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NOT ALWAYS A FULL HOUSE EFFECT IN LUPUS NEPHRITIS, A CASE REPORT

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ABSTRACT The most common type of renal involvement in systemic lupus erythematous (SLE) is lupus nephritis which is a form of immune complex-mediated glomerulonephritis and is considered as one of the severe organ manifestations of SLE . The pathogenesis involves immune complex deposition, which leads to glomerular inflammation and typically presents as a "full-house" pattern on immunofluorescence microscopy. Beyond glomerular involvement, other forms of lupus -related kidney damage include tubulointerstitial nephritis,vascular diseases like thrombotic microangiopathy and lupus podocytopathy which are rarely observed in patients with systemic lupus erythematosus. Pauci-immune glomerulonephritis (PIGN) is the pattern of injury commonly observed in patients with antineutrophilic cytoplasmic autoantibody glomerulonephritis. The pattern of pauci-immune crescentic glomerulonephritis is focal necrotizing and crescentic glomerulonephritis with little or no glomerular staining for immunoglobulin by immunofluorescence microscopy. Almost all cases of pauci-immune glomerulonephritis are ANCA positive,10-30% are ANCA negative[1] . PIGN is an uncommon manifestation of SLE patients compared to lupus nephritis. About 2% of SLE patients have overlap features of ANCA vasculitis [2] We report a very rare case of ANCA negative pauci-immune crescentic glomerulonephritis in a SLE patient of whom otherwise characterised by immune complex phenomenon.

KEYWORDS : Necrotizing And Crescentic Glomerulonephritis, mps iv, Cyclophosphamide Pulse, Positive Ana, Anca Associated Vasculitis, Antiphospholipid Antibody (apla), Lupus Nephritis, Systemic Lupus Erythema

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder. Lupus nephritis is the most common form of renal involvement in SLE which is a form of immune complex-mediated glomerulonephritis and one of the most severe organ manifestations of SLE that can lead to end stage renal disease . It can develop in approximately 20% to 65% of patients with SLE based on prior cohort studies [3][4][5]. Pauci-immune crescentic glomerulonephritis (PICGN) is the pattern of injury seen with antineutrophil cytoplasmic autoantibody (ANCA)- associated glomerulonephritis. This may present as granulomatosis with polyangiitis (GPA), microscopic polyangiitis, eosinophilic GPA, or renal limited vasculitis [6]. Morphologically characterised by focal necrotizing and crescentic glomerulonephritis with little or no glomerular staining for Ig by immunofluorescence (IF) [7] . PICGN is rarely documented in the course of autoimmune diseases. We report an infrequent case of ANCA-negative PICGN in a patient with systemic lupus erythematosus.

Case Presentation

A 32 year female, presented with complaints of fever for 2 months associated with headache, pedal edema, hair loss and frothy urine for 1 month. There is no history of oligouria , hemoptysis and hematuria . There is diminution of bilateral vision. She had a history of four abortions 5 years back for which she received anticoagulation during her antenatal period. She was hypertensive which was diagnosed 2 years back and compliant to tablet amlodipine 5mg once a day.

Physical examination revealed alopecia, pallor and bilateral pedal edema .Fundus examination revealed bilateral papilloedema. Blood pressure was 180/110 mmHg in the right arm sitting position.

The hemogram was suggestive of microcytic, hypochromic anemia, hemoglobin level of 8.2gm/dl, white blood cell count of 13,600/cmm and platelet count of 4.3 lacs/cmm. Erythrocyte sedimentation rate was 89 mm/h. Her serum urea was 45.6 mg/dl, serum creatinine was 3.0 mg/dl. Serum albumin was 2.5gm/dl. On urine routine microscopy albumin 2+,RBC:15-20/hpf and pus cells were 5-6 /hpf . The 24 hour urine protein was 4.6 gram per day for 2500 ml of urine. Complement levels were normal, serum C3 was 164.56 mg/dl and serum C4 was 25 mg/dl.

Autoimmune serological workup included the following: antinuclear antibody(IF assay) was positive at 1:1000 with a homogeneous pattern ,grade 3+ and positive for dsDNA. Anti- nucleosomes and anti-ku antibodies were weakly positive. pANCA , cANCA were negative by indirect immunofluorescence. In view of bad obstetric history her APLA profile was done it showed lupus anticoagulant positive, ACLA: IgG positive, Beta 2 GP1:IgG+ve. Ultrasonography of kidneys showed right kidney of 8.3 * 4 cm and left kidney of 11.2* 3.5 cm size with maintained corticomedullary junction . Doppler study of renal vessels showed non significant bilateral renal artery stenosis. Non enhanced contrast CT brain showed calcifications in bilateral frontal lobes. MRI brain was normal. She underwent a renal biopsy .

Light Microscopy:

Total 10 glomeruli , 1 globally sclerosed, 3 glomeruli had cellular crescents, 4 glomeruli had fibro cellular crescents and one glomerulus had fibrous crescent. Neutrophilic infiltrate and karyorrhectic debris seen in the occasional segment of 3 glomeruli. Tubules showed variable atrophy and tubular injury. Moderate to severe lymphoid infiltration (50%) .

IFTA-30%. Vessels had mild thickening. No changes of vasculitis.

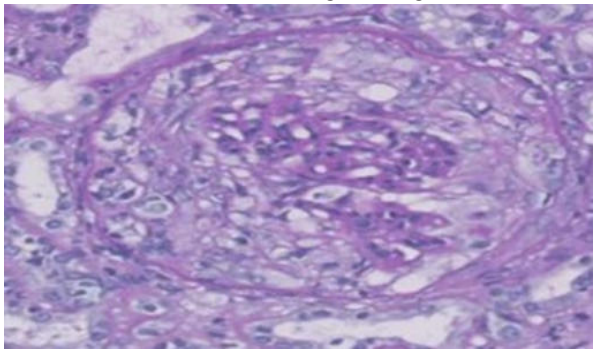

Figure 1: Light microscopy showing hematoxylin and eosin staining of cellular crescent . Immunofluorescence was negative for IgA,IgG,C4,C1q, fibrinogen with IgM and C3 (-/+ ve).

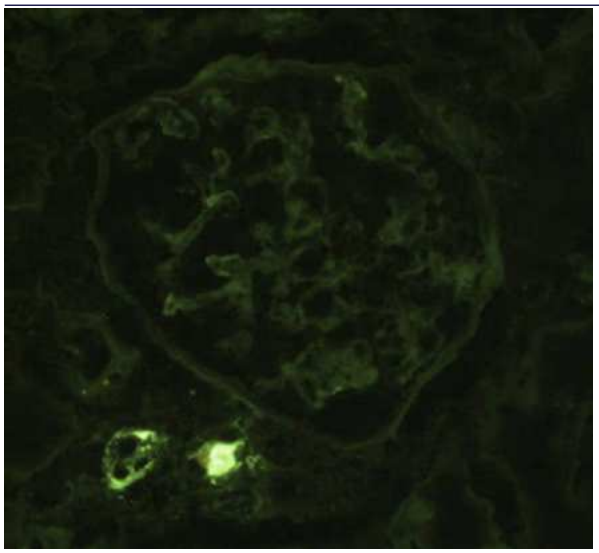

Figure 2: Immunofluorescence showing Pauci immune glomerulonephritis.

Electron Microscopy:
Four glomeruli examined . Two appeared sclerosed . Other two glomeruli showed no proliferation of endothelial, mesangial cells . No organized deposits and no crescents are observed.

Taken together, this renal biopsy was summarized as ANCA negative pauci-immune crescentic glomerulonephritis with secondary antiphospholipid syndrome to systemic lupus erythematosus.

Induction treatment was started with intravenous methylprednisolone 1gm per day for 3 days followed by oral steroids on tapering doses. She received 6 monthly intravenous cyclophosphamide 0.75 g/m^2 as per NIH regimen. Prophylactic low dose tablet Aspirin 75 mg was started considering her positive status for antiphospholipid autoantibodies and bad obstetric history.

At last follow up , her serum creatinine remained at 2.2mg/dl and 24 hour urine protein was 0.230 g for 3 litres of urine.

DISCUSSION

In patients with SLE, lupus nephritis is the most common kidney complication. The pathogenesis involved glomerular immune complex deposition, which leads to glomerular inflammation and typically exhibits a "full-house" pattern on IF. The International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classify LN based on the location of accumulation of immune complexes in the glomeruli, presence or absence of mesangial or endocapillary proliferation, overall extent of glomerular involvement [9]. The kidney may also sustain damage by other mechanisms, such as thrombotic microangiopathy and lupus podocytopathy. Thus renal biopsy plays an important role in confirming the diagnosis .

Our patient fulfilled the 2019 European League against Rheumatism/American College of Rheumatology classification for SLE (six criteria: hematologic, mucocutaneous, musculoskeletal, renal involvement , presence of anti-dsDNA antibody Lupus anticoagulant and antiphospholipid antibodies) [8].The biopsy in our patient revealed pauci-immune crescentic glomerulonephritis with negative ANCA serology. Pauci immune crescentic glomerulonephritis is a type of proliferative glomerulonephritis generally noted in association with conditions such as microscopic polyangiitis and granulomatous polyangiitis. Pauci-immune crescentic glomerulonephritis is a focal necrotizing and crescentic glomerulonephritis with little or no glomerular staining for immunoglobulin by immunofluorescence microscopy [7], observed in patients with antineutrophilic cytoplasmic autoantibody-associated glomerulonephritis. Characteristics of these three diseases were not found in our renal specimen and ELISA test for ANCA was also negative in our patient.

Cases of such pauci-immune crescentic glomerulonephritis occurring in SLE are very rare. Schwartz et al. [10] in 1983 reported 4 cases of PIGN with SLE . Charney et al indicated that the glomerular feature of pauci-immune lupus nephritis isintracapillary hypercellularity with occasional crescents [11]. In contrast, ANCA-associated pauci-immune glomerulonephritis is characterized by focal segmental necrotizing glomerulonephritis associated with extracapillary proliferation of cells in Bowman's space to form glomerular crescents with no or minimal intracapillary hypercellularity. There is greater disruption of Bowman's capsule than in those occurring in immune complex crescentic glomerulonephritis [12]

The pathogenesis that is distinct from all other immune complex-mediated glomerulonephritis cases, namely, immune complex deposition and anti- glomerular membrane antibody reaction . Development of diffuse proliferation with scanty immune deposits remains unclear. It is proposed that delayed-typed hypersensitivity is involved which is a manifestation of cell-mediated rather than antibody/immune complex-mediated glomerular injury to explain "pauci-immune" proliferative crescentic glomerulonephritis[13].

Cunningham et al had found the role of cell mediated immunity in the development of crescents with absence of antibodies and complements [13]. This would involve the interaction of endothelial cells with lymphocytes, monocytes, and neutrophils, activated to cause glomerular injury independent of antibodies or immune complexes .More than 90% of patients with PICGN have circulating ANCA. The role of ANCAs in the pathogenesis of glomerulonephritis is not fully understood, although it has been suggested that ANCAs activate neutrophils and monocytes within the glomerular capillaries, resulting in necrotizing glomerular injury. In light microscopy of PICGN, glomeruli showed segmental glomerular basement membrane breaks, necrosis, and crescents, often at varying stages of organization, ranging from cellular to fibrocellular to fibrous [14]. Unaffected portions of the glomeruli do not show significant proliferation [6]. Renal biopsy of our patient showed endocapillary hypercellularity with evidence of cellular/fibrocellular crescent. These features are suggestive of lupus nephritis . However, the IF examination of our patient's renal biopsy showed negative staining for immunoglobulins. Thus, it does not fulfill the ISN/RPS classification for lupus nephritis.

Hence our patient had pauci-immune crescentic glomerulonephritis in the background of SLE.

No standard treatment protocol has been followed for PICGN in SLE because cases are rare, but the use of the combination of cyclophosphamide and corticosteroids with variable evolution is common [11][15]. Cases reported by Akhtar et al. [15] had responded to steroids and cyclophosphamide treatment. Three of five patients presented by Charney et al. [11] also responded to therapy. Our patient had responded well to cyclophosphamide and prednisolone.

CONCLUSIONS

In conclusion, ANCA-negative pauci-immune glomerulonephritis cases in patients with systemic lupus erythematosus are rare and should be considered as a distinctive identity . Cell mediated immunity with T cell activation is the likely pathogenesis for underlying glomerular injury. Such patients should be treated as ANCA associated pauci-immune crescentic glomerulonephritis . Further research studies are required to study risk factors , treatment protocols and prognosis.

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