INTRODUCTION
The renal involvement is common in any form of systemic vasculitis. These include classic polyarteritis nodosa, Wegener’s granulomatosis, microscopic polyarteritis, Churg-Strauss syndrome, and the hypersensitivity vasculitides (including Henoch-Schönlein purpura, mixed cryoglobulinemia, and serum sickness). Also vasculitis secondary to rheumatological disorders such as rheumatoid arthritis can lead to renal involvement. We will discuss the clinical manifestation and approach to each sub category of the renal involvement secondary to vasculitis.

PATHTOLOGY
Vasculitis can lead to renal involvement in multiple ways. Involvement of medium-sized arteries is characteristic of classic polyarteritis nodosa (PAN). In comparison, the smaller vessels — venules, capillaries, arterioles —are typically involved in microscopic polyarteritis nodosa (mPAN) and Wegener’s granulomatosis (WG). In this setting, the major finding is a focal (involving some but not all glomeruli), necrotizing glomerulonephritis, often with prominent crescent formation. There are several lines of evidence to suggest that the finding of a necrotizing glomerulonephritis without immune deposits reflects a systemic vasculitis in most cases. Many patients already have systemic symptoms suggestive of a systemic vasculitis. Those patients with disease limited to the kidney often subsequently develop systemic findings, such as pulmonary lesions in Wegener’s granulomatosis. Patients with limited renal involvement typically have circulating antibodies directed against neutrophilic cytoplasmic antigens, a finding that is primarily seen in only two other disorders: Wegener’s granulomatosis and microscopic polyarteritis.

Crescentic Glomerulonephritis: It is a pathologic term which correlates to the clinical term rapidly progressive renal failure. It is secondary to disruption of glomerular capillaries characterized morphologically by extensive crescent formation. It is the most aggressive structural phenotype in the continuum of glomerular inflammation. It is a nonspecific response in vasculitic disorders wherein rents are induced in the glomerular capillary wall. Crescents are secondary to movement of

Fig 1a: Hypercellular circumferential crescent
plasma products including fibrinogen into bowman’s space with subsequent fibrin formation and excessive proliferation of the parietal cells of the glomeruli which are secondary to release of pro-inflammatory cytokines. The stage of active inflammation is often followed by the development of fibrocellular and fibrous crescents. This is important clinically because fibrous crescents represent a stage of the disease that is not likely to respond to immunosuppressive therapy.

Renal diseases other than crescentic glomerulonephritis that can cause rapidly progressive renal failure (RPRF) which should be considered as differential to renal involvement in vasculitis include acute thrombotic microangiopathy, atheroembolic renal disease, acute tubular necrosis, acute tubulointerstitial nephritis, acute cortical necrosis and collapsing focal segmental glomerulosclerosis (FSGS). Crescentic glomerulonephritis can be classified based on immunopathologic categories into 4 types (Table1). These have different frequencies based on the age group.

ANTIGBM ANTIBODY

In cases of anti-GBM antibody disease circulating antibodies are directed against an antigen intrinsic to the glomerular basement membrane. This disorder may present with glomerulonephritis alone. Depending on the presence or absence of renal involvement the disease is labeled as Goodpasture’s syndrome and Goodpasture’s disease respectively. Circulating autoantibodies, directed against an antigen intrinsic to GBM {principal target being NC1 domain of the alpha-3 chain of type IV collagen (alpha-3(IV) chain)},

![Fig 1b: Normal glomerulus](image1)

![Fig 2a: Characteristic breaks in the glomerular basement membrane](image2)

![Fig 2b: normal glomerular capillary loop showing the fenestrated endothelial cell, glomerular basement membrane, and podocytes](image3)

![Table 1: Classification of Crescentic glomerulonephritis](table1)

<table>
<thead>
<tr>
<th>Type of Crescentic Glomerulonephritis</th>
<th>Syndrome</th>
<th>Age preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Anti-GBM</td>
<td>More common in children</td>
</tr>
<tr>
<td>Type 2</td>
<td>Immune complex</td>
<td>More common in children</td>
</tr>
<tr>
<td>Type 3</td>
<td>Pauci-immune</td>
<td>More common in adults</td>
</tr>
<tr>
<td>Type 4</td>
<td>Double-antibody positive disease</td>
<td></td>
</tr>
</tbody>
</table>
I. Minimal mesangial LN

Class/Type: I.

Features: Normal glomeruli by all techniques. Normal on LM but deposits on immunohistology & or EM.

Subtype: I.

II. Mesangial proliferative LN

Class/Type: II.

Features: A. Mesangial widening & /or mild hypercellularity
B. Mesangial cell proliferation

Subtype: II.

III. Focal proliferative (< 50% of glomerulus) LN

Class/Type: III.

Features: A. Active lesions
B. Active and chronic lesions
C. Chronic lesions

Subtype: III.

IV. Diffuse proliferative LN (Severe mesangial/mesangiocapillary with extensive subendothelial deposits. Mesangial deposits always present & frequent subepithelial deposits)

Class/Type: IV.

Features: A. with segmental lesions
B. with active necrotising lesions
C. with active & sclerosing lesions
D. with sclerosing lesions

Subtype: IV.

V. Membranous LN

Class/Type: V.

Features: A. Pure membranous GN
B. associated with lesions of category II

Subtype: V.

VI. Advanced sclerosing (> 90%) LN

Class/Type: VI.

Features: Normal glomeruli by all techniques. Normal on LM but deposits on immunohistology & or EM.

Subtype: VI.

Table 2: Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class/Type</th>
<th>Features</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Minimal mesangial LN</td>
<td>Normal glomeruli by all techniques. Normal on LM but deposits on immunohistology &amp; or EM</td>
<td>I.</td>
</tr>
</tbody>
</table>
| II. Mesangial proliferative LN | A. Mesangial widening & /or mild hypercellularity
B. Mesangial cell proliferation | II. |
| III. Focal proliferative (< 50% of glomerulus) LN | A. Active lesions
B. Active and chronic lesions
C. Chronic lesions | III. |
| IV. Diffuse proliferative LN (Severe mesangial/mesangiocapillary with extensive subendothelial deposits. Mesangial deposits always present & frequent subepithelial deposits) | A. with segmental lesions
B. with active necrotising lesions
C. with active & sclerosing lesions
D. with sclerosing lesions | IV. |
| V. Membranous LN | A. Pure membranous GN
B. associated with lesions of category II | V. |
| VI. Advanced sclerosing (> 90%) LN | Normal glomeruli by all techniques. Normal on LM but deposits on immunohistology & or EM | VI. |

in response to an unknown inciting stimulus. Typically these antibodies are of IgG subtype but sometimes IgA or IgM subtypes are also seen.

**Epidemiology** – It is a rare disease. It is estimated to occur in less than one case per million population and fewer than 20% of cases of rapidly progressive glomerulonephritis. Younger patients (<30 years) are more likely to present with the full constellation of Goodpasture’s syndrome whereas older patients (>50 years) present with isolated glomerulonephritis. Slight male predominance in the younger age group and a female predominance in the older age group is seen.

**Clinical presentation** – Major manifestations include acute renal failure and pulmonary manifestations (variable presence). Systemic complaints and signs, such as malaise, weight loss, fever, or arthralgia, are typically absent. The presence suggests concurrent systemic vasculitis. **Diagnosis** - Acute glomerulonephritis, particularly if accompanied by rapid progression and pulmonary hemorrhage suggests the possibility of anti-GBM disease. Demonstration of anti-GBM antibodies and renal biopsy aid in establishing the diagnosis. Renal biopsy on light microscopy usually shows crescentic glomerulonephritis, immunofluorescence microscopy demonstrates pathognomonic finding of linear deposition of IgG along the glomerular capillaries. **Treatment** – Plasmapheresis remains the mainstay of treatment with removal of 2-4 L of plasma with replacement through 5% albumin or FFP. Other immunomodulatory therapy with corticosteroids (methylprednisolone pulse @ 1 mg/kg body wt) and cytotoxic therapy (cyclophosphamide - 2 mg/kg daily, Azathioprine - 1-2 mg / kg daily) have also been tried in these patients.

**LUPUS NEPHRITIS**

Probably the most serious complication of SLE with 30-50% patients detected to have lupus nephritis at diagnosis. 60% adults and 80% children with SLE develop renal abnormalities. The renal manifestations of SLE tend to appear within the first 2 yrs of SLE. Almost half of these cases have asymptomatic urine abnormalities. Proteinuria is a dominant feature with haematuria almost always present but never in isolation. It can present as nephritic syndrome, severe nephritis, occasionally ARF and rarely with decreased GFR as primary manifestation. The lupus nephritis is lately classified by the WHO (Table 2).

**Lab investigations** - Monitoring of cases of LN is done with regular urinalysis and serum creatinine levels. Screen all patients with proteinuria for ANA. Anti ds DNA is present in about 60% with SLE and levels often reflect disease activity. Anti ds DNA decrease with treatment whereas ANA remains persistently positive. Complement levels are decreased in ¾ of untreated patients especially with nephritis. APLA is positive in 30-50 % cases and associated with renal arterial, venous & glomerular thrombosis.

**Indication for biopsy in LN:** Initial biopsy before treatment is indicated in cases with nephritic urine sediment and glomerular hematuria with proteinuria (0.3-0.5g/day) + low C3 + anti ds-DNA positive. Initial biopsy is also indicated to classify the LN. Repeat biopsy (during or after treatment) is indicated when patients have unexplained worsening proteinuria, unexplained worsening of renal function, persistent glomerular hematuria with proteinuria, persistent nephrotic syndrome, persistent active sediment, recurrence of active urinary sediment after remission and persistent activity on serology despite adequate treatment. Predictors of poor prognosis include black race, male, anaemia, increased creatinine levels, nephrotic range proteinuria, glomerular and tubulointerstitial scarring, severe tubulointerstitial nephritis and chronicity index > 3. Treatment aims to recognise early renal involvement, induce and maintain remission, decrease risk of progression to ESRD and minimise treatment related toxicity (esp. during maintenance phase). Summary of the specific immunosuppressive treatment options for LN are enumerated in table 3. ACR criteria to define response are enumerated in table 4.
necrotizing glomerulonephritis which is pauci-immune on microscopic polyangiitis there is necrotizing inflammation involving medium sized muscular arteries is seen whereas in Classic pattern (PAN) systemic necrotizing vasculitis.

Both the conditions can be differentiated on renal biopsy. In Classic pattern (PAN) systemic necrotizing vasculitis involving medium sized muscular arteries is seen whereas in microscopic polyangiitis there is necrotizing inflammation.

Table 3: Summary of the treatment of LN

<table>
<thead>
<tr>
<th>Class of LN</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Class I and II</td>
<td>No specific treatment</td>
</tr>
<tr>
<td>Class III mild disease with subnephrotic proteinuria and stable GFR</td>
<td>No specific treatment</td>
</tr>
<tr>
<td>Class III with karyorrhexitis, necrosis or crescents on biopsy, nephrotic range proteinuria or progressive renal failure</td>
<td>Treat as class IV</td>
</tr>
<tr>
<td>Class IV mild or no renal failure</td>
<td>MMF and steroids</td>
</tr>
<tr>
<td>Class IV moderate to severe renal failure</td>
<td>Cyclophosphamide pulses and steroids</td>
</tr>
<tr>
<td>Class V with subnephrotic proteinuria and stable GFR</td>
<td>No specific immunsuppression</td>
</tr>
<tr>
<td>Class V with nephrotic proteinuria and progressive renal failure</td>
<td>Choice between cyclosporin, alkylating agents and MMF</td>
</tr>
<tr>
<td>Mixed class V and class IV</td>
<td>Multi-target therapy with tacrolimus, MMF and steroids</td>
</tr>
</tbody>
</table>

Table 4: ACR criteria to define response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Improved</th>
<th>No Change</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function</td>
<td>&gt;25% increase in GFR from baseline</td>
<td>Stable values</td>
<td>&gt;25% decrease in GFR from baseline</td>
</tr>
<tr>
<td>Proteinuria (protein:creatinine ratio)</td>
<td>Partial response: &gt;50% lower and between 0.2 and 2.0</td>
<td>Complete response if ratio is &lt;0.2</td>
<td>&gt;100% increase in ratio</td>
</tr>
<tr>
<td>Active sediment</td>
<td>Active urine sediment changes to an inactive sediment</td>
<td>No specific treatment</td>
<td>Previously inactive sediment becomes an active sediment</td>
</tr>
</tbody>
</table>

PAUCI IMMUNE GN – ANCA ASSOCIATED VASCULITIS

The pauci immune glomerulonephritis is generally secondary to ANCA associated vasculitis. Two main types of ANCA assays include indirect immunofluorescence assay which is more sensitive and enzyme-linked immunosorbent assay using purified specific antigen which is more specific. The major vasculitic disorders included in this subgroup include Wegener’s granulomatosis, microscopic polyangiitis and Churg Strauss syndrome.

WEGENER’S GRANULOMATOSIS

Essentially all patients with classic or limited Wegener’s granulomatosis have upper airway or pulmonary involvement. In patients of renal failure with persistent rhinorrhoea, nasal discharge (purulent / bloody), dyspnoea or hemoptysis, Wegener’s remain one of the major differential. Patients with renal failure in Wegener’s granulomatosis can have other systemic involvement in the form of joints (myalgias, arthralgias, arthritis), eyes (conjunctivitis, episcleritis, uveitis), skin (vesicular, purpuric lesion), CNS (cerebral hemorrhage), external ophthalmoplegia, tinnitus, hearing loss) and Heart (pericarditis, myocarditis). Diagnosis is mainly based on tissue biopsy from the site of active disease (nasopharyngeal lesion preferred) which reveals inflammation with granulomatous lesions. Kidney biopsy reveals segmental necrotizing glomerulonephritis which is pauci-immune on immunofluorescence.

MICROSCOPIC POLYANGITIS VS CLASSIC PAN

Both the conditions can be differentiated on renal biopsy. In Classic pattern (PAN) systemic necrotizing vasculitis involving medium sized muscular arteries is seen whereas in microscopic polyangiitis there is necrotizing inflammation of small arteries and veins. In microscopic PAN involvement of interlobular arteries and arterioles is seen with histology revealing focal segmental necrotizing glomerulonephritis. Pulmonary involvement is less common in microscopic PAN. However, only a small number of vessels are usually obtained by percutaneous biopsy and it is common to see no affected vessels on this limited specimen. Urinalysis typically reveals active urine sediment in renal vasculitis due to acute glomerulonephritis/ necrosis. One exception may occur in patients with classic polyarteritis nodosa in which the muscular arteries are involved particularly when it leads only to incomplete narrowing, then there may only be glomerular ischemia (not necrosis) and the urinalysis may be relatively normal.

CHURG STRAUSS SYNDROME

It is a multsystem disorder associated with allergic rhinitis, asthma, and peripheral eosinophilia. Most common organ involved is lung followed by skin. Renal involvement is rare. The main pathologic features of CSS include granulomatosis, vasculitis, and eosinophilia. The pathogenesis is likely to be auto immune with prominence of allergic features, heightened T cell immunity, altered humoral immunity and immune complex disease. The clinical features include prodromal phase (characterized by atopic disease, allergic rhinitis, and asthma), eosinophilic phase (features of the eosinophilic phase include peripheral blood eosinophilia and eosinophilic infiltration of multiple organs) and vasculitis phase - nonspecific constitutional symptoms and signs, especially fever, weight loss and malaise. The renal involvement is seen either in the eosinophilic phase or more commonly in the vasculitic phase in the natural history of the disease.

RENAI INVOLVEMENT IN RA ASSOCIATED VASCULITIS

Renal disease, compared to the skin, peripheral nerves, and eyes, the kidneys are much less likely to be involved in extra-articular RA. Nevertheless, several forms of renal disease are known to occur. The major forms of renal disease in RA patients are acute
Renal Involvement in Vasculitis

tubular necrosis related to nonsteroidal anti inflammatory drug use, secondary amyloidosis due to the chronic inflammation, nephrotic syndrome secondary to membranous nephropathy, and, in a small number of cases, true vasculitis, consisting of either necrotizing glomerulonephritis or destructive inflammation within the walls of renal arteries. Secondary amyloidosis is now relatively rare in RA, because of more effective means of controlling inflammation. In addition, because gold and penicillamine are now rarely used in RA, membranous nephropathy is observed less often than in the past.

Both renal artery involvement similar to that which occurs in polyarteritis nodosa (without aneurysm formation) and glomerulonephritis reminiscent of the type associated with microscopic polyangiitis or Wegener’s granulomatosis are well described in the medical literature. Theglomerular pathology caused by vasculitis in RA is a pauci-immune glomerulonephritis (similar to that seen in Wegener’s granulomatosis), sometimes associated with crescent formation and the presence of antineutrophil cytoplasmic antibodies (ANCA). This type of glomerular disease contrasts with common beliefs about the pathophysiology of RV in other organs, generally considered to result from an immune complex-mediated process characterized by the organ deposition of rheumatoid factor, complement components, and other immunoreactants.

SomereportedcasesofglomerulonephritisinRAmayrepresent the co-occurrence of two diseases (eg, an ANCA-associated vasculitis and RA). However, a number of glomerulonephritis cases accompanied by typical RV manifestations in other organs have occurred in settings classic for the development of RV. Thus, it seems safe to conclude that in a minority of patients with RV, clinically significant renal disease does occur.

In contrast to other diseases associated with pauci-immune glomerulonephritis, however, anti-neutrophil cytoplasmic antibodies (ANCA) do not appear to play a role in necrotizing glomerulonephritis in RV. One report indicated that RA patients with renal disease are more likely to have circulating ANCA, but this finding has not been duplicated by other investigators. Moreover, the antigens against which these ANCA are directed are neither proteinase-3 nor myeloperoxidase, the two antigens most strongly associated with the ANCA response in systemic vasculitis. In short, there is no compelling evidence that ANCA have any role in RV, even in the rare cases of glomerulonephritis. When ANCA directed against proteinase-3 or myeloperoxidase do occur in RA accompanied by clinical findings compatible with vasculitis, the simultaneous occurrence of two diseases must be considered.

REFERENCES
3. Dubois textbook - LE
6. Archives of Internal Medicine 2001;161