Renal pathological findings in infective endocarditis

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Abstract

Background. Accounts of renal pathological findings in infective endocarditis are mostly based on studies from many years ago. We reviewed a group of patients with infective endocarditis in the light of modern concepts of renal pathology, including the largest reported series of renal biopsies in this condition.

Methods. Renal tissue was available for retrospective study from 62 patients with confirmed infective endocarditis out of 354 diagnosed with the disease between 1981 and 1998 inclusive. Twenty patients had a renal biopsy and 42 a necropsy.

Results. Common renal lesions noted were localized infarcts in 31%, noted only in necropsy material, and acute glomerulonephritis in 26%, noted in biopsy and necropsy material. The commonest type of glomerulonephritis was vasculitic, without deposition of immunoglobulins in glomeruli. Of the renal infarcts over half were due to septic emboli, mostly in patients infected with Staphylococcus aureus. Acute interstitial nephritis was found in 10% but was more common in biopsy material and seemed attributable to antibiotics. Renal cortical necrosis found in 10% was apparent only at necropsy. There were various other findings in the kidney.

Conclusions. The kidneys are commonly affected in infective endocarditis by a variety of complications of clinical significance. The commonest type of glomerulonephritis does not appear to be attributable to deposition of immune complexes. A renal biopsy may be helpful in the investigation of renal impairment in a patient with infective endocarditis.

Keywords: glomerulonephritis; infective endocarditis; renal infarction; vasculitis

Introduction

In 1858 Virchow described systemic embolization as a complication of endocarditis [1]. Common renal lesions in endocarditis described in the literature since then are renal infarction, glomerulonephritis and acute interstitial nephritis. The glomerular lesions are often said to be focal and diffuse proliferative glomerulonephritis and assumed to be immune complex mediated [2]. Most descriptions are based on series of post-mortem kidneys from the pre-antibiotic era.

Endocarditis has changed since then due to altered patient characteristics and different medical and surgical practices. Infective endocarditis is now the preferred term rather than acute endocarditis and subacute endocarditis. New routes of infection have appeared with invasive critical care support, prosthetic heart valves and parenteral drug abuse. Staphylococcus aureus has become the commonest causative organism in patients with endocarditis of short duration [3]. In general the prevalence of glomerulonephritis and other types of renal involvement has diminished since the advent of antibiotics [4]. Prompt diagnosis of endocarditis, facilitated by techniques such as transoesophageal echocardiography, has enabled earlier diagnosis and treatment with antibiotics and valve replacement surgery. Due to the ready availability of dialysis, patients now rarely die from uraemia.

The impact of these changes on the renal disease in infective endocarditis has not been assessed for some time, especially in the light of modern concepts of renal pathology. We, therefore, studied patients with infective endocarditis over the past few years in whom renal tissue had been available for examination by a pathologist. The aim was to categorize their renal disease according to current pathological views.

Patients and methods

Records from 1981 to 1998, inclusive, in the Department of Pathology, University of Birmingham, were reviewed. Patients in whom a sample of renal tissue had been available for pathological examination from a percutaneous biopsy or a necropsy or both, and in whom the diagnosis of infective endocarditis was likely or possible, were identified. Infective endocarditis was confirmed either by the examination of cardiac valves at surgery or necropsy, or by inspection of clinical records to confirm that the Duke clinical criteria...
were satisfied [5]. Clinical codes at discharge from hospital or death during the same period were used to determine the total number of patients with infective endocarditis. Renal biopsy specimens were fixed in formal saline, embedded in paraffin wax and serially sectioned to give at least one set of 10 consecutively numbered slides with six to eight sections on each. These were stained with haematoxylin and eosin, haematoxylin van Gieson, periodic acid-methenamine silver and Congo red, and with other stains if appropriate, such as Gram stain. Extra sections were cut and stained by an immunoperoxidase method to detect immunoglobulins and complement, a method that was validated and reliable [6]. Necropsy specimens were first stained with haematoxylin and eosin. Other stains were used when necessary, including the immunoperoxidase method either at the time of necropsy or on review for this study.

Findings such as distribution of infarcts were obtained from necropsy reports. Renal disease was diagnosed on standard criteria [7]. Localized infarction or just infarction was used when there was a wedge-shaped area of necrosis in the kidney ascribable to blockage of an artery. Renal cortical necrosis was used when there was damage ascribable to underperfusion of the kidney that produced irregular areas of necrosis mainly in the mid-cortex of any size. The diagnosis of vasculitic glomerulonephritis was used in this study as an alternative to terms such as acute crescentic glomerulonephritis, focal segmental necrotizing glomerulonephritis with crescents and focal embolic glomerulonephritis. All these terms had been used to describe glomerular abnormalities with various amounts of thrombosis, tuft disruption and accumulation of cells in Bowman’s space, although none of the names was satisfactory (Fig. 1) [8]. Glomerular capillaries were usually the only vessels with evidence of vasculitis. All patients with acute renal impairment had acute damage to tubules, often called acute tubular necrosis, and the diagnosis of pure acute tubular damage was only used when there was no associated lesion in the kidney such as an acute glomerular disorder. Where tubular damage could be identified with certainty on necropsy material, by features such as flattened epithelium or casts, the diagnosis was made. Vasculitic and other types of acute glomerulonephritis were usually associated with an interstitial infiltrate of inflammatory cells and the term acute interstitial nephritis was used only when there was no glomerular disorder [9].

Blood culture was used to detect micro-organisms by standard methods. Bacteria belonging to the genus Streptococcus were considered a group because of the changing taxonomic definitions during the period of study. Enterococcus, once considered as Lancefield group D streptococcus or faecal streptococcus and now accorded its own genus, was separated from streptococci. In some patients anti nuclear antibodies (ANA) and anti neutrophil cytoplasmic antibodies (ANCA) were investigated by indirect immunofluorescence and anti-glomerular basement membrane antibodies (AGBM) by enzyme linked immunosorbent assay. Standard chemical, haematological and immunological investigations were performed.

No clinical details were sought on the patients who had no material available for pathological study.

Results

Patients

During the years 1981–1998, inclusive, 354 patients had a diagnosis of infective endocarditis at the time of discharge from hospital or death, and 101 were known to have died by the time of this study. Of these, 49 had a necropsy, but four had no specimen of kidney taken for microscopy and one was excluded because of death 15 months post successful valve replacement. In 62 out of the 354 patients (18%), renal tissue was available for pathological examination: these were the subjects in this study. Diagnosis of infective endocarditis was confirmed in 14 by examination of cardiac valves at surgery, in 11 by fulfilment of the Duke clinical criteria, and in 37 by necropsy. Twenty patients underwent a percutaneous renal biopsy and two of these also had a necropsy, but their necropsy findings were the same as those in the biopsy and they were only considered in the biopsy series. Forty-two other patients had renal tissue available from necropsy within 4 weeks of presentation with endocarditis. In the series of 62, the median age was 57 years (range 15–85 years). Thirty-nine (63%) were male. The median duration of symptoms before presentation to hospital was 3 weeks. Twelve patients (19%) presented initially to nephrologists with abnormal renal function and/or abnormal urinalysis and were subsequently found to have infective endocarditis.

Cardiac disease

Fifty-six (90%) patients had involvement of native cardiac valves and six of prosthetic valves. Of those with native valve infections 20 were known to have pre-existing valvular heart disease and 10 of these had a history of rheumatic fever. Eight patients had tricuspid valve endocarditis and two of these were parenteral drug abusers. Fourteen patients required cardiac valve repair or replacement surgery and there was one peri-operative death.
Microbiological findings

*Staphylococcus aureus* was the commonest single causative organism, found in 17/50 (34%) of all the patients in whom blood culture reports were available and 14/44 (32%) of the fatal cases with infective endocarditis. Various organisms belonging to the genus *Streptococcus* also accounted for 17/50 (34%) of infections, 16 of the greening, alpha haemolytic, viridans type and one *Streptococcus pyogenes*. Of the patients with prosthetic valves, two out of four in whom an organism was identified had been infected by *Staphylococcus epidermidis*, which was also found in two patients without prosthetic valves. Other organisms identified were *Enterococcus* in three patients and a *Proteus* species, *Escherichia coli* and a *Candida* species in one patient each. In six patients no organism was detected on blood culture and all had been previously treated with antibiotics.

Pathological findings in the kidney: renal biopsy series (Tables 1 and 2)

The main indication for a renal biopsy in all 20 patients was marked renal impairment (serum creatinine concentration at least 170 μmol/l) despite appropriate antibiotic treatment for at least 2 weeks. Also, nearly all had proteinuria and/or haematuria. No complications were noted from renal biopsy.

Nine of 20 had acute glomerulonephritis of whom six had vasculitic glomerulonephritis (Fig. 1), two had subendothelial (or type 1) membranoproliferative glomerulonephritis, and one had acute post-infective glomerulonephritis. There was granular deposition of various amounts of IgG and complement in glomeruli with acute post-infective glomerulonephritis and heavy deposition of IgM and complement in glomeruli with membranoproliferative glomerulonephritis but none of the patients with vasculitic glomerulonephritis showed significant deposition of immunoglobulins or complement in glomeruli. Of the patients with vasculitic glomerulonephritis who were investigated for autoantibodies, ANCA were detected at a titre of 1:25 in one of five, and ANA and AGBM were not identified in any of the six tested. Serum concentrations of complement components C3 and C4 were normal in all patients with vasculitic glomerulonephritis.

Two patients had IgA nephropathy, one had diabetic glomerulopathy and one had lupus nephritis, assumed to be coincidental findings.

An acute interstitial nephritis was diagnosed in five patients, all of whom had received antibiotics, namely amoxicillin, gentamicin and vancomycin; ampicillin, flucloxacillin, fusidic acid, gentamicin, rifampicin and vancomycin; gentamicin and vancomycin; benzylpenicillin, gentamicin, netilmicin, rifampicin, teicoplanin and vancomycin; and cefuroxime, ciprofloxacin, flucloxacillin, fusidic acid and vancomycin. Of the four patients with pure acute tubular damage, all had received nephrotoxic agents, namely vancomycin, gentamicin or non-steroidal anti-inflammatory drugs.

Table 2 also gives details of patients who received immunosuppression for treatment of acute interstitial nephritis or acute vasculitic glomerulonephritis following control of infection. Of the series of 20, 12 patients recovered renal function at a median of 4 months after biopsy, although one of these died 6 years later from relapse of vasculitis without evidence of relapse of infective endocarditis. Seven other patients died within 1 year of biopsy and another one had residual renal impairment (serum creatinine concentration 170 μmol/l). All six who had a peak serum creatinine concentration under 300 μmol/l recovered normal renal function. Six of eight patients who required dialysis died and two improved to be dialysis independent, but only one recovered normal renal function.

Pathological findings in the kidney: necropsy series (Table 1)

Localized infarction was the commonest renal lesion, found in 19 patients out of 42. In 10 patients, infarction was a result of septic embolism, and seven of these were infected with *S. aureus*. No infarcts were due to vasculitis in arteries. Acute glomerulonephritis was found in seven patients. Two types were noted: vasculitic glomerulonephritis in five and acute post-infective glomerulonephritis in two.

Renal cortical necrosis was detected only at necropsy. In the whole series, renal impairment with serum creatinine concentration above 126 μmol/l was noted in 45 out of 53 patients (85%) in whom chemistry reports were available. Sixteen of these patients received dialysis, and in these renal cortical necrosis was the predominant lesion (5/16). Pre-existing diabetic glomerulopathy was present in one patient and another had bilateral hydronephrosis from prostatic enlargement. Seven patients had multiple renal lesions.

Table 1. Findings in the kidney in 62 patients with infective endocarditis: some kidneys had more than one disorder

<table>
<thead>
<tr>
<th>Findings in the kidney</th>
<th>Renal biopsy (n=20)</th>
<th>Necropsy (n=42)</th>
<th>Total (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized infarction</td>
<td>0</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Pure acute tubular damage</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Cortical necrosis</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pre-existing glomerular disorder or <em>hydronephrosis</em></td>
<td>4</td>
<td>1+1*</td>
<td>5+1*</td>
</tr>
<tr>
<td>Normal kidney</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
### Table 2. Details of 20 patients with infective endocarditis who had a renal biopsy

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Findings in kidney</th>
<th>Organism in blood</th>
<th>Peak serum creatinine (µmol/l)</th>
<th>Serum creatinine at recovery (µmol/l)</th>
<th>Immunosuppression</th>
<th>Duration of dialysis (days)</th>
<th>Valve replacement surgery</th>
<th>Outcome at time after biopsy (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>24</td>
<td>IgA nephropathy + acute interstitial nephritis</td>
<td>None grown</td>
<td>336</td>
<td>121</td>
<td>pred</td>
<td>0</td>
<td></td>
<td>Alive and well at 12 m</td>
</tr>
<tr>
<td>F</td>
<td>26</td>
<td>Acute interstitial nephritis</td>
<td>Viridans streptococcus</td>
<td>277</td>
<td>79</td>
<td>nil</td>
<td>0</td>
<td>A</td>
<td>Alive and well at 3 m</td>
</tr>
<tr>
<td>M</td>
<td>44</td>
<td>Membrano-proliferative glomerulonephritis</td>
<td>None grown</td>
<td>279</td>
<td>99</td>
<td>nil</td>
<td>0</td>
<td>A</td>
<td>Alive and well at 5 m</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>Pure acute tubular damage</td>
<td>None grown</td>
<td>400</td>
<td>104</td>
<td>nil</td>
<td>0</td>
<td></td>
<td>Alive and well at 12 m</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>Vasculitic glomerulonephritis acute and healed</td>
<td>None grown</td>
<td>697</td>
<td>110</td>
<td>pred, cyclo</td>
<td>0</td>
<td></td>
<td>Alive and well at 12 m</td>
</tr>
<tr>
<td>M</td>
<td>46</td>
<td>Acute interstitial nephritis</td>
<td>S. mutans</td>
<td>727</td>
<td>558</td>
<td>pred, cyclo</td>
<td>40</td>
<td>A</td>
<td>Died at 2 m; no pm</td>
</tr>
<tr>
<td>M</td>
<td>50</td>
<td>Diabetic glomerulopathy</td>
<td>None grown</td>
<td>560</td>
<td>560</td>
<td>nil</td>
<td>0</td>
<td></td>
<td>Died at 12 m; no pm</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>Membrano-proliferative glomerulonephritis</td>
<td>None grown</td>
<td>1077</td>
<td>552</td>
<td>nil</td>
<td>30</td>
<td></td>
<td>Died at 4 m; no pm</td>
</tr>
<tr>
<td>F</td>
<td>56</td>
<td>Acute interstitial nephritis</td>
<td>S. aureus</td>
<td>525</td>
<td>115</td>
<td>nil</td>
<td>0</td>
<td>A</td>
<td>Alive and well at 24 m</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>Acute vasculitic glomerulonephritis</td>
<td>S. aureus</td>
<td>214</td>
<td>69</td>
<td>pred, cyclo</td>
<td>0</td>
<td>A</td>
<td>Alive and well at 72 m</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>Lupus nephritis, membranous pattern</td>
<td>E. coli</td>
<td>368</td>
<td>272</td>
<td>pred, cyclo</td>
<td>10</td>
<td></td>
<td>Died at 1 m; myocardial infarct; pm</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>Pure acute tubular damage</td>
<td>S. aureus</td>
<td>672</td>
<td>564</td>
<td>nil</td>
<td>14</td>
<td></td>
<td>Died at 1 m; no pm</td>
</tr>
<tr>
<td>M</td>
<td>60</td>
<td>Acute post-infective glomerulonephritis</td>
<td>None grown</td>
<td>260</td>
<td>118</td>
<td>nil</td>
<td>0</td>
<td>A</td>
<td>Alive and well at 3 m</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>Acute vasculitic glomerulonephritis</td>
<td>Enterococcus</td>
<td>700</td>
<td>170</td>
<td>nil</td>
<td>25</td>
<td>A + M + P</td>
<td>Alive and well at 44 m</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>Acute interstitial nephritis</td>
<td>Viridans streptococcus</td>
<td>170</td>
<td>125</td>
<td>pred, cyclo</td>
<td>0</td>
<td></td>
<td>Alive and well at 24 m</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>Vasculitic glomerulonephritis acute and healed</td>
<td>S. aureus</td>
<td>1060</td>
<td>113</td>
<td>pred, cyclo</td>
<td>56</td>
<td></td>
<td>Died at 72 m; nopm</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>Pure acute tubular damage</td>
<td>S. pyogenes</td>
<td>223</td>
<td>115</td>
<td>nil</td>
<td>0</td>
<td></td>
<td>Alive and well at 6 m</td>
</tr>
<tr>
<td>F</td>
<td>65</td>
<td>IgA nephropathy + acute interstitial nephritis</td>
<td>S. aureus</td>
<td>728</td>
<td>109</td>
<td>pred, cyclo</td>
<td>33</td>
<td></td>
<td>Alive and well at 24 m</td>
</tr>
<tr>
<td>F</td>
<td>77</td>
<td>Acute vasculitic glomerulonephritis</td>
<td>S. bovis</td>
<td>666</td>
<td>166</td>
<td>pred, cyclo</td>
<td>30</td>
<td></td>
<td>Died at 3 m; no pm</td>
</tr>
<tr>
<td>M</td>
<td>79</td>
<td>Pure acute tubular damage</td>
<td>S. aureus</td>
<td>448</td>
<td>191</td>
<td>nil</td>
<td>0</td>
<td></td>
<td>Died at 4 m of sepsis; pm</td>
</tr>
</tbody>
</table>

pred, prednisolone; cyclo, cyclophosphamide; A, aortic; M, mitral; P, pulmonary; m, months.
The patient with acute interstitial nephritis had received co-amoxiclav.

**Tricuspid valve endocarditis**

Renal findings in the eight patients with tricuspid valve endocarditis were vasculitic glomerulonephritis in two, one of whom also had acute post-infective glomerulonephritis; acute post-infective glomerulonephritis in another one; acute interstitial nephritis in one, who also had IgA nephropathy; pure acute tubular damage in two; localised infarction in one; and normal kidney in one.

**Discussion**

This study was of a subpopulation, 18%, of patients with infective endocarditis, selected because they had had either a renal biopsy or a necropsy. These patients are unlikely to be representative of all patients with endocarditis because those with a biopsy were considered appropriate for this investigation by a nephrologist and those with a necropsy were more likely to have severe or undiagnosed endocarditis. To assess the true prevalence and nature of renal abnormalities in endocarditis, a prospective study would have to be performed with renal biopsy specimens from all patients. Such a study has not been undertaken and would be difficult to carry out.

The present paper reports the largest series of renal biopsies in this condition. Because this study is retrospective, as all previous studies were, we cannot be sure that all patients with renal impairment had a biopsy. Most, if not all, with severe impairment were referred to a nephrologist and many of these had a biopsy. Most previous studies of renal disease in infective endocarditis either guessed the cause of renal failure in life [10] or were based on necropsy findings. Necropsy studies probably overestimated the prevalence of severe renal lesions that either contributed to death or reflected the haemodynamic effects of severe heart disease. Reports from clinical observations without pathological confirmation are unreliable because glomerulonephritis may occur in the absence of clinical manifestations, or with only mild features [10,11].

The terms focal and diffuse glomerulonephritis, used in previous papers, are no longer adequate descriptions of glomerular lesions in infective endocarditis. Diffuse glomerulonephritis was used to describe acute post-infective endocardial proliferative glomerulonephritis, subendothelial (or type 1) membranoproliferative glomerulonephritis and even some forms of vasculitic proliferative glomerulonephritis [8]. Because of differences in prognosis and treatment of these lesions outside the setting of infective endocarditis we have classified them separately. Vasculitic glomerulonephritis in infective endocarditis has a poor prognosis if untreated [12].

In this study we have re-examined the renal disease in infective endocarditis in the light of current pathological concepts. As others had found since the late 1960s, *S. aureus* was the predominant single infective organism [3,13,14].

Infective endocarditis can present as apparently primary renal disease and a fifth of our patients were referred initially to nephrologists with abnormal renal function or abnormal urinalysis. Localized renal infarction was the most common renal lesion in our series, as in others [2,15]. Infarction was not detected on biopsy specimens but an infarct may be sampled by chance at biopsy. The clinical significance of infarcts depends on their size. Radionuclide, computerized tomographic or magnetic resonance imaging studies may help to detect these lesions in life. In this study most infarcts were due to septic embolism, particularly in *S. aureus* endocarditis, the most likely type to be complicated by cerebral embolism and renal abscesses [16].

Neugarten and others in a study similar to ours reported focal glomerulonephritis in 8% of patients and diffuse glomerulonephritis in 14%, with glomerular crescents in half of each type, which suggests that vasculitic lesions were included in both types [17]. Toth reported eight patients with infective endocarditis and crescentic glomerulonephritis [12]. In the present study there was a lack of immunoglobulin and complement deposits in glomeruli in patients with vasculitic lesions, but not in other types of glomerulonephritis. This finding has been reported by others in glomerulonephritis associated with endocarditis [3,11,18,19]. The explanation of this is unclear but the consistency of the finding makes the association unlikely to be a result of chance. Cell-mediated immunity may be important because memory T cells co-localized with macrophages within glomeruli in ANCA associated glomerulonephritis [20]. Vasculitic glomerulonephritis was induced by T cells sensitized to an antigen planted in glomeruli [21]. Staphylococcal glomerulonephritis was associated with endocarditis [3,11,18,19]. Necropsy studies probably overestimated the prevalence of infarcts [19,22]. Staphylococcal enterotoxins may act as superantigens, which stimulate clonal expansion of T cells and result in production of T cell cytokines [23]. Endocarditis in rabbits produced by infection with *Streptococcus sanguis* was associated with glomerulonephritis with little evidence of immune complex deposition in glomeruli [24]. Immune complexes do not appear to account for all glomerular complications of infective endocarditis.

Acute interstitial nephritis has been reported in infective endocarditis [3,4,11]. This can be part of vasculitis and other disorders but we only diagnosed acute interstitial nephritis in the absence of glomerulonephritis [8,9]. Pure acute tubular damage in endocarditis can follow a hypotensive episode due to cardiac failure or sepsis, bilateral renal emboli, or use of nephrotoxic agents [2]. In our series most patients with pure acute tubular damage had received a drug known to be nephrotoxic. Renal cortical necrosis can complicate severe hypotension or severe septicemia with thrombotic microangiopathy [2]. Patients with this complication were frequent in the group who was
dialysed and their outcome was poor. All died and the diagnosis was made at necropsy.

Patients with infective endocarditis who presented with advanced renal failure have usually had a poor outcome [25]. Generally, patients with infective endocarditis and renal failure requiring dialysis died, but if they survived they usually recovered useful renal function [3,18]. An abnormal urinary sediment has been known to persist for months or years after bacteriological cure of infective endocarditis [3,11]. In the present study of the patients who had a renal biopsy, all with milder degrees of renal impairment recovered renal function, but those who required dialysis had a high mortality. Advanced renal failure requiring dialysis therefore was a predictor of poor outcome.

References


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