EXCEPTIONAL CASE

Treatment of fibrillary glomerulonephritis with use of repository corticotropin injections

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ABSTRACT

Fibrillary glomerulonephritis (FGN) is a rare idiopathic condition linked to malignancy, autoimmune disorders, monoclonal gammopathies and hepatitis C virus. It usually has a poor prognosis, resulting in progression to end-stage renal disease within a few years, given the lack of standardized treatment. Repository corticotrophin (RC) injections are approved for use in a variety of nephrotic syndromes, but are not routinely considered for treatment of FGN. We present a case in which a patient with FGN began treatment with RC 3 months after diagnosis. The patient has attained partial remission with complete resolution of nephrotic syndrome and stabilization of renal function.

Keywords: fibrillary glomerulonephritis, immunotherapy, nephrotic-range proteinuria, partial remission, repository corticotropin

INTRODUCTION

Fibrillary glomerulonephritis (FGN) remains an uncommon pathology found in only 1% of renal biopsies. FGN is identified by the aggregation of randomly arranged fibrils or microtubular structures, 10–20 nm in diameter. Diagnosis is made by electron microscopy. FGN fibrils stain dominantly or codominantly for immunoglobulins G4 and IgG1 with C3 staining and are distinguished from amyloid fibrillary deposition disease by staining negative for Congo red [1].

The etiology of FGN appears idiopathic but is associated with autoimmune disorders, monoclonal gammopathies, malignancy and hepatitis C virus in up to 33% of cases. Poor prognosis is typical and invariably results in end-stage renal disease (ESRD) within 2–6 years [2, 3].

CASE REPORT

A 66-year-old African American man was referred for outpatient nephrology evaluation in October 2013 for chronic kidney disease, which had progressed to Stage 4 over several years.

His medical history included uncontrolled hypertension, hyperlipidemia, hyperthyroidism treated with radioactive iodine 10 years prior and obesity. Prescribed medications included amlodipine, lisinopril, levothyroxine and aspirin.

Physical examination revealed an obese man with body mass index 35.6 kg/m^2, blood pressure of 162/90 mmHg and 2+ pitting edema of the lower extremities. The remainder of his examination was unremarkable.

The creatinine level declined from 2.2 to 2.7 mg/dL within a month. He had nephrotic-range proteinuria of 5.1 g/day as well as hematuria. Results for other analyses, including hepatitis B and C viral serologies, human immunodeficiency virus status, antineutrophilic cytoplasmic antibody, serum and urine protein electrophoreses, complement levels and renal ultrasound were unremarkable. His renal biopsy in December 2013 showed advanced-stage FGN.

Light microscopy of paraffin sections stained with hematoxylin and eosin, periodic acid–Schiff (PAS) and PAS-trichrome

showed prominent mesangial expansion and widespread, segmental irregular capillary loop thickening. Two-thirds of the renal cortices showed interstitial fibrosis and tubular atrophy. A Congo red stain was negative.
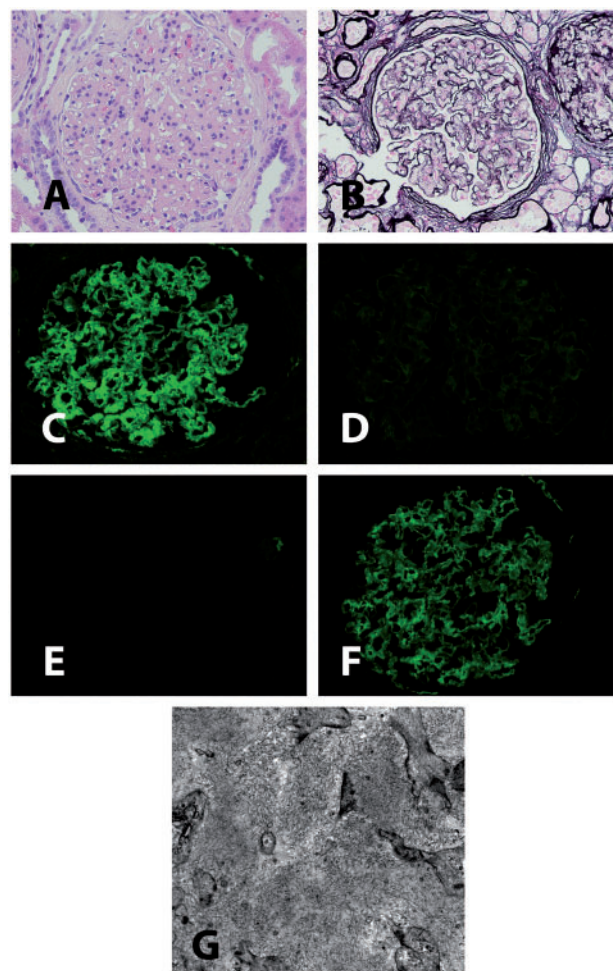
Direct immunofluorescence (DIF) of the renal cortex showed strong smudgy-to-granular glomerular staining for IgG and the kappa light chains. Slightly weaker, moderate and weak glomerular staining was noted for C3 and the lambda light chains, respectively. Immunofluorescence with the IgG subclass antibodies revealed strong glomerular staining for IgG1, weak staining for IgG4 and no staining for IgG2 and IgG3 (Figure 1).

Electron microscopy revealed abundant deposition of randomly arranged rigid fibrillary material in the mesangium and along the glomerular capillary loops within the thickened glomerular basement membrane. Fibril diameter was 19.0 ± 1.8 nm.

Three months after his biopsy-proven diagnosis, the patient agreed to a trial of treatment with repository corticotrophin (RC), which is approved for use in a nephrotic-range proteinuria. This medication was chosen in order to avoid the severe systemic immunosuppressive effects of alternative cytotoxic agents such as rituximab, particularly, at his level of progressed fibrosis and interstitial scarring.

He was started on RC 40 U/mL twice weekly for 2 weeks, after which the dose was increased to 80 U/mL twice weekly. We initially observed a rise in proteinuria, with a peak of 8.9 g/day 1 month into treatment, followed by a decline over the following several months with edema resolution and stabilization of the creatinine. After 6 months of treatment, the dose of RC was reduced to 40 U/mL twice weekly in order to minimize the potential adverse effects. Within 8 months of initiating RC treatment, proteinuria resolved to <1 g/day. The patient tolerated the therapy quite well and had no worsening of hypertension control, hypokalemia or hyperglycemia. He experienced mood swings and mild darkening of the skin, but surprisingly reported improved level of energy and memory. After 4 years of follow-up, he has attained partial remission, with complete resolution of nephrotic syndrome and stabilization of renal function completing 45 months of therapy.

DISCUSSION

Various immunosuppressive agents such as rituximab, cyclophosphamide and steroids have been used for FGN to demonstrate partial remission and/or stabilization of renal function for a period ranging from months to a few years only, before progression to ESRD [3–5].

RC has demonstrated a plausible therapeutic effect on an array of glomerulopathies with nephrotic syndrome. The whole spectrum of RC mechanisms is currently under investigation. Direct immunomodulation of melanocortin receptors to mediate podocyte apoptosis and effacement is of particular interest. It has been suggested that the action of RC has an inherent anti-inflammatory property, reducing B- and T-cell activity via steroidogenesis upon binding to the adrenal cortex melanocortin receptor [5].

While our initial intention was to treat our patient with RC therapy for 6 months, per the manufacturer's recommendations, in order to improve proteinuria and stabilize renal function, we continued the patient on therapy for a longer duration to sustain the achieved partial remission and to postpone progression to ESRD. We observed an excellent response over the course of the first 45 months of treatment.

Few observational reports have demonstrated variable outcomes with use of RC in patients with FGN. Our case supports the consideration of trying this agent as a first-line therapy in patients with advanced disease in the hope of avoiding side effects of other immunosuppressive or cytotoxic agents. Further analyses are necessary to establish a sustainable and reproducible response to therapy.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

FIGURE 1: (A) Enlarged glomerulus with mesangial expansion and segmental glomerular capillary thickening, hematoxylin and eosin, ×400. (B) Methenamine silver stain is weak to negative in the expanded mesangium. Jones methenamine silver, ×400. (C) DIF with antibody to immunoglobulin G1 (IgG1) shows smudgy mesangial and segmental glomerular capillary staining, ×400. (D) DIF with antibody to IgG2 is negative, ×400. (E) DIF with an antibody to IgG3 is also negative, ×400. (F) DIF with antibody to IgG4 shows similar staining to IgG1, ×400. (G) Electron microscopy of the mesangium reveals prominent deposition of fibrillary material. Uranyl acetate-lead citrate, original magnification ×30 000.

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