Case of the Week 3

CLINICAL HISTORY:
46 year old female, known Type 2 diabetic since 6 years and hypertensive since 8 years on treatment with ACE inhibitors, suffered a fall at home 3 weeks back and fractured her left neck of femur. Hospital investigations at presentation revealed proteinuria (urine dipstick 2+) and serum creatinine of 1.7 mg% (150.28 μmol/L). Four days into hospital stay she developed high grade fever and creatinine progressively rose to 3.5 mg% (309 μmol/L) associated with reduction in urine output and dialysis dependent status by two weeks after onset of fever. There was no history of sore throat or upper respiratory tract infection.

EXAMINATION:
Mild pedal edema +, Fundus grade 2 diabetic retinopathy, Systemic examination: no signs of neuropathy, no organomegaly.
BP: 160/98 mmHg (at presentation)

INVESTIGATIONS:
Echocardiography: LV hypertrophy
Urine Albumin 2+, Sugar- present, ketones- absent, RBC: 20-25/hpf, 30% dysmorphic, Pus cells 8-10/hpf, Casts: Granular casts and few RBC casts +.
Urinary culture: no growth
Urea: 89 mg% (32.1 mmol/L), Creatinine: 3.5 mg% (309 μmol/L)
HIV/HBsAg/HCV/ANA/anti dsDNA/ANCA/anti GBM antibodies/ASO titres: Negative
Total protein/Albumin/Glob: 5.2/2.4/2.8 g/L
Complement C3: 98 mg% (0.98g/L), C4: 36 mg% (0.36 g/L)
USG abdomen: B/L normal sized kidneys
Hemoglobin:12 g% (120 g/L), TLC:18,900/mm3, DLC: P87 L10 E1 M2, Platelets:300 X 10 3/mm3 (300 x 10 9/L)

In view of rapidly progressive renal failure (RPRF) a renal biopsy was performed. Representative images of light microscopy and DIF studies (IgA, IgG and C3) are provided. The glomeruli were negative for IgM and C1q and showed equi intense staining for both kappa and lambda light chains.
MICROSCOPY
Microscopic examination shows enlarged glomeruli exhibiting diffuse mesangial matrix expansion, and capillary wall thickening. Few glomeruli show hyalinosis lesions (subendothelial deposition of hyaline material) and segmental solidification of the tufts. In addition, there is segmental and global, diffuse intracapillary neutrophil infiltration with varying degree of mesangial cell proliferation. The thickened capillaries do not show membrane texture alterations in silver methenamine stained sections. An occasional glomerulus (not shown) revealed extracapillary proliferation and partial cellular crescent formation. There was no evidence of tuft necrosis. Arteries showed marked fibrointimal hyperplasia and arterioles (including the hilar branches) showed marked transmural hyalinosis lesions.

In a patient with diabetes mellitus, the features were suggestive of a proliferative glomerulonephritis arising in a background of diabetic nephropathy.

**DIRECT IMMUNOFLUOROSCENCE EXAMINATION**
DIF studies revealed intense 3+ mesangial and segmental capillary wall coarse granular/confluent staining for IgA, 1+/2+ similar segmental staining for IgG, and 3+/4+ staining for C3. Kappa and lambda chains showed equi-intense 3+ mesangial and capillary wall granular staining. The glomeruli were negative for IgM and C1q.

Linear smudgy staining along the glomerular capillaries, Bowman’s capsule and tubular basement membranes for IgG, characteristically seen in diabetic nephropathy was also noted. EM studies (performed at another centre) revealed subendothelial and mesangial electron dense deposits with few subepithelial humps.

**DIAGNOSIS:**

Considering the clinical scenario and pathological findings, a diagnosis of IgA dominant post infectious glomerulonephritis occurring in a background of diabetic nephropathy was rendered.

**FOLLOW UP:**

Further investigations revealed an abscess at the site of femoral fracture and culture yielded growth of Methicillin resistant Staphylococcal aureus (MRSA). A repeat serum complement assay showed hypocomplementemia (low C3 with normal C4 levels).

Renal dysfunction persisted despite vigorous antibiotic treatment, wound debridement and other supportive measures including a short course of steroids. The patient continues to be dialysis dependent 12 weeks after the disease onset.

**DISCUSSION:**

IgA dominant post infectious glomerulonephritis is relatively recently recognized entity with a distinct clinical spectrum and characteristic pathological findings [1]. Since it is associated with Staphylococcal infection in vast majority of cases, it has also been called as “IgA dominant post staphylococcal glomerulonephritis”.

IgA-dominant PIGN is most frequent in older patients. Underlying diabetes mellitus is among the most common systemic diseases [6], present in 55% of patients in a large series [2]. Less frequently reported predisposing conditions to infection include malignancy, IV drug use, alcoholism, HIV infection and atopic dermatitis.
The most common site of infection is skin; other sites, including lung, urinary tract, bone, heart, deep-seated abscesses and upper respiratory tract have also been reported. The infectious agent is Staphylococcus in vast majority (mainly Staphylococcus aureus with few cases showing presence of coagulase negative staphylococcal epidemidis)[4,5]. Several patients (nearly 50%) in a large series show MRSA (Methicillin resistant Staphylococcal aureus) infection [2].

The commonest histologic pattern of glomerular injury in IgA-dominant PIGN is endocapillary proliferative and exudative glomerulonephritis, identical to that seen in the conventional (non IgA dominant) post streptococcal glomerulonephritis. Few cases showing pure mesangial proliferative glomerulonephritis, crescentic glomerulonephritis and rarely membranoproliferative pattern of injury have also been described.

DIF studies reveal dominant deposits of IgA, with or without IgG, which is typically weaker in intensity and distribution. C3 staining is usually more intense than IgA. C1q staining is either absent or weak in majority of cases. Kappa and lambda stain with equal intensity, an important feature to distinguish this entity from IgA nephropathy which usually shows a lambda light chain dominant staining pattern (owing to lower than normal serum IgA1 kappa: lambda ratio). Ultrastructural studies show mesangial electron dense deposits and subepithelial humps. Subendothelial deposits are less common.

The pathogenetic mechanisms of the selective IgA deposition in patients with post staphylococcal glomerulonephritis are not well understood, but are likely to involve specific host-pathogen interactions. Some of the reported cases had increased serum IgA levels, suggesting activation of selective IgA immune responses. As majority of patients with IgA-dominant APIGN are diabetics, and several studies have shown that diabetics have increased serum IgA and IgA-containing circulating immune complexes compared with nondiabetics, a specific initiation of IgA mediated immune response in these patients is likely. Proposed explanations for the high serum IgA levels in diabetics include decreased IgA hepatic clearance caused by serum IgA1 hypersialylation and increased synthesis of IgA in association with subclinical mucosal infection or as a potential immune response to advanced glycation endproducts (AGE’s).[10-15]

Differential diagnosis includes mainly IgA nephropathy/HSP nephritis, which need to be carefully distinguished.[16]

Features favouring IgA-dominant APIGN over IgA nephropathy include:

**Clinical features**

- Intercurrent culture-documented staphylococcal infection
- Hypocomplementemia
- Presentation in older age
- History of diabetes mellitus
- Acute renal failure at presentation

**Pathologic features**

- Endocapillary proliferation with neutrophil infiltration on LM
- Stronger staining for C3 than IgA on IF
- ‘Starry sky’ pattern on IF
- Lack of lambda chain dominance in DIF studies
- Subepithelial ‘humps’ on EM

Prognosis of IgA dominant PIGN is generally considered unfavourable. In a large series of patients [2], 43% had persistent renal dysfunction and 41% progressed to ESRD. Full recovery was noted in only 16% of patients. Treatment strategies are not yet standardized however the current body of evidence does not support role for steroids in addition to therapy aimed at containing the infectious focus.

REFERENCES:


