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Recognized by None: Tubulointerstitial Nephritis and Uveitis syndrome

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Abstract

The authors discussed a case of tubulointerstitial nephritis and uveitis (TINU) syndrome in a woman with renal insufficiency and a history of uveitis. The diagnosis is confirmed with renal biopsy and the patient is treated with prednisone with stabilization of renal function and resolution of uveitis.

Key words

Tubulointerstitial nephritis and uveitis (TINU) syndrome; Renal failure; Granulomatous uveitis; Modified C-reactive protein (mCRP); sarcoidosis; Sjogren syndrome

Case history

The patient is 63-years, Caucasian female with past medical history of hypertension, type-2 diabetes mellitus, and hyperlipidemia. She came to the hospital with three-week history of low-grade fever, fatigue, and arthritis of her left knee. Her laboratory investigation revealed high blood urea nitrogen (BUN of 43mg/L) and creatinine of 2.3mg/L. She has normal complete blood count (CBC), creatinine phosphokinase (CPK), and raised C-reactive protein of 62. Urine analysis revealed low grade proteinuria of 700mg/G of creatinine, and pyuria, with negative urine culture. Her ultra-sound of the kidneys revealed normal sized kidneys with no obstruction or stones. Her extended work-up revealed normal thyroid function, and negative vasculitis rheumatological screen. Her serum and urine protein electrophoresis and immunoelectrophoresis were negative for myeloma.

The hospital course is complicated by pain and blurred vision in her left eye and her slit lamp examination revealed bilateral anterior granulomatous uveitis. She was treated with topical steroids and cyclopentolate. In the interim, her renal function deteriorated with increased BUN and creatinine. A decision was made for her to undergo renal biopsy which showed areas of atrophic tubules, diffuse moderate to severe mononuclear inflammatory cell infiltration. Finding suggestive for tubule-interstitial nephritis (TIN).Given her history and physical examination of bilateral anterior granulomatous uveitis and TIN, a diagnosis of TINU was made. She was started on high dose of prednisolone with gradual resolution of renal dysfunction and stabilizations of her uveitis. Her steroid was tapered over two-months to 10mg/day and her latest eGFR is 54ml/min.

Case discussion

This unique syndrome, tubulointerstitial nephritis and uveitis (TINU) is first described in 1975 [1], since then more than 250 cases have been reported in the literature [2,3]. Most cases have been described in pediatric nephrology and ophthalmology via case reports and small illustrative series.

The pathogenesis of TINU rests on the believe that modified C-reactive protein (mCRP), a common autoantigen to uvea and renal tubular cells is involved in the pathogenesis of the syndrome [4]. In reported series of 97 patients with various renal diseases and 40 healthy controls, the prevalence of immunoglobulin G (IgG) antibodies to mCRP was significantly higher in TINU patients (100%) than those with Sjogren's associated interstitial nephritis (29%), drug-induced interstitial nephritis (36%), or healthy controls (0%), [2,4]. TINU is thought to be T-lymphocyte driven inflammation with paradoxical suppression of cytokine production and a decrease in peripheral immune response as demonstrated by skin anergy testing which is akin to sarcoidosis [5,6].

The risk factors to TINU are prior viral or bacterial infection with hantavirus, cytomegalovirus, Epstein-Barr virus (EBV) or HIV and tuberculosis, legionella, and histoplasmosis [7,8]. The use of specific drugs is also associated with the syndrome, like antibiotics, non-steroidal anti-inflammatory (NSAIDS) or auto-immune diseases e.g.

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hypoparathyroidism, thyroid disease, IgG4-related diseases, and rheumatoid arthritis [2,9-13].

Most patients with TINU are young females with a median age of 15-years [14], although the syndrome is reported in all age groups [15,16]. The male to female ratio favored female preponderance with no racial peculiarity [2,9]. Strong association of the syndrome to HLA-DQA1*01, HLA-DQB1*05, and HLA-DQB1*01 have been described in a series of 18 patients [17].

Systemic findings of TINU are non-specific and including fever, weight loss, fatigue, malaise, abdominal and flank pain, arthralgia, myalgia, polyuria or nocturia. Signs of uveitis including bilateral eye pain, redness, photophobia, and decreased visual acuity may follow renal disease by periods of up to 12-months.

Renal manifestations of flank pain, sterile pyuria, hematuria, proteinuria (sub-nephrotic), renal insufficiency, and acute renal failure (ARF) have been well recognized. Proximal and distal tubulopathies with aminoaciduria, glucosuria, phosphaturia, and acidification defects are well documented features of TINU [18-20]. Renal biopsy consistent with acute interstitial nephritis with tubulointerstitial edema, mon-cellular inflammatory infiltrates with lymphocytes, plasma cells, histocytes, eosinophils and sometimes non-caseating granuloma. The glomeruli and the vascular structures are usually spared.

Laboratory findings, including eosinophilia, anemia, abnormal liver function tests, and elevated erythrocyte sedimentation rate (ESR). Association with the presence of antinuclear antibody (ANA), antinuclear cytoplasmic antibodies (ANCA), rheumatoid factor (RF), and hypocomplementemia have also been reported [21-23].

Renal disease in TINU is usually variable. Patients with progressive renal insufficiency are typically treated with prednisolone for a period of 3-6 months, depending on the response, and then slowly tapered. Uveitis requires early referral to an ophthalmologist as the disease is associate with recurrence and relapses and the use of the steroid-sparing immunosuppressive agents such as cyclosporine, methotrexate, and mycophenolate mofetil are needed.

The differential diagnosis of interstitial nephritis with ocular findings is broad and the following disorders should be included; sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus (SLE), granulomatosis with polyangiitis (GPA), Behcet's syndrome, and infectious diseases like tuberculosis, brucellosis, toxoplasmosis, and histoplasmosis. Sarcoidosis and Sjogren's syndrome share many features with TINU making the diagnosis very difficult in the absence of other organ involvement.

In conclusion

Our patient was diagnosed with TINU and was treated with high doses steroids with slowly tapering that resulted in stabilization of her renal function and uveitis. Thinking outside the box is important to identify atypical conditions or syndromes.

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