Plasmapheresis for treatment of immune complex-mediated glomerulonephritis in infective endocarditis: a case report and literature review

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.5414/CNCS109082</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:34492251">http://nrs.harvard.edu/urn-3:HUL.InstRepos:34492251</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Plasmapheresis for treatment of immune complex-mediated glomerulonephritis in infective endocarditis: a case report and literature review

Meredith Halpin1,2, Olga Kozyreva3,2, Vanesa Bijol4,5, and Bertrand L. Jaber1,2

1Department of Medicine, Division of Nephrology, St. Elizabeth’s Medical Center, 2Department of Medicine, Tufts University School of Medicine, 3Department of Medicine, Division of Hematology & Oncology, St. Elizabeth’s Medical Center, 4Department of Pathology, Brigham and Women’s Hospital, and 5Harvard Medical School, Boston, MA, USA

Abstract. We report the case of a 57-year-old man who presented with subacute bacterial endocarditis secondary to Streptococcus mutans complicated by biopsy-proven immune complex-mediated glomerulonephritis (ICGN). Despite initial treatment with antibiotics and a short course of corticosteroids, the kidney function further deteriorated, and plasmapheresis was introduced as third-line therapy to remove circulating immune complexes. Following 7 treatment sessions, the patient recovered kidney function. We discuss the potential merit of plasmapheresis for patients with subacute bacterial endocarditis who develop ICGN.

Introduction

Immune complex-mediated glomerulonephritis (ICGN) is a known complication of infective endocarditis, in particular subacute bacterial endocarditis [1, 2, 3]. Infections with less virulent bacterial organisms, by virtue of their indolent subacute course, promote an antibody response that predisposes to the formation of immune complexes and the development of glomerulonephritis. In patients with subacute bacterial endocarditis, circulating immune complexes deposit on the glomerular basement membrane and activate the complement system, leading to an immune response and glomerular injury [1, 4, 5]. Control of the infection generally leads to resolution of the glomerular inflammation and normalization of kidney function. The use of plasmapheresis as salvage therapy for patients with bacterial endocarditis-associated ICGN is controversial [6].

Case report

We present the case of a 57-year-old man who presented with biopsy-proven ICGN in the setting of bacterial endocarditis secondary to Streptococcus mutans. Despite conservative management, and in light of worsening kidney function and elevated levels of circulating immune complexes, he was empirically treated with plasmapheresis, which was followed by improvement in kidney function. We review the existing literature on the potential role of plasmapheresis as an adjunct to the treatment of ICGN in the setting of bacterial endocarditis.
creatinine of 1.0 mg/dL. On presentation, he reported cola-colored urine, and was found to have acute kidney injury with a serum creatinine of 3.0 mg/dL. The urinalysis revealed 2+ protein and large blood, and the urine sediment dysmorphic red blood cells and red blood cellular casts. Levels of complement factors C3 and C4 were low at 24 mg/dL (normal range, 75 – 175 mg/dL) and 5 mg/dL (normal range, 14 – 40 mg/dL), respectively. The ANA screen was positive with a titer of 1 : 160, but the antmyeloperoxidase, antiproteinase 3, anti-GBM, and anti-DS DNA antibody titers were nonreactive. The rheumatoid factor was present but the cyclic citrullinated peptide antibody was negative. The serum protein electrophoresis detected no monoclonal proteins.
<table>
<thead>
<tr>
<th>Age (years)/sex</th>
<th>Urinalysis</th>
<th>Initial serum creatinine</th>
<th>C3/C4 levels</th>
<th>Serological workup</th>
<th>Blood culture</th>
<th>Echocardiographic findings</th>
<th>Kidney biopsy findings</th>
<th>Antibiotics</th>
<th>Immunosuppressive drugs</th>
<th>Hemodialysis</th>
<th>Cardiac surgery</th>
<th>Immunofluorescence</th>
<th>Duration of follow-up</th>
<th>Last serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>53M</td>
<td>Not reported</td>
<td>10.4 mg/dL</td>
<td>Low/low</td>
<td>Nonreactive anti-GBM antibody</td>
<td>Nonreactive antibody</td>
<td>Elevated</td>
<td>LM: Focal segmental crescentic glomerulonephritis (60% of glomeruli)</td>
<td>C3 and C1q granular deposits</td>
<td>Cefazolin</td>
<td>Not reported</td>
<td>Not required</td>
<td>None</td>
<td>C3, C4, IgG, and IgM granular deposits</td>
<td>132 days</td>
</tr>
<tr>
<td>50F</td>
<td>Not reported</td>
<td>3.9 mg/dL</td>
<td>Low/low</td>
<td>Nonreactive ANA, anti-DS-DNA antibody, ANCA, and anti-GBM antibody</td>
<td>Low</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Prednisone 2 mg/kg/day and azathioprine 1 mg/kg/day (initiated on day 16 due to rising serum creatinine)</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Phlebotomy and vein closure on day 60</td>
<td>C3 and C1q granular deposits</td>
<td>43 days</td>
</tr>
<tr>
<td>59M</td>
<td>Not reported</td>
<td>13.8 mg/dL</td>
<td>Normal</td>
<td>Nonreactive ANA, ANCA, and anti-DS-DNA antibody</td>
<td>Streptococcus viridans</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Piperacillin, amoxicillin, and cefazolin</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>None</td>
<td>C3 and C1q granular deposits</td>
<td>60 months</td>
</tr>
<tr>
<td>57M</td>
<td>Not reported</td>
<td>13.0 mg/dL</td>
<td>Low/low</td>
<td>Nonreactive ANA, SO-DNA antibody, ANCA and anti-GBM antibody, cryoglobulin</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Ceftriaxone (initiated on day 1)</td>
<td>Methylprednisolone 250-500 mg for 5 days followed by prednisone 1 mg/kg/day tapered over 14 days</td>
<td>Initiating on day 5 and 6 for a total of 11 sessions; 3-L exchange per session with 50% salt-poor albumin</td>
<td>Valvular replacement on day 90</td>
<td>C3 and C1q granular deposits</td>
<td>13 months</td>
<td>2.7 mg/dL</td>
</tr>
</tbody>
</table>

M = male; F = female; LM = light microscopy; IF = immunofluorescence; *The C1q binding assay measures circulating immune complexes. Note: Conversion factor for creatinine in mg/dL to mmol/L multiply by 88.4.
On hospital day 4, he underwent a percutaneous kidney biopsy, which revealed diffuse proliferative glomerulonephritis with global involvement of glomeruli and evidence of endocapillary and mesangial proliferation (Figure 1A–D). The immunofluorescence microscopy revealed heavy granular deposits of IgG, C3, and C1q as well as some IgM in the mesangium and along the glomerular basement membranes, consistent with ICGN. The patient was treated empirically with a short course of corticosteroids, consisting of pulse intravenous methylprednisolone (dose of 250 – 500 mg) for 5 days followed by an oral prednisone (starting dose of 60 mg) taper over 14 days.

Despite appropriate antibiotics and a short course of corticosteroids, the patient’s kidney function continued to worsen and the serum creatinine rose to 5.7 mg/dL. On hospital day 11, in light of the presence of circulating immune complex, as detected by the C1q binding assay C1q level of 63 EU/mL (< 20 EU/mL), and a rheumatoid factor level of > 130 IU/mL (< 14 IU/mL), as well as persistent hypocomplementemia, he was started on an empirical course of plasmapheresis. During each session, 4.5 L of plasma were removed, and 50% was replaced with fresh frozen plasma, and 50% with albumin. After the completion of 7 sessions, there was an improvement in his kidney function, coinciding with a marked decline in the rheumatoid factor level to 39 IU/mL and near normalization of serum complement levels (C3 level 53 mg/dL and C4 level 9 mg/dL). He was discharged on hospital day 27 with a serum creatinine of 2.8 mg/dL (Figure 1E), and 13 months after resolution of the bacterial endocarditis and resolution of the glomerular inflammation, his kidney function had fully normalized, with a return of the serum creatinine to 0.8 mg/dL.

**Discussion**

The clinical and morphological features of acute glomerulonephritis that develops during the course of bacterial endocarditis have extensively been characterized [1, 4, 7]. Post-mortem kidney biopsies obtained from patients with bacterial endocarditis during the period of 1965 – 1979 reveal an incidence rate of acute glomerulonephritis of 22.4% [7]. However, its incidence rate in the setting of acute and subacute bacterial endocarditis in the modern era of medicine with improved access to medical care and widespread use of antibiotics is less clear. In a more recent period covering 1981 – 1998, on kidney histology available from both biopsies and necropsies from patients with confirmed bacterial endocarditis, the most commonly described kidney lesion was localized renal infarcts (31% noted only on autopsy and primarily observed in patients infected with *Staphylococcus aureus*), followed by ICGN (26%), acute interstitial nephritis (10%, attributed to antibiotics), and cortical necrosis (10%) [5].

The typical histological expression of subacute bacterial endocarditis in the kidneys is a proliferative glomerulonephritis as a result of formation of circulating immune complexes that activate the complement system by the classic pathway, deposit in the glomeruli in the process of glomerular filtration, and elicit an inflammatory reaction.

Our case describes a man with previously normal kidney function who presented with acute kidney injury and biopsy-proven ICGN in the setting of subacute bacterial endocarditis due to *Streptococcus mutans*. Despite appropriate antibiotic therapy and resolution of the bacteremia, his kidney function further declined. Given the lack of response to an empirical course of corticosteroids, he was initiated on plasmapheresis in light of the presence of circulating immune complexes, as detected by the C1q binding assay and rheumatoid factor level. After 7 sessions of plasmapheresis, the serum creatinine greatly improved, and more than a year later, the kidney function normalized.

The premise of plasmapheresis is the removal of a pathologic substance from the circulation that is causing damage, and by removing the unwanted substance (e.g., a circulating auto-antibody, immune complex, cryoglobulin, or a monoclonal light chain), this can prevent or attenuate further tissue deposition and damage. The American Society for Apheresis has published guidelines on the indications for plasmapheresis [6]. While a category-1 indication would be for a disorder where plasmapheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other
modes of treatment, a category-4 indication would be for a disorder where the plasmapheresis might be ineffective or harmful. The potential role for plasmapheresis for ICGN falls under a category-3 indication, where the optimum role of plasmapheresis therapy has not been established and decision making should be individualized. In bacterial endocarditis, it can be hypothesized that circulating immune complexes are pathogenic, and their removal by plasmapheresis would attenuate immune deposits in the glomeruli, thereby limiting kidney injury.

A review of the literature identifies several case reports of ICGN in the setting of bacterial endocarditis, initially treated with appropriate antibiotics but where second-line therapy with a short course of corticosteroids [8, 9] and even cytotoxic drugs, such as cyclophosphamide [10] and azathioprine [11, 12], was added to assist in the recovery of kidney function.

The potential role of plasmapheresis as an adjunct or third-line therapy for the treatment of ICGN in the setting of bacterial endocarditis has received less attention and originates from very few published case reports. Table 1 summarizes the 5 published cases (including our case) where plasmapheresis was successfully used for this indication [11, 13, 14, 15]. All 5 patients presented with subacute endocarditis associated with a Streptococcus species, although in 1 case the incriminated bacterium was not reported by the authors but the patient had undergone dental extraction weeks prior to presentation [13]. Four of the 5 patients were men, and the age ranged from 25 to 57 years old. All patients presented with acute kidney injury, and 2 required hemodialysis at the initial presentation due to kidney failure [13, 15]. The urinalysis revealed hematuria and proteinuria, and serum complement levels were low. The rheumatoid factor, assayed in 3 cases, was present [11, 14], and circulating immune complexes, as detected by the C1q binding assay, were present in 4 cases [11, 13, 14]. In 4 of the 5 patients, the kidney biopsy revealed fibrocellular crescentic glomerulonephritis on light microscopy, contrasting with our case where diffuse endocapillary and mesangial proliferative glomerulonephritis was observed. Immunofluorescence microscopy depicted granular glomerular immune deposits of complement components and immunoglobulins in 4 cases [11, 13, 14], whereas the 5th case described a pauci-immune glomerulonephritis with nonreactive circulating ANCA and anti-GBM antibody titers [15]. Corticosteroids were used in 4 patients [11, 13, 14], and azathioprine in 1 patient [11]. Plasmapheresis was initiated at an average of 14 days from initial presentation (range, 5 – 27 days), 2 – 4.5 L of plasma were exchanged per session and replaced with either albumin or a combination of albumin and fresh frozen plasma, and patients received an average of 8 sessions (range, 5 – 14). Following plasmapheresis, the kidney function improved in all 5 patients, and there was a documented parallel decrease in levels of circulating immune complexes, as detected by the C1q binding assay in 3 patients where this marker was trended [11, 13, 14]. In our patient, the initial C1q level was markedly elevated but it was not repeated following plasmapheresis to document its removal, although the treatment coincided with improvement in the kidney function. In our case however, the rheumatoid factor level dropped significantly, which has been shown to correlate with levels of circulating immune complexes in patients with endocarditis [16]. In one study, rheumatoid factor was present in 24% of intravenous drug users presenting with endocarditis due to Staphylococcus aureus [17], and elevated rheumatoid factor levels in endocarditis may be part of a host-induced antibody response to elevated levels of circulating immune complexes [16]. While the observed improvement in kidney function is coincidental, we can only speculate that plasmapheresis might have shortened the natural history of the glomerulonephritis by promoting the removal of circulating immune complexes, and accelerating the resolution of the glomerular inflammation.

When considering plasmapheresis for endocarditis-associated ICGN where its role has not been established, potential risks of the therapy need to be considered, including hypotension, removal of antibiotics, immune suppression, and bleeding; and as a result, decision making should be carefully individualized.

Three of the 5 patients ultimately required cardiac surgery [13, 14, 15]. A repeat kidney biopsy was performed in 2 patients [13, 14], one performed 2 months later show-
ing sclerosis in 17% of the glomeruli and old crescents in 13% of the glomeruli, and no deposits on immunofluorescence microscopy [14], and one performed 125 days after initiation of plasmapheresis, revealing sclerosing focal segmental glomerulonephritis [13]. At the end of the follow-up period, which ranged from 43 days to 2 years, all 5 patients were alive, and the average serum creatinine was 1.7 mg/dL (range, 0.8 – 2.7 mg/dL).

In conclusion, we report on the successful use of plasmapheresis for the removal of circulating immune complexes in a patient who presented with subacute bacterial endocarditis complicated by acute kidney injury due to ICGN, and who had initially failed to respond to first- and second-line therapy with antibiotics and a short course of corticosteroids. The prognosis of ICGN in patients with bacterial endocarditis is usually good, and is related to the prompt eradication of the infection, using appropriate antibiotics for 4 – 6 weeks [18]. While there is equipoise on the role of plasmapheresis for ICGN, the observed favorable renal outcome raises the hypothesis as to whether plasmapheresis has a potential role as adjunctive therapy for the treatment of this kidney-related complication of endocarditis. Future studies are needed to assess the merit as well as the efficacy and safety of plasmapheresis for the removal of circulating immune complexes in patients who present with bacterial endocarditis complicated by ICGN.

Support

There was no support/funding for this report.

Conflict of interest

There were no potential conflicts of interest noted.

References


