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Dr. Ponneyinchelvi AS
Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Dr. G Barathi
Department of Pathology, Sri Ramachandra Institute of Higher Education and Research. Chennai, Tamil Nadu, India

Dr. Subalakshmi Balasubramanian
Department of Pathology, Sri. Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Corresponding Author:
Dr. Ponneyinchelvi AS
Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

ANCA associated pauci immune glomerulonephritis in a known case of rheumatoid arthritis

Dr. Ponneyinchelvi AS, Dr. G Barathi and Dr. Subalakshmi Balasubramanian

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Abstract
Rheumatoid arthritis [RA] is a multisystem disorder in which prevalence of renal abnormalities ranges from 8 to 90%. ANCA associated pauci immune glomerulonephritis occurs as a rare late manifestation and results in poor prognosis. Most of these cases are associated with Myeloperoxidase[MPO] ANCA or previously called as p-ANCA positivity. It may occur as a part of RA associated with systemic vasculitis or an isolated disorder. We present a case of 45 year old male patient who is a known case of rheumatoid arthritis presented with renal failure and was diagnosed with Anti Neutrophill Cytoplasmic Antibody[ANCA] associated pauci immune glomerulonephritis.

Keywords: MPO ANCA, rheumatoid arthritis, pauci immune glomerulonephritis, vasculitis

Introduction
Rheumatoid Arthritis [RA] is a multisystem chronic autoimmune disorder. Renal disease is an important cause of morbidity and mortality in patients with RA and chiefly comprises of three main categories: Secondary Amyloidosis, complications of drug therapy and primary renal diseases related to RA. Pauci immune ANCA associated glomerulonephritis is one such rare manifestation in RA and MPO-ANCA is observed commonly with this category. This can be associated with cutaneous or multisystem vasculitis [1].

Case Report
A 45 year old male, known case of Rheumatoid arthritis, presented with hematuria and rapidly progressive renal failure. In view of rising creatinine and abnormal urinary findings, patient was subjected to complete biochemical and clinic pathological examinations which is given in table1 and based on the report of serum ANCA positivity, a renal biopsy was planned. USG guided renal biopsy was sent to our laboratory and was processed for light microscopy. H&E[Haematoxylin and Eosin], PAS[Periodic Acid Schiff], GMS[Gomorri's Methanamine Silver] and MT[Masson's Trichrome] stains were done. Another core was subjected to immunofluorescence study with a panel of immune globulins consisting of IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen and albumin.
On Light microscopy glomeruli showed presence of diffuse cellular crescents (figure1, figure 4), focal segmental vasculitis(figure3), and fibrinoid necrosis(figure3). These findings were highlighted by special stains. Tubules showed focal tubulitis, tubular injury and tubular atrophy [20%]. Interstitium showed patchy dense inflammation composed of lymphocytes, plasma cells and few eosinophills. Blood vessels showed mucoid degeneration of intima and medial wall thickening with luminal narrowing [20%]. All conjugates were found to be negative on Immuno flouroscence. With clinical history of rheumatoid arthritis, laboratory investigations confirming hematuria, renal failure and MPO-ANCA positivity, Light microscopy revealing necrotizing crescentic glomerulonephritis and Immunofluoresence showing all conjugates to be negative, correlating all the findings a diagnosis of ANCA associated Pauci immune crescentic glomerulonephritis was arrived.

Table 1: Laboratory investigations

Parameter	Observed Value	Interpretation
BUN	36mg/dl [7.9-20mg/dl]	Elevated
Serum creatinine	2.16mg/dl [0.8-1.3mg/dl]	Elevated
Urine protein	1+ [Negative]	Proteinuria
Urine RBC	5+ [Negative]	Hematuria
MPO ANCA	75.36AU/ml [less than 20]	Elevated
PR3 ANCA	2.78AU/ml [less than 20]	Normal
dsDNA	Negative	Negative

[Normal range are given within brackets**]**

HPE Pictures

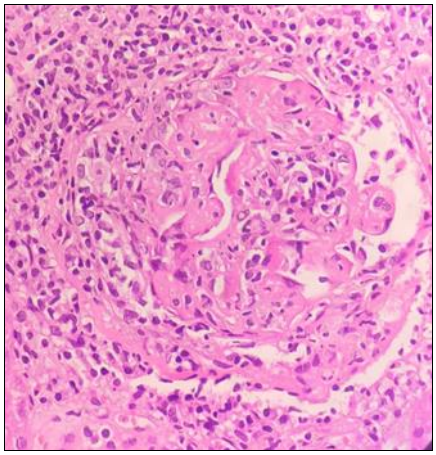

Fig 1: H and E, 400x, Glomeruli showing presence of cellular crescents.

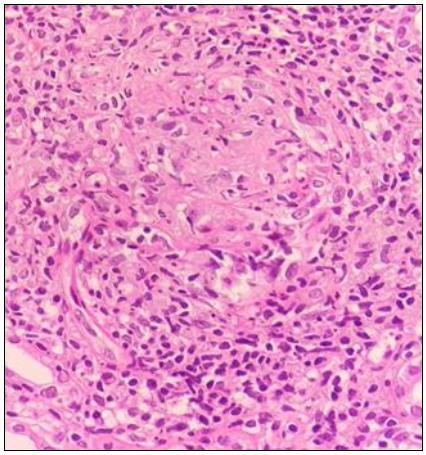

Fig 2: H and E, 400x, Picture showing features of Necrotising glomerulonephritis.

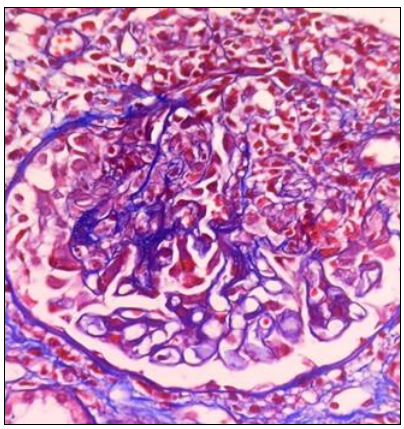

Fig 3: MT, 400x, Glomeruli showing presence of fibrinoid necrosis.

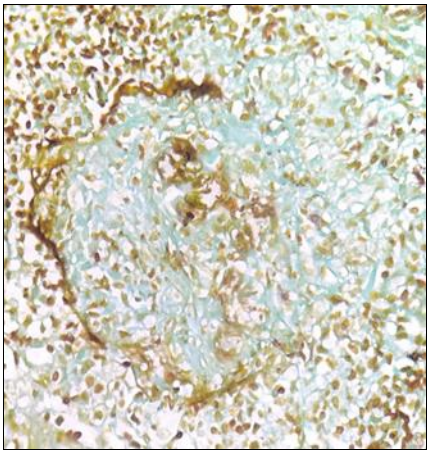

Fig 4: GMS, 400x, Glomeruli showing breach in the bowman's capsule

Discussion

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the joints. Renal involvement in rheumatoid arthritis (RA) is common and has a negative impact on patient survival [2]. It has a wide spectrum of lesions, consisting of glomerular damage mainly due to secondary amyloidosis and membranous nephropathy (related to gold salts, D-penicillamine) and also tubular damage (due to analgesic and nonsteroidal anti-inflammatory drugs [NSAIDs] [3]. Necrotizing glomerulonephritis (GN) associated with myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) is a rare complication. Only few cases have been reported.

Necrotizing GN may occur as a manifestation of RA-associated vasculitis with a multi-organ involvement, affecting the eye, nose, throat, lung and skin or it may appear as an isolated disorder [4]. ANCA Associated Vasculitis (AAV) are autoimmune systemic diseases characterized by necrotizing inflammation of small to medium-sized vessels associated with the detection of myeloperoxidase (MPO) or proteinase-3 (PR3) -ANCAs in serum [5]. Three entities are differentiated on the basis of clinical and pathological criteria, with overlapping clinical spectra: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). MPO-ANCAs are mainly observed in association with MPA, while PR3-ANCAs are more frequent in patients with GPA [6].

Our patient had severe renal impairment with rapid decline in renal function in the form of hematuria, proteinuria, elevated BUN & serum creatinine and high titres of MPO ANCA and renal biopsy proven Crescentic glomerulonephritis. Similar findings were observed in studies done by Yoshihara *et al*. [7] and Harper *et al*. [8]

The development of the overlap syndrome of RA and vasculitis may be explained on basis of the common pathogenic pathways. The classical target antigens of ANCAs are: proteinase-3 (PR3), highly associated with granulomatosis with polyangitis, and MPO, mainly related with microscopic polyangiitis. In cases of vasculitis observed in patients with RA, association with MPO-ANCA is more common. This finding is highlighted in study conducted by Szilasi *et al*. [9]

In these patients, where MPO ANCA is associated, RA tends to occur at an younger age, with fewer extrarenal manifestations, longer duration from onset of symptoms and end up in advanced glomerular scarring. In our case it

occurred as an isolated disorder in kidney, progressing to renal failure with elevated BUN and serum creatinine. There were no extra renal manifestations. Necrotising GN, associated with ANCA in a RA patient carries a poor prognosis. Study done by Mustila *et al* showed that MPO ANCAs were associated with disease activity, severity and an independent predictor of RA-associated nephropathy [10].

Another differential diagnosis considered in our patient was Drug associated ANCA associated vasculitis (DAV). Our patient was on treatment with Anti-Tumor Necrosis Factor alpha (Anti TNF-α) for RA. An etiologic role for anti-TNF alpha agents is supported by (i) the temporal relation of new onset glomerular disease to drug use in patients with long-standing RA of many years, duration and no prior renal disease, and (ii) the improvement of clinical symptoms and laboratory abnormalities after drug withdrawal and addition of immunosuppressive therapy in the majority of patients. New onset of glomerular disease following anti-TNFα therapy may reflect induction of RA-related nephropathy or de novo autoimmune disorders secondary to immune dysregulation.

Reitblat and Reitblat [11] reported two patients with ANCA associated vasculitis who was under antiTNF-α. In these cases, it is a challenge to know whether the vasculitis is a complication of the RA or a consequence of the treatment. It is well recognized that immune dysregulation caused by anti-TNF-α, which is associated with the development of autoantibodies, not only ANCA, but also antinuclear antibodies (ANA), antiphospholipids and anti-double-stranded DNA antibodies (anti-dsDNA). Our patient only had positive ANCA titers, but negative for ANA and dsDNA, hence ruling out the possibility of DAV.

Conclusion

ANCA associated Necrotising glomerulonephritis is a rare renal manifestation associated with RA. Immunoflouroscense study is mandatory to categorise it as pauci immune cresentic glomerulonephritis. MPO ANCA is more commonly positive in these patients. A known case of RA, if presenting with rapidly progressive renal failure, should prompt the treating physician to do further workup including a renal biopsy. With high clinical suspicion, if screening for MPO ANCA is done early in the course of the disease, detection of development of necrotising glomerulonephritis will be earlier and appropriate treatment can be started in advance. This will help in prognosis of the patient. Hence a collective approach is needed in handling such patients and a thorough work up is necessary.

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