Teclistamab therapy for refractory type 1 cryoglobulinemia

Monoclonal gammopathy of clinical significance (MGCS) encompasses a range of disorders characterized by the production of monoclonal immunoglobulin by a clonal B-cell population, often leading to organ damage through various pathogenic mechanisms.[1] Type 1 cryoglobulinemia (CG) is defined by the presence of monoclonal immunoglobulin in the serum that precipitates at temperatures <37°C usually associated with a lymphoproliferative or plasma cell disorder. While type 1 CG can be asymptomatic, it may also present as a life-threatening condition when associated with multi-organ involvement, including dermatologic, renal, neurologic or cardiac involvement, or with hyperviscosity syndrome.[2,3] The diagnosis is based on clinical presentation, detection and typing of the serum cryoglobulin along with an organ biopsy showing mainly vascular thromboses.

Management of type 1 CG may require urgent interventions such as cold avoidance and plasma exchange, alongside targeted therapy for the underlying B-cell clone. In patients with a lymphoid proliferation, an anti-CD20-based regimen is usually the first option while a proteasome inhibitor-based regimen or anti-myeloma regimen is preferred for a plasma cell proliferation. Impact of novel agents, such as monoclonal antibodies, T-cell engagers or bispecific antibodies is largely unknown in MGCS and type 1 CG.[4]

We report here a case of refractory type 1 IgG λ CG presenting with severe dermatologic manifestations and renal failure requiring hemodialysis, successfully treated with the bispecific antibody teclistamab, which targets both CD3 and B-cell maturation antigen (BCMA).

A 65-year-old patient with medical history of hypertension, right renal artery stenosis, stage 2 chronic kidney disease and localized prostate cancer status post prostatectomy and radiation therapy presented with acute kidney injury with serum creatinine elevation to 4.5 mg/dL and a non-blanching purpuric rash on his lower extremities. Laboratory evaluation revealed nephritic syndrome with macroscopic hematuria, uncontrolled hypertension and non-nephrotic range proteinuria (24-hour urine protein excretion of 1 g). Urinalysis showed hematuria (2+ blood), proteinuria (3+), and no cellular casts on microscopy. Complete blood count showed isolated normocytic anemia and peripheral blood smear showed aggregates of basophilic material. Serum protein electrophoresis and immunofixation electrophoresis were notable for a monoclonal IgG λ immunoglobulin with an M-spike measuring 0.33 g/dL along with normal serum free light chain ratio and no immunoparesis. A serum cryoglobulin with a cryocrit level of 28% was detected, with undetectable or low complement fractions (C3, C4, CH50). Hepatitis B, C, HIV, ANA, and rheumatoid factor were negative. Bone marrow biopsy revealed 8% of λ-restricted plasma cell infiltration, with fluorescence *in situ* hybridization (FISH) positive for t(4;14). Positron emission tomography/computed tomography imaging did not show any bone lesions, and renal biopsy confirmed cryoglobulinemic glomerulonephritis with a membranoproliferative pattern and monoclonal IgG λ deposits. The patient's underlying condition was classified as MGCS.[1]

He began treatment with eight cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD), achieving improved renal function (creatinine nadir 1.94 mg/dL) and a hematologic very good partial response (M-spike nadir <0.10 g/dL), though serum cryoglobulins and low complement levels persisted. After ten cycles of bortezomib (BTZ) maintenance, he relapsed with worsening renal function and rising monoclonal IgG λ. He then received six cycles of single-agent daratumumab, which led to transient improvement before relapsing again with worsening renal function, severe hypertension, and rising IgG λ levels. Given his prior good response and tolerance to bortezomib, it was added to daratumumab (DVd regimen) for three cycles, resulting in a partial hematologic response. However, due to recurrent hospitalizations for hypertensive urgency and COVID-19 infection, he developed end-stage renal failure and required hemodialysis. He relapsed again and presented with multiple lower extremity necrotic ulcerations and severe Raynaud syndrome with finger ischemia. He was restarted on DVd with no response and then transitioned to lenalidomide, cyclophosphamide, and dexamethasone. After two cycles, he was noted to have progressive disease with worsening dermatologic (large lower extremities necrotic ulcerations, finger necrosis) and renal (macroscopic hematuria) involvement along with worsening cardiac dysfunction (left ventricular ejection fraction estimated at 25% with global hypokinesia, and NT-pro-BNP level above the measurable range, recurrent hypertensive crises).

In light of his refractory disease, the patient was treated with teclistamab, which is currently approved by the Food and Drug Administration in multiple myeloma after four lines of treatment.[5] He tolerated step-up dosing without cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). At initiation, plasma markers included M-spike (0.42 g/dL), λ free light chains (172.3 mg/L), κ free light chains (122.0 mg/L), and cryocrit (25%). After three cycles, serum immunofixation became negative but hematologic complete response could not be confirmed without a repeat bone marrow biopsy. Complement levels normalized while cryoglobulin testing remained weakly positive with a cryocrit <1% potentially falling within the laboratory's margin of error. He was transitioned to biweekly injections at cycle 3 and then monthly at cycle 6. Despite early initiation of IVIG in context of profound hypogammaglobulinemia and antibiotic prophylaxis, his course was complicated by three serious episodes of infection (1 cavitary pneumonia, 2 methicillin-resistant

staphylococcus aureus facial cellulitis) requiring intravenous antibiotics and hospital admissions. He remained hemodialysis-dependent, but he had complete resolution of Raynaud syndrome and lower extremity ulcerations with only residual post inflammatory hyperpigmentation (Figure 1), resolution of recurrent hypertensive crises and resolution of macroscopic hematuria, and cardiac function improvement. Overall, despite hemodialysis dependence

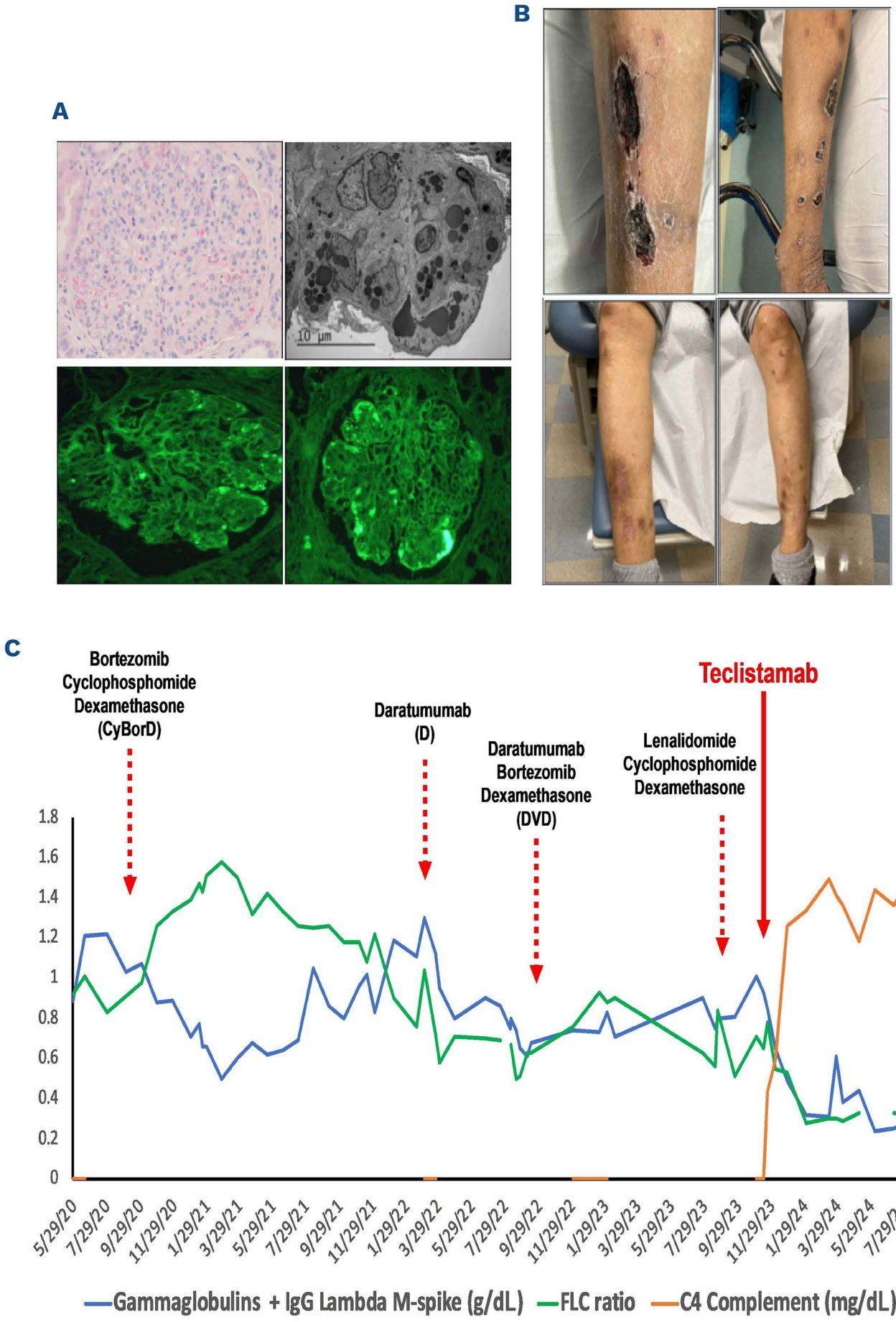

Figure 1. Renal biopsy, lower extremity ulcerations, and trend in disease markers with treatment. (A) Renal biopsy (clockwise from upper left: hematoxylin-eosin, electron microscopy, λ and IgG3 immunofluorescence). Glomeruli exhibit a membranoproliferative pattern of injury (upper left), and subendothelial/endocapillary deposits that exhibit the ultrastructural features of cryoglobulins (upper right). Immunofluorescence shows restricted immunoreactivity for IgG3 and λ light chains in some glomerular segments (lower panels) (upper left and lower panels pictures: original magnification × 400). (B) Bilateral lower extremities ulcerations before and after teclistamab therapy. (C) Trend in gammaglobulin (total IgG and IgG λ M spike), serum free light chain and complement component 4 (C4) level.

at treatment initiation and severe cardiac dysfunction, he rapidly achieved hematologic and clinical response and remains on teclistamab with a sustained response to therapy. Bispecific antibody targeting BCMA efficacy has been reported in AL Amyloidosis,[6] but this case represents, to our knowledge, the first reported use of teclistamab in type 1 CG with multi-organ failure, confirming the feasibility of administering bispecific antibodies in patients with renal failure with appropriate monitoring and prophylaxis. Given a lower tumor burden in MGCS and the risk of serious infectious complications, treatment intensity with rapid spacing and fixed duration should be considered. Anti-infectious prophylaxis and IVIG should be administered to maintain an IgG level ≥400 mg/dL, as recommended by the International Myeloma Working Group. Further studies are needed to delineate the role and safety of teclistamab in type 1 CG and other MGCS.

This manuscript describes a single case report conducted according to standard clinical practice and does not constitute research requiring Institutional Review Board approval. The patient consented to treatment and the publishing of his case follows institutional policy and national ethical standards.

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Contributions

JB and RS performed data collection, wrote the manuscript, and generated the figure. JH assisted in generating images for the figure and reviewed the manuscript. VS reviewed the manuscript.

Data-sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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