

CASE STUDIES

The co-occurrence of anti-CCP positive RA with IgA nephropathy

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Abstract

Very few studies have explored the renal involvement in RA. This co-occurrence could be attributed to the disease itself or drug induced. The present case study discussing the co-occurrence of anti-CCP positive RA and IgA nephropathy highlights the need for having a collaborative treatment approach for managing the patients.

Keywords: IgA nephropathy, anti-CCP, RA, rheumatoid arthritis

Introduction

Renal involvement in RA could be attributed to the disease itself or drug induced. There are studies reporting the association between the use of Gold and penicillamine in the past and secondary membranous nephropathy. Amyloidosis, glomerulonephritis, tubulointerstitial nephritis, and drug toxicity are the major causes of renal diseases in RA. Moreover, the course and prognosis of the disease are influenced by the presence of comorbidities such as atherosclerosis and hypertension.¹ There are very few Indian studies evaluating the renal involvement in RA. The present case study discusses the rare occurrence of anti-CCP positive RA along with IgA nephropathy.

Case report

A 32-year-old male presented with around 2-year history of arthritis of small joints of hands and foot. The patient was undergoing intermittent treatment with NSAIDs, steroids and alternative medicines for the past 2 months. Physical examination revealed minimal pedal edema on both the feet. Clinical evaluation demonstrated that the patient had anti-CCP +ve RA (334 u/mL), creatinine 1.9, albumin 3.2, protein 3+, 24hr urine 1.2g/day, HbA1c-5.4%, RBS-120 mg/dL, FBS-98 mg/dL, and PPBS-138mg/dL. Other findings of urine examination were unremarkable. He was found to be negative for ANA by ELISA, c-ANCA, and p-ANCA, and the levels of creatine phosphokinase and complements were

normal.

The presence of blood pressure 140/90 mm Hg with proteinuria was suggestive of renal parenchymal disease. Renal biopsy indicated chronic sclerosing glomerulonephritis, severe tubular atrophy, and interstitial fibrosis (>50%). All the viable glomeruli demonstrated diffuse and mesangial proliferation (Fig.1), one of them demonstrated segmental sclerosis with reactive podocyte proliferation (Fig.2). Mild intimal sclerosis was noted in interlobular arteries and some of the arterioles demonstrated circumferential hyalinosis. The renal biopsy findings were suggestive of IgA nephropathy. Ultrasonography of the abdomen and pelvis revealed bilateral small kidneys with grade II changes of renal parenchyma. Glomerular mesangial immunofluorescence findings revealed IgA immune deposits (3+, Fig.3). The diagnosis was concluded as early RA (6 months) with stage 2 IgA nephropathy. He was treated with 1 mg/kg body weight prednisolone, 50 mg/day of steroids tapered to 5 mg over period of 3 months, azathioprine as steroid-sparing medication, and hydroxychloroquine (HCQ) 200 mg BD. His arthritis responded well to the treatment and reduction in urine protein was also noted. He was prescribed with losartan 25 mg BD to manage hypertension. He was asked to continue omnacortil 5 mg with HCQ and azathioprine 50 mg daily. But his creatinine was 1.8 mg/dL at 6 months.

Fig.1: Glomerulus with diffuse mesangial proliferation

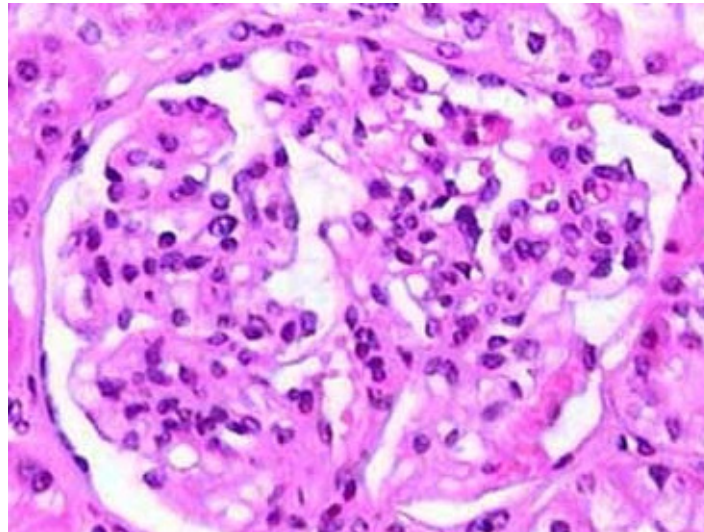
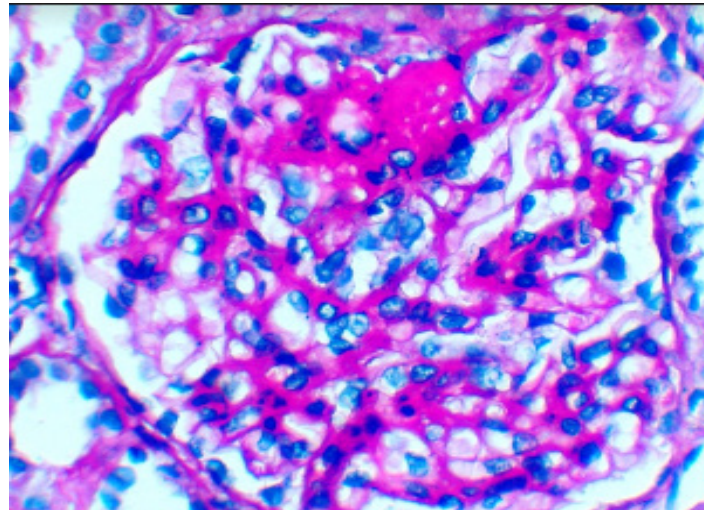


Fig. 2: Glomerulus with segmental sclerosis and synechiae formation



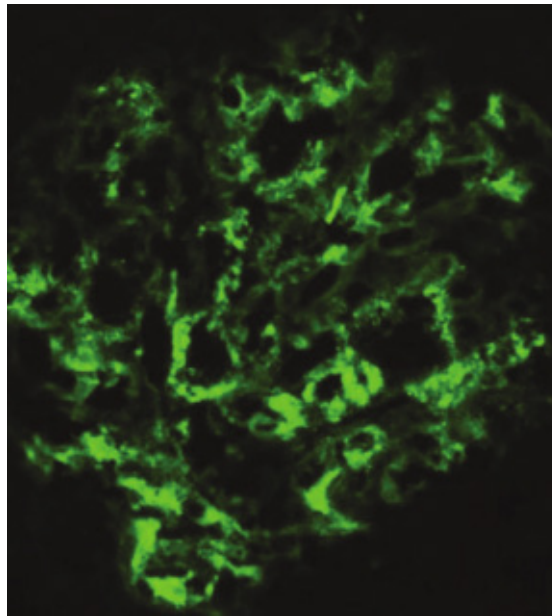
Discussion

Rheumatoid nephropathy in RA is marked by an initial presentation of proteinuria and microhematuria, which subsequently progresses to chronic renal failure. A 2003 study by Kanevskaia and Varshavskii has highlighted that morphological signs of renal pathology is more serious than clinical symptoms. They have also noted that in patients with uncontrolled RA, nephritis of any type may progress to amyloidosis.² The researchers investigated clinical and morphological variants and frequency of renal involvement in 117 patients diagnosed with chronic pyelonephritis. They identified around 35 patients with drug-related nephropathy, among them 26 subjects had symptoms of pyelonephritis before the onset of RA. Rheumatoid nephropathy is mediated either by an immunological inflammation or by the nephrotoxic effects of various drugs

indicated for the management of RA such as NSAIDs and DMARDs. Amyloidosis, glomerulonephritis, and interstitial nephritis are the commonly noted renal lesions associated with rheumatoid nephropathy. Management strategies include removing the suspected causal drug and initiating the specific immunosuppressive therapy.

The pathogenesis of IgA nephropathy is linked to the accumulation of immune complex, formed by the synthesis and binding of antibodies directed against galactose-deficient IgA1, in the glomerular mesangium. The accumulation of immune complexes results in renal injury via activation of mesangial cells, induction of extracellular matrix, and secretion of cytokines/ chemokines. Recent genome-wide association studies have identified the following candidate mediators that are potentially

Fig. 3: Mesangial granular IgA immune deposits (3+) noted in immunofluorescence



linked to IgA nephropathy pathogenesis: five distinct susceptibility loci in the MHC on chromosome 6p21, the complement factor H locus on chromosome 1q32, and a cluster of genes on chromosome 22q22.³ Galesić *et al.* have underscored the need for closely monitoring the parameters of renal function in all patients with RA and conducting renal biopsy in patients with pathologic results.⁴ The researchers conducted renal biopsy in 15 patients and the histopathological findings revealed IgA nephropathy in 3 patients, amyloidosis in 5 patients, focal segmental glomerulosclerosis in 3 patients, mesangial proliferative glomerulonephritis in 3 patients, minimal change disease, pauci-immune glomerulonephritis and thin membrane disease in 1 patient. However, a literature review by Icardi *et al.* has reported that there is no agreement on the prevalence of renal diseases in RA patients. The study has identified mesangial glomerulonephritis as the most frequent RA nephropathy (35-60%), followed by minimal change glomerulopathy (3-14%) and p-ANCA positive necrotizing crescentic glomerulonephritis. Amyloidosis has been identified as the key factor responsible for increased morbidity, impaired survival rate and progression to end stage renal disease in patients with RA and nephropathy.⁵

The probable reason for the development of IgA nephropathy in the current patient could be the treatment with NSAIDs, steroids and alternative medicines. Studies suggest that the use of NSAIDs (including cyclooxygenase-2 inhibitors) can induce acute renal impairment and this is more prevalent in elderly and patients having CKD, heart failure and volume depletion. In CKD patients, it is advocated

to use acetaminophen, glucocorticoids, metamizole/dipyrone or opioids, instead of NSAIDs. As per the international recommendations, the use of cyclosporine is contraindicated in RA patients with renal impairment, as the treatment can cause ischemic scarring, obliterative arteriopathy, and tubular atrophy. Dose reductions in azathioprine, antimalarials, and sulfasalazine have been proposed in subjects with GFR <50 ml/minute due to the risk of partial renal excretion. Renal insufficiency may also affect the excretion of certain DMARDs, which may contribute to non-renal toxicity. It is also necessary to start appropriate lipid-lowering therapy in patients receiving tacrolimus and tocilizumab to avoid hyperlipoproteinemia.⁶

The current case study holds greater significance, as the review of previous literature shows that there are very limited studies that have explored the co-occurrence of anti-CCP positive RA with IgA nephropathy. A 2019 study by Premužić *et al.* has reported the development of IgA nephropathy as a potential consequence of anti-TNF-alpha therapy. The study also highlighted the need of long-term close monitoring and judicious use of TNF-alpha inhibitors in RA patients at high risk of developing renal disorders.⁷ A systematic literature review by Piga *et al.* has identified that the use of biologics namely etanercept, adalimumab, infliximab, tocilizumab and abatacept are frequently associated with the development of autoimmune renal disorders. The study also concluded that in patients showing symptoms of renal disorders, it is necessary to terminate the biologics treatment and treat the subjects according to the clinical symptoms and renal biopsy.⁸

The current patient had predominant arthritis and needed frequent follow-up for blood pressure, proteinuria and serum creatinine. He visited nephrologist once in a year.

Conclusion

The present study underscores the need for developing a collaborative treatment regimen by both rheumatologist and nephrologist for managing patients having rheumatic disease and renal co-morbidity. It is also paramount to monitor blood and urinary parameters for concomitant CKD, which could develop as a manifestation of the systemic or unrelated renal disease or as nephrotoxic effects of various drugs.

Competing interests

The authors declare that they have no competing interests.

Citation

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