Renal Sciences - Clinical Forum Renal Involvement in Bacterial Endocarditis

Valentine Lobo*, Shishir Gang, SA Kale, N Kulkarni, LJ Shah, MM Rajapurkar and VN Acharya

Bacterial endocarditis is not an uncommon disorder in clinical practice. The 4 cases presented here represent a major part of the spectrum of renal involvement in bacterial endocarditis.

Introduction

Bacterial endocarditis is not an uncommon disorder in clinical practice. When it presents with renal symptoms; it’s important to make a proper diagnosis to enable appropriate management the end result of which could be most gratifying as illustrated by these 4 cases.

Case 1

A 22 years old housewife not previously known to have any major illness was admitted in our hospital for complaints of moderate grade fever and chills intermittently for 6 months, oliguria and haematuria for 10 days and rapidly progressive swelling of the face, feet and abdomen over 4-5 days. She also had occasional shortness of breath for 3 months and her urinalysis prior to referral showed 4+ albuminuria and serum creatinine of 1.38 mg/dl.

Examination revealed a young female patient of height 145 cm, weighing 39.2 kg, with a regular pulse of 96/minute, blood pressure of 130/80 mmHg with no postural drop, a raised JVP with prominent C-V complexes, 5+ oedema, marked pallour and finger clubbing. Her temperature was 99.2°F, respiratory rate 26/min, she had few purpuric patches on the lower limbs and the fundus showed a single Roth spot.

Cardiovascular system revealed a hyperdynamic apex beat, dilated left ventricle; long standing right ventricular hypertrophy and systolic and diastolic thrills. Auscultation revealed a loud pulmonary 2nd heart sound, a prominent S3 gallop, a grade IV/VI murmur of mitral regurgitation and tricuspid regurgitation and a mid-diastolic rumbling murmur of mitral stenosis.

She also had fine basal rales in the chest, abdominal ascites, a tender hepatomegaly and a palpable splenic tip. Her routine investigations are shown in Table 1 and chest roentgenogram in Fig. 1. 2D-echocardiography revealed tight mitral stenosis, mitral regurgitation, moderate pulmonary hypertension and large vegetations on the tip of the anterior mitral leaflet.

Renal biopsy revealed diffuse proliferative glomerulonephritis with partial cellular crescents in 4 out of 9 glomeruli; polymorphonuclear exudate and interstitial oedema, while immunofluorescence showed coarse granular mesangial deposits of IgG and C3.

Address for correspondence:
*Department of Nephrology,
Puljibhai Patel Urological Hospital,
Dr. V.V. Desai Road, Nadiad - 387 001, Gujarat.

Case 1. (Silver methanamine x 200).
Diffuse proliferative glomerulonephritis.
She was treated initially with 2 million units of crystalline penicillin every 6 hours, bed rest, salt restriction and intravenous frusemide. She achieved good diuresis with weight loss and disappearance of oedema; but took discharge against medical advice after 7 days and has since been lost to follow up.

Case 2

A 10 years old boy, a product of a non-consanguineous marriage, with repeated lower respiratory tract infections in childhood. He was referred to our OPD with complaints of 3 months high-grade fever with chills and throat pain, not responding to erythromycin and paracetamol, gradual development of eyelid and facial puffiness, pedal oedema; red to cola-coloured urine and then decreased urine output for 10 days. Urinalysis showed 4+ albuminuria, pyuria 15-20 cells HPF and 50-70 RBCs HPF.

Examination revealed a child of height 128 cm; weighing 25 kg with a normal regular pulse of 90/minute, blood pressure of 120/80mmHg, temperature of 99°F; mild pallor, clubbing and grade 3+ bilateral pitting pedal oedema.

Examination of the cardiovascular system revealed long standing right ventricular enlargement; normally situated slightly hyperdynamic apex; a loud pulmonary component of the 2nd sound and an S4 gallop; with a grade III/VI left parasternal pansystolic murmur of ventricular septal defect and an ejection systolic right sided murmur.

All other systemic examination was unremarkable. Chest chest x-ray showed a pulmonar plethora and ECG an incomplete right bundle branch block. 2D-echocardiography revealed a moderate sized septum secundum atrial septal defect, a 2.5 mm muscular ventricular septal defect with dual left to right shunt and a pulmonary to systemic blood flow of 2:1.

Renal biopsy showed diffuse endocapillary and mesangial proliferative glomerulonephritis with a polymorphonuclear exudate and coarse granular mesangial deposits of IgG, IgM and C3 on immunofluorescence.

The patient was treated initially with intravenous crystalline penicillin and gentamicin for 2 weeks and thereafter with intravenous Ceftriaxone once daily for 4 weeks on an out patient basis.

His initial improvement was rapid but haematuria and proteinuria (up to 2.5 g/24 hours) persisted for 3 months before complete resolution and he is now scheduled to undergo cardiac catheterization and corrective surgery in June, 2000.

Case 3

A 28-year-old staff nurse was admitted from our OPD in August, 1999 with complaints of high-grade fever and chills 2 months earlier; which had been treated with intravenous ofloxacin followed by eyelid puffiness, progressive swelling of face, feet and whole body, gross oedema, haematuria, decreased urine output albuminuria of 2+, mildly increased serum creatinine of 1.7 mg/dl, weakness and easy fatigability.
for 1 month. She had been previously diagnosed as having ventricular septal defect at the age of 15 years which she had forgotten and she had not undergone recent instrumentation; dental extraction, or surgery.

Examination revealed a young female patient of height 162 cm weighing 45 kg with a regular pulse of 88/min, haemodynamically stable with a temperature of 99°F, respiratory rate of 18/min, mildly raised jugular venous pressure with prominent a waves and finger clubbing.

Examination of the cardiovascular system revealed a hyperdynamic laterally displaced apex beat, a right ventricular heave, an accentuated pulmonary second heart sound, a prominent S3 gallop, a harsh grade V/VI pansystolic murmur in the left parasternal region radiating to the right side of the sternum and a pulmonary area grade III/VI ejection systolic murmur. She also had a tender hepatomegaly.

Chest roentgenography (Fig. 3) revealed massive cardiomegaly and a dilated pulmonary artery and ECG showed biventricular hypertrophy. 2D-echocardiography revealed a moderate sized perimembranous ventricular septal defect with a large left to right shunt, severe pulmonary hypertension and a suspicion of jet lesion in the right ventricle.

As the patient was allergic to penicillin; she was treated with intravenous cefazolin 2 g 8 hrly for 6 weeks with 160 mg of gentamicin for the first 2 weeks.

Three months after treatment she had marked decrease in proteinuria and haematuria; the infection was under control and she is currently planned for defect closure surgery.

Case 4

A 50-year-old patient who underwent cardiac surgery for atrial septal defect closure in October, 1999 developed fever; recurrence of dyspnoea and palpitations in January, 2000; which did not respond to oral amoxicillin clavulinate. Her echocardiogram showed development of fresh tricuspid regurgitation. A diagnosis of infective endocarditis complicating cardiac surgery was made and she was treated outside with intravenous vancomycin 1.0 g 12 hrly and amikacin 500 mg 12 hrly for 14 days. Although her fever responded to this treatment she developed anorexia, vomiting and increase in serum creatinine from 1.1 mg/dl to 4.3 mg/dl. She was switched to cefazidine 1.0 g daily and ticloplatin 400 mg daily but became progressively anuric with further rise in serum creatinine to 8.3 mg/dl and was admitted in emergency in our hospital in March, 2000.

Examination revealed an ill looking middle aged female patient weighing 55kg with an irregularly irregular pulse of 102/min and an apex pulse deficit of 15-16 beats/min. She was haemodynamically stable slightly tachypnoeic with a temperature of 99°F. She had a markedly raised JVP with prominent C-V complexes, pallor, clubbing and bilateral grade 3+ pitting pedal oedema.

Cardiovascular examination revealed an enlarged right ventricle a normally split second heart sound; with an accentuated pulmonary component, and a parasternal grade II/VI pansystolic murmur of tricuspid regurgitation.

She also had ascites, tender hepatomegaly and bilateral moderate sensorineural deafness.

Her chest roentgenogram revealed mild cardiomegaly with hilar congestion and a left lower zone opacity. Serial ECGs revealed an atrial flutter with a 2:1 and 3:1 block acceleration dissociation. 2D-echocardiography showed normal valves and an intact inter atrial septum; while renal biopsy showed moderately severe diffuse mesangial proliferative glomerulonephritis, patchy acute tubular necrosis regeneration and an interstitial infiltrate; while coarse granular mesangial deposits of IgG and C3 were seen on immunofluorescence.

The patient remained on alternate day haemodialysis for 3 weeks, her heart rate was controlled with oral verapamil 40 mg tds. Her output increased to more than 2 litres daily. She has become dialysis independent and will be followed up as her serum creatinine remains at 2.1 mg/dl at the time of discharge.

Discussion

The 4 cases presented here represent a major part of the spectrum of renal involvement in bacterial endocarditis. Renal failure has been noted to occur in 36% of bacterial endocarditis patient in a series of 204 cases [Conlon 1998] and to increase the odds ratio of dying by 5. It constituted the commonest chronic infection, associated with glomerulonephritis in the records of the Medical Research Council registry [Boulton-Jones 1986].

The pattern and incidence of renal involvement in infective endocarditis has changed considerably owing to the availability of antibiotics; better diagnostic aids; overall decline in rheumatic fever in western countries and the higher incidence of invasive procedures and cardiac surgery. Diffuse proliferative glomerulonephritis, secondary to fastidious or atypical organisms and an increased incidence among intravenous drug abusers have replaced the classical focal proliferative glomerulonephritis seen earlier in patients with structural heart disease and viridans streptococcal infections [Neugarton and Baldwin 1984].

The first case presented here however is a prototype of the cases seen in India where rheumatic heart disease and its complications are estimated to be responsible for 25-60% of all hospitalizations for heart disease. More than 1 million people are believed to suffer from rheumatic heart disease with an estimated 50,000 new cases being added every year. Severe symptomatic disease at an early age of around
**Table 1. Laboratory parameters at admission.**

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Pt. 1</th>
<th>Pt. 2</th>
<th>Pt. 3</th>
<th>Pt. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g%)</td>
<td>9.8</td>
<td>8.3</td>
<td>11.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Total leukocyte count</td>
<td>7700 mm</td>
<td>14100 mm</td>
<td>8100 mm</td>
<td>17100 mm</td>
</tr>
<tr>
<td>Sr. creatinine (mg/dl)</td>
<td>1.3</td>
<td>1.1</td>
<td>1.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Blood culture</td>
<td>No growth</td>
<td>No growth</td>
<td>No growth</td>
<td>No growth</td>
</tr>
<tr>
<td>Urease/albumin</td>
<td>3+</td>
<td>4+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td>Pus cells / HPF</td>
<td>5-10</td>
<td>2-5</td>
<td>2-5</td>
<td>-</td>
</tr>
<tr>
<td>Erythrocytes Casts</td>
<td>Plenty</td>
<td>25-30</td>
<td>5-0</td>
<td>-</td>
</tr>
<tr>
<td>WBC and RBC</td>
<td>Granular</td>
<td>Granular</td>
<td>Granular</td>
<td>Epithelial</td>
</tr>
<tr>
<td>24 hours urine protein</td>
<td>1.5 g</td>
<td>2.5 g</td>
<td>1.9 g</td>
<td>-</td>
</tr>
<tr>
<td>Serum protein (g%)</td>
<td>5.4 g</td>
<td>4.5 g</td>
<td>6.6 g</td>
<td>5.2 g</td>
</tr>
<tr>
<td>Albumin (g%)</td>
<td>2.8 g</td>
<td>2.5 g</td>
<td>3.2 g</td>
<td>2.9 g</td>
</tr>
</tbody>
</table>

20 years with no prior history of rheumatic fever in around 50% of patients and progression to critical heart disease or bacterial endocarditis within just 1-2 years are all salient feature all of which are noted in our first patient.

The predominance of renal symptoms; haematuria proteinuria; facial puffiness and decreased urine output compared to relatively mild or absent cardinal manifestations of cardiac disease like dyspnoea chest pain palpitations; changing murmers; embolic phenomena and skin lesions were particularly noticeable in our first 3 patients. One of them (patient 2) had actually been treated with steroids before referral and led to this patient having undiagnosed cardiac disease and being seen primarily in a specialist nephrology clinic. Renal dysfunction as the presenting manifestation of bacterial endocarditis leading to a clinical diagnosis of primary renal disease has been previously noted by Lerner and Weinstein 1966 and Neugarten and Baldwin 1984.

At the other end of the spectrum is the 4th case where several factors contributed to renal failure in a known case of cardiac disease following surgery. Immune complex nephritis; sepsicaemia and toxic tubular necrosis due to drugs; and even a possible interstitial nephritis all have been implicated in this form of renal failure which is now becoming commoner [Burton D Rose 1999].

The incidence and pattern of renal disease has been markedly altered by antibiotic therapy. Focal and diffuse proliferative glomerulonephritis were noted in a total of 75% of cases at autopsy in the pre-anti-biotic era with a higher incidence in subacute cases as compared to acute cases.

Kaufmann, et al. 1981 studied 99 patients with fever and underlying heart disease and defined renal involvement as one or more of the following findings present on at 2 occasions.

1. Red cell of 3+ casts or at least 10 red cells per high power field.
2. Proteinuria of 3+ on a random specimen or more than 500 mg/24 hours.
3. A decrease in creatinine clearance below 80 ml/min or serum creatinine at least 1.5 times the initial value.

In this study, 24 of 40 patients who had proven infective endocarditis, had glomerulonephritis and high titres of circulating immune complexes by conglutin assay; but these findings were absent in 59 patients with other causes of fever and heart disease glomerulonephritis has in fact been included in the Dukes criteria for endocarditis [Durack, et al. 1994].

The causes of renal failure in bacterial endocarditis in a study or 204 cases over 20 years has been reported by Conlon, et al. [1998]. Twenty-eight of these patients had immune complex nephritis; 19 patients had tubular necrosis due to drug toxicity. The septic syndrome accounted for 7 renal failure cases; followed by cardiac surgery in 6 cases; and 11 had other causes; while 8 patients had 2+ proteinuria, but normal serum creatinine.

**Aetiopathogenesis**

Circulating immune complexes have been linked most commonly to the development of infective endocarditis. Those patients with prolonged illness and antibody excess have been shown to have focal glomerular lesion and
subendothelial deposition of immune complexes containing IgG and C3; and were associated with activation of the classical complement pathway.

A unique role for *Staphylococcus aureus* with acute bacterial endocarditis has been proposed in the pathogenesis. Deposition of complexes containing staphylococcal antigen have been found in the glomerular basement membrane at subepithelial location during periods of antigen excess and associated with the direct activation of the alternative pathway by *Staphylococcus aureus*: Bayer and Theofilopoulos have mentioned that immune complexes may in fact be formed in situ in cardiac valves; and vegetations, which have been shown to contain IgG and IgM. This may provide a reservoir of immune complexes, that periodically enter the blood stream and also contribute to the destructive valvulitis previously considered to be purely ‘infectious’ in etiology.

Subra has reported two cases of bacterial endocarditis with c-ANCA positivity and no systemic vasculitis but nephrotic range proteinuria and rapidly progressive glomerulonephritis on renal biopsy. These cases as well as other reported by Wagner 1991 and Anganco 1993 whose patient had ineffective endocarditis with 3 different organisms and a pauci immune necrotizing crescentic glomerulonephritis with a single large subepithelial done shaped dense deposit on electron microscopy appear to indicate that c-ANCA may play a role in the pathogenesis of endocarditis related glomerulonephritis. The generation of c-ANCA may be secondary to a bacterial endocarditis associated, vasculitis which has been implicated in findings like Osler’s nodes and Janeway lesions.

**Pathology**

The 3 cases submitted to biopsy in our series showed evidence of a diffuse proliferative glomerulonephritis with mesangial deposits of IgG, IgM and C3 the classical pattern seen in immune complex glomerulonephritis. In our 4th case, we also found evidence of ischaemic and toxic tubular necrosis with recovery and an interstitial infiltrate similar to the case described by Anganco 1993 in which he found diffuse mesangial, endothelial and epithelial proliferation a focal fibrinoid necrosis neutrophilic exudate, cellular crescents in 1/3 of the glomeruli and acute tubular necrosis.

In addition Subra has described a necrotizing crescentic glomerulonephritis and membrano-proliferative glomerulonephritis with immune complex deposition that have also been mentioned in a number of cases.

**Clinical features and treatment**

The first 3 cases presented here are unique in their predominantly renal symptoms and signs with a total ignorance of severe pre-existing cardiac lesions in 2 of the patients. It is possible that other such cases may occur and be misdiagnosed as primary glomerulonephritis and treated with immunosuppressive therapy. For this reason and given the high frequency and unique clinical presentation of juvenile rheumatic heart disease in India, a thorough search to rule out bacterial endocarditis is warranted. Because of the widespread empirical treatment of fever with antibiotics blood culture also may prove unhelpful and clinical examination and 2D-echocardiography may clinch the diagnosis.

Case No. 4 is more typical of the cases routinely seen with renal failure being caused by sepsis, drugs and glomerulonephritis in a setting of bacterial endocarditis after cardiac surgery. Beaufils 1981 has shown that the renal biopsy may be particularly useful here to distinguish between glomerulonephritis caused by endocarditis and tubular necrosis caused by drug toxicity although the two may quite clearly co-exist as seen in this patient. The incidence of renal failure in bacterial endocarditis was reported to be 36% in Colons 1998 study. The risks associated with development of acute renal failure were identified as increased age, a history of hypertension, thrombocytopenia, the presence of *Staphylococcus aureus* and prosthetic valve infection.

All our 4 patients responded well to prolonged antibiotic therapy, even patient 4 became dialysis independent. This pattern was also observed by Beaufils 1981 with complete recovery and indefinite preservation of normal renal function occurring when infection was brought under prompt control. It appeared that with removal of the antigenic stimulus renal lesions healed completely.

This happy state of affairs did not occur when infection persisted. No recovery was then observed regardless of the histological pattern and the situation resembled more closely that of other chronic infections like shunt nephritis. Bayer, et al. 1990, Neugarten 1984 and Kaufmann 1981 found a very strong co-relation between titres of circulating immune complexes and resolution of infection. Persistent high titres were associated with failure to eradicate infection and ongoing glomerulonephritis, loss of GFR and progression of renal disease.

**Conclusion**

It appears that bacterial endocarditis can occasionally masquerade as primary glomerulonephritis. The causes of renal involvement in this condition are myriad and more than one cause may co-exist in a patient. Indiscriminate drug usage may contribute to morbidity, but with correct early diagnosis the response to antibiotic therapy is satisfactory.