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CLINICAL VIGNETTE

Acthar Gel in Treatment of Idiopathic Membranous Nephropathy-Associated Nephrotic Syndrome

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Case Report

A 69-year-old male was referred to renal clinic for 2-month history of peripheral edema and proteinuria. He reported more than thirty pounds of weight gain over the past two months. His past medical history was remarkable for asthma, prediabetes and allergic rhinitis. He had no history of prior kidney disease. Physical examination showed pitting edema in lower extremities up to his knees. Laboratory tests showed a urine protein creatinine ratio (Up/Ucr) of 6.9 with trace hematuria. Microscopic examination of urine showed 6 RBC per uL and 3 WBD per uL. Creatinine was of 1.1 mg/dL and he was diagnosed with idiopathic nephrotic syndrome (INS). Additional laboratory tests including ANA, complements C3 and C4, hepatitis panel, HIV and ANCA antibodies were negative. He underwent kidney biopsy for nephrotic range proteinuria which showed membranous nephropathy, stage 1 of 4 with mild tubulointerstitial changes. His nephrotic syndrome was related to idiopathic membranous glomerulonephritis. He was initially started on angiotensin converting enzyme inhibitor, Lisinopril, with no improvement in his nephrotic range proteinuria. Prednisone 10 mg every other day and cyclosporine, initially at 75 mg two times a day, were added with no improvement. The dose of cyclosporine was increased to 150 mg orally two times a day. Significant proteinuria persisted for more than 4 months with peaked Up/Ucr greater than 8 and he developed increased serum creatinine up to 1.7 mg/dL while receiving cyclosporine 150 mg two times a day, prednisone 10 mg every other and Lisinopril 40 mg two times a day. Given the resistance to first line therapy, he was started on Acthar gel (adrenocorticotropic hormone, ACTH). The patient was initially started on 40 units subcutaneously every 72 hours. He had no significant improvement in nephrotic range proteinuria after 2 months (Up/Ucr 8.3). Acthar dose was increased to 80 units every 72 hours, patient started having decreased proteinuria while on ACTH 80 units every 72 hours, and Lisinopril 40 mg two times a day after 3 months (Up/Ucr 4.6). Patient was continued on Acthar 80 units every 72 hours for the next 11 months and serum createnine ranged between 1.1-1.3 mg/dL and Up/Ucr continued to decrease. After 15 months of treatment with Acthar he had resolution of his nephrotic syndrome symptoms and had a serum creatinine of 1.3 mg /dL and Up/Ucr of 0.3 when the treatment was discontinued. At follow up 8 months later, off Acthar and on Lisinopril 40 mg, his serum creatinine was 1.2 mg/dL and Up/Ucr 0.3.

Discussion

Glomerular nephropathies are a group of kidney diseases associated with glomerular injury presenting with proteinuria and hematuria. Nephrotic Syndrome is a constellation of clinical and laboratory findings related to glomerular nephropathies. Main clinical features include weight gain and peripheral edema are related to severe fluid retention secondary to heavy proteinuria. Laboratory findings associated with NS is specifically defined by hypoalbuminemia (less than 3.0g/dL, heavy proteinuria (greater than 3.5 g/24 hours) and hyperlipidemia. Membranous nephropathy (MN) is a common cause of nondiabetic NS. The majority cases of MN are idiopathic. Immune suppressive therapy is the cornerstone of treatment in idiopathic membranous nephropathy (IMN). Given the severe adverse effects of immune suppressive therapy in one hand and spontaneous resolution of (IMN) on the other hand, risks stratification for progression to severe kidney disease should be considered for each individual patient with IMN before initiating treatment.[1]

Older age (greater than 50), male sex, heavy proteinuria (greater than 8 g/24 hours), persistent proteinuria (for more than three months) and an increased serum creatinine at the time of presentation are clinical findings associated with higher risk of developing end-stage renal disease.[2,3] Glomerular scarring (glomerular sclerosis) and tubulointerstitial fibrosis are among histologic findings in renal biopsy. Tubulointerstitial fibrosis correlates more closely with outcomes and progression to end-stage renal disease.[4]

Our patient's clinical and laboratory findings put him in the high-risk group of patients with IMN. He was started on immune suppressive therapy as the first line treatment and continued for 4 months with no improvement in renal function and proteinuria. The patient responded to Acthar and continued to have persistent stable renal function off Acthar.

ACTH is a well-known medication in treating INS. Clinicians started to use ACTH in 1950s to treat INS in children and adults. ACTH dramatically changed the outcome in patients with INS, from severe edema, disability and increased mortality rates to sustained proteinuria remission, resolution of edema and drop in mortality rates.[5-7] ACTH has re-emerged as a treatment for first line treatment–resistant INS over the past decade. It has been used in patients with INS associated with different types of idiopathic glomerular nephropathies who did

not respond to first line, immune suppressive, treatments. These patients responded to ACTH and had improvement in their clinical symptoms and laboratory abnormalities.[8-9]

The mechanism of action of ACTH in acute kidney injury remains unclear. Both steroidogenic–dependent and –independent mechanisms are considered involved in protection of renal cells against injuries.[9] The non-steroidogenic mechanism of ACTH Reno protection is believed to be through melanocortin system.[10-11] ACTH is an agonist of melanocortin 1 receptor (MC1R). MC1R is extensively expressed in renal tubules. In animal models with acute kidney injuries, Acthar gel suppressed the tubulointerstitial inflammation, fibrosis and tubular atrophy through anti-inflammatory effects mediated by MC1R receptor on tubular epithelial cells.[12]

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