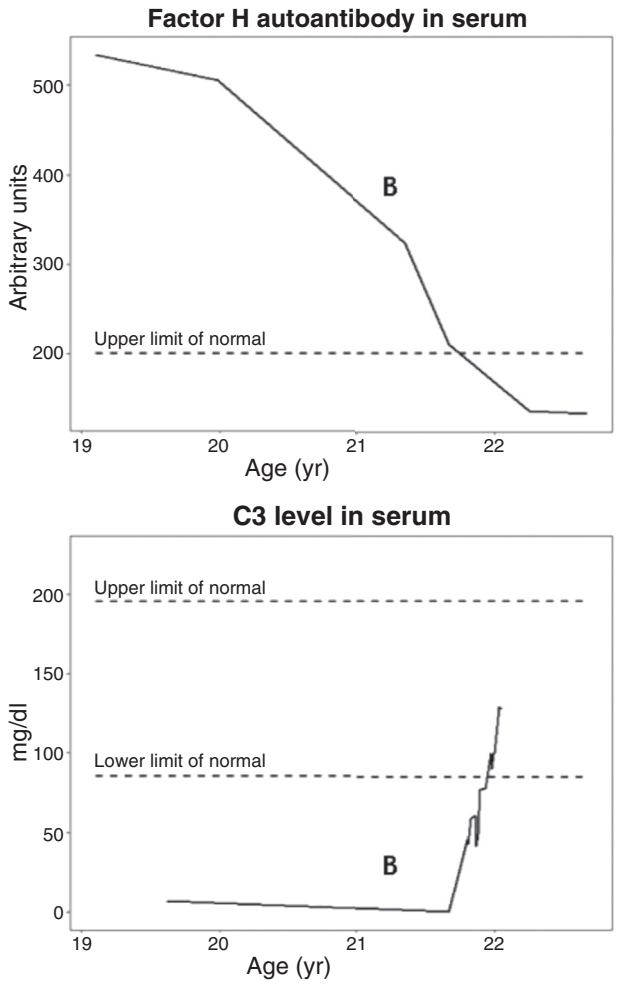

Figure 2. Serum C3 and factor H autoantibody levels before and after the start of bortezomib. C3 and factor H autoantibody levels both normalized following the initiation bortezomib. B, bortezomib.

stabilized, with significant improvement of his nephritic and nephrotic clinical features. He no longer required diuretics and remained on only 1 antihypertensive agent, lisinopril.

After 4 months of therapy, his serum C3 level increased to the normal range, which was the first time that it had been detectable in 15 years (Figure 2, Table 1). Subsequent renal biopsy at the age of 22 years showed no glomerular endocapillary hypercellularity, stable mesangial hypercellularity, mild interstitial fibrosis, and evolving changes of focal segmental glomerular sclerosis with 10% global and 15% segmental sclerosis. Glomerular basement membrane C3 deposition was less prominent than in prior biopsy samples (Figure 1c). Despite the much-improved glomerular C3 deposition, the patient continues to have significant proteinuria (Table 1). He remains on bortezomib on the dosing schedule of 1.6 mg once weekly for 2 weeks, then 1 week off. Side effects of the treatment have been limited to nausea and decreased appetite, but no peripheral neuropathy.

Table 2. Teaching points

Patients with C3 glomerulopathy have dysregulation of the alternative complement pathway, which is caused by circulating Igs, autoantibodies that bind to factor H, or genetic dysregulation.
Current treatment includes a combination of immunosuppression (mycophenolate and prednisone) and complement pathway inhibition (eculizumab), which is often only partially effective and is not a curative treatment.
Use of a plasma-cell directed therapy, such as bortezomib, should be considered for refractory disease, as it can reverse the underlying alternative pathway abnormality and can even improve renal pathology.

DISCUSSION

To our knowledge, this is the first report of the use of bortezomib for the treatment of factor H autoantibody–associated C3G. Thus far, the use of plasma cell targeted therapies such as bortezomib has been limited to renal pathology associated with myeloma, monoclonal gammopathy, or monoclonal immune deposits.[6–8] Treatment of C3G associated with nephritic factor or factor H autoantibody, on the other hand, typically involves the use of plasmapheresis, mycophenolate, prednisone, rituximab, and eculizumab. With the exception of rituximab, these therapies do not address the underlying cause of complement dysregulation in autoantibody-associated C3G. This case presentation provides preliminary evidence that plasma-cell–directed therapies could reverse the alternative pathway abnormality in patients with factor H autoantibodies and C3G, particularly if targeting B cells with rituximab was ineffective (Table 2). Given this patient's course, it is warranted to study this treatment in a larger cohort of C3G patients.

DISCLOSURE

BHR is on the advisory board of Admirx, Aurinia Pharmaceuticals, Biogen Idec, Bristol Myers Squibb, Callidatis, Chugai Pharma, EMD Serono, Genentech, Janssen, Lupus Foundation of America, AstraZeneca, MorphoSys, Novartis, Omeros, Pfizer, and Retrophin. He is a clinical trial principal investigator for Aurinia Pharmaceuticals, Biogen Idec, Genentech, Astra Zeneca, Retrophin, LuCIN, Human Genome Sciences, and ChemoCentryx. All the other authors declared no competing interests.

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