Acute glomerulonephritis occurring during immunoadsorption with staphylococcal protein A column (Prosorba®)

Jose Iglesias¹, Vivette D. D’Agati² and Jerrold S. Levine³

¹The Department of Medicine, Division of Nephrology, Jersey Shore University Medical Center, The Robert Wood Johnson School of Medicine U.M.D.N.J., Neptune, NJ, ²The Department of Pathology Columbia University, College of Physicians and Surgeons, New York, NY and ³The Department of Medicine, Division of Nephrology, University of Illinois at Chicago, Chicago, IL, USA

Abstract

Background. Apheresis of patient plasma by immunoadsorption with a staphylococcal protein A (SPA) column is used in a variety of autoimmune disorders. Leukocytoclastic vasculitis is an uncommon severe complication that can occur during immunoadsorption with SPA (Prosorba®).

Methods. We report a case of immune complex glomerulonephritis occurring during Prosorba® immunoadsorption in a patient with rheumatoid arthritis (RA). Using a Medline literature search and information provided by Cypress Bioscience/Fresenius Hemocare, we review renal complications associated with Prosorba® immunoadsorption.

Results. We identified seven additional potential cases of glomerulonephritis (GN) in association with Prosorba® immunoadsorption. Five of these patients were being treated for RA, and two for idiopathic thrombocytopenia purpura (ITP). Renal biopsies were performed on four patients, all of whom had evidence of immune complex GN. Among RA patients treated with Prosorba®, the incidence of GN closely paralleled that of leukocytoclastic vasculitis at 1.75%. The presence of leukocytoclastic vasculitis was a significant risk factor for the development of GN (relative risk = 75.95, CI 7–1869, P = 0.00021). In contrast, among more than 10000 ITP patients treated with Prosorba®, there were only two potential cases of GN. The risk of developing GN in association with Prosorba® immunoadsorption was significantly greater for patients with RA than for those with ITP (relative risk = 62.95, CI 10–453, P = 0.00002).

Conclusion. This case series highlights the risk of GN among patients undergoing SPA immunoadsorption. The development of GN is associated with the presence of leukocytoclastic vasculitis. Patients with RA seem to be at particular risk.

Keywords: glomerulonephritis; immunoadsorption; leukocytoclastic vasculitis; Prosorba; staphylococcal protein A immunoadsorption

Introduction

Glomerular disease, other than mild mesangial glomerulonephritis (GN), is an uncommon extraarticular manifestation of rheumatoid arthritis (RA) [1]. More commonly, glomerular disease occurs as a consequence of pharmacologic therapy with disease-modifying anti-rheumatic drugs (DMARDs) [1]. Membranous nephropathy is a frequent complication in patients treated with gold and penicillamine [1]. In addition, there have been case reports of rapidly progressive glomerulonephritis associated with the use of leflunomide and minocycline [2,3].

Apheresis of patient plasma by immunoadsorption with a staphylococcal protein A (SPA) column has been used in a variety of autoimmune disorders refractory to conventional therapy [4,5]. A SPA-silica column (Prosorba®; Cypress Bioscience, San Diego, CA; Fresenius Hemocare, Redmond, WA) has recently been used in patients with severe RA, who have failed therapy with DMARDS [4,5]. Leukocytoclastic vasculitis is a recognized but uncommon severe complication occurring during treatment with Prosorba® immunoadsorption [4,6,7]. Renal involvement has previously been reported in a patient with leukocytoclastic vasculitis [4]. Here we present a case of GN with nephrotic range proteinuria in the absence of leukocytoclastic vasculitis in a patient with RA after 11 Prosorba® treatments. Through a literature search and information provided by Cypress Bioscience/Fresenius...
Hemocare, we review renal complications associated with Prosorba® immunoadsorption.

Case report

Clinical course

A 70-year-old Caucasian woman with a history of severe RA developed worsening lower extremity oedema, haematuria, and new onset proteinuria after 11 weekly Prosorba® treatments. She had a 12 year history of severe RA refractory to treatment with gold, leflunomide, and anti-TNF-α antibody therapy. DMARDS therapy had been discontinued 6 months prior to initiating Prosorba® therapy. At the time of initiation of Prosorba®, she was receiving only prednisone, 20 mg/day. One year before Prosorba® therapy, the patient had developed a generalized vasculitis with necrotic ulcers on her toes. Skin and sural nerve biopsies were non-diagnostic. Vasculitis responded to high-dose steroid therapy.

Physical examination revealed a chronically ill woman, with a weight of 132 pounds and height of 62 inches. She was afebrile, with a blood pressure of 150/80 mmHg and a respiratory rate of 18 breaths/min. Her neck was supple, without jugular venous distention. Her heart sounds were regular, without any murmur. Her lungs were clear to auscultation and percussion. Her abdomen revealed no hepatosplenomegaly. Her extremities had pitting oedema. Her skin had no petechiae, purpura or cutaneous ulcers.

Laboratory evaluation revealed a haemoglobin of 11 g/dl, haematocrit 35%, blood urea nitrogen 29 mg/dl and serum creatinine 1.3 mg/dl. Twenty-four hour urinary protein excretion was 8 g. Physical examination of her urine revealed multiple red blood cell casts, 10 red blood cells per high-power field, and 5–10 white blood cells per high-power field. Rheumatoid factor was 649 IU/ml, C4 was <10 mg/dl (normal 20–60), and C3 was 98 mg/dl (normal 92–130). Serologies and immunofluorescent studies for anti-proteinase 3, anti-myoeloperoxidase, anti-double-stranded DNA, hepatitis B surface antigen, hepatitis C and cryoglobulins were all negative. Serum and urine immunofixation electrophoresis revealed no evidence of monoclonal gammopathy.

Renal biopsy findings

Light microscopic analysis revealed diffusely enlarged glomeruli, with global mesangial and endocapillary hypercellularity, including focal infiltrating monocytes and neutrophils (Figure 1). PAS and trichrome staining delineated mesangial and segmental large subendothelial deposits (Figure 1). Large deposits forming focal intracapillary protein thrombi were also evident. Immunofluorescence examination revealed global mesangial and segmental glomerular capillary wall granular staining for IgG (1–2+), IgM (1+), IgA (2–3+), C3 (2+), kappa (1–2+) and lambda (2–3+), with negative staining for C1 (Figure 2). No deposits were identified involving the tubulointerstitial or vascular compartments. Electron microscopy revealed abundant mesangial and subendothelial electron dense deposits, associated with partial mesangial interposition and ~75% effacement of overlying foot processes. The deposits displayed a granular texture, without evidence of organized substructure. No endothelial tubulo-reticular inclusions were identified.

Post biopsy clinical course

Repeat serum cryoglobulins were negative. The patient was pulsed with 1000 mg of methylprednisolone intravenously for 3 days, followed by an oral corticosteroid taper over 3 months. Concurrently, she also received a 7 day course of daily plasmapheresis, using 1.5 volume fresh frozen plasma exchanges, plus mycophenolate mofetil 500 mg two times per day. Over a 3 month period, her serum creatinine decreased to 0.9 mg/dl, and her urinary protein excretion decreased to 200 mg/day.

Results

A search for events in association with Prosorba® revealed seven additional potential cases of GN and
quences of Prosorba itself may constitute a risk factor for the development of the relative risk of developing leukocytoclastic vasculitis in association with Prosorba renal function. Of the seven patients with Prosorba-associated GN, five were being treated for RA, and two for ITP. The baseline characteristics of these seven patients are summarized in Table 1. At the time of the renal adverse event, two patients were receiving DMARD, and four patients had concurrent leukocytoclastic vasculitis (defined as new-onset palpable purpura and/or biopsy-proven leukocytoclastic vasculitis with onset during therapy with SPA). Renal biopsies were performed on four of the seven patients, and in all four cases revealed evidence of an immune complex GN (one membranoproliferative GN, and three diffuse proliferative GN). In the majority of these seven patients, treatment of GN consisted of cessation of Prosorba, high-dose steroids and pulse cyclophosphamide. Clinical resolution occurred in all patients.

We next estimated the incidence of Prosorba-associated GN among patients with RA. The five additional cases we identified through our search occurred in the time period from September 2000 to May 2001. During this same period, an estimated 400 patients with RA received Prosorba. Prior to this time, treatment of refractory RA with Prosorba had not entered clinical practice. This yields an estimated incidence of Prosorba-associated GN of 1.25% among patients with RA. In contrast, during a 12 year period from 1987 to 1999, out of more than 10 000 patients who received Prosorba for ITP, there were only two reported cases of potential GN, both presenting as renal failure in association with haematuria. Thus, the incidence of Prosorba-associated GN among ITP patients is only ~0.02%, strikingly lower than that among RA patients. The risk of developing Prosorba-associated GN was significantly greater for RA patients than for ITP patients (relative risk = 62.95, CI 10–453, \( P = 0.00002 \)) (Table 2). These results suggest that RA itself may constitute a risk factor for the development of Prosorba-associated GN. In support of the concept that RA patients may be predisposed to Prosorba-associated adverse events, the relative risk of developing leukocytoclastic vasculitis in association with Prosorba therapy was similarly increased among RA patients as compared to ITP patients. Out of 400 RA patients receiving Prosorba \( ^{(7)} \), seven developed leukocytoclastic vasculitis, for an incidence of 1.75% (Table 2). The incidence of Prosorba-associated leukocytoclastic vasculitis among RA patients is thus similar to that of Prosorba-associated GN. In contrast, among an estimated 10 000 ITP patients treated with Prosorba between 1987 to 1999, there were only 20 cases (0.2%) of leukocytoclastic vasculitis. Thus, just as for Prosorba-associated GN, the relative risk of developing Prosorba-associated leukocytoclastic vasculitis was significantly greater among RA patients than among ITP patients (relative risk = 8.95 CI 3–21, \( P = 0.00005 \)) (Table 2). Thus, the risk for two Prosorba-associated adverse events, GN and leukocytoclastic vasculitis, is significantly increased among RA, as compared to ITP, patients.

Of note, three of the five RA patients who developed GN also had suspected or confirmed leukocytoclastic vasculitis. In addition, one of the two ITP patients who developed GN also had leukocytoclastic vasculitis. This association between leukocytoclastic vasculitis and GN was statistically significant not only for the combined population of RA and ITP patients receiving Prosorba \( ^{(8)} \) (\( P < 0.00001 \)), but also for the subpopulations of RA patients alone \( (P < 0.00001) \) and ITP patients alone \( (P < 0.00001) \). These data suggest that the risk factors that predispose patients to the development of GN are similar to those predisposing them to the development of leukocytoclastic vasculitis, and the presence of leukocytoclastic vasculitis may serve as a marker for those patients more likely to develop renal involvement.

Discussion

SPA columns have increasingly been used in the treatment of a number of refractory autoimmune disorders, including RA and ITP. SPA binds with greater affinity to the Fc portion of free uncomplexed IgG than to the Fc portion of complexed IgG \([6]\). Thus, the efficacy of plasma immunoadsorption with SPA in the treatment of autoimmune disease may be attributable in part to the removal of pathogenic circulating immune complexes containing IgG \([4–6]\).

SPA is associated with a number of serious potentially life-threatening side effects, including angioedema in patients receiving concurrent angiotensin converting enzyme inhibitors, thrombosis, serum sickness, and vasculitis. SPA-induced vasculitis typically presents as palpable purpura, in association with fever and arthralgias. A total of 15 cases of biopsy-confirmed leukocytoclastic vasculitis have been reported \([4,7,8]\).

In the present report, we present evidence that GN should be added to the list of SPA-associated serious adverse events. The risk of GN appears to be substantially increased among patients with RA as compared to ITP \((\sim 60\)-fold, Table 2). The risk of leukocytoclastic vasculitis was similarly increased among RA patients. Moreover, there was a statistically significant concordance between the development of GN and that of leukocytoclastic vasculitis, suggesting that the same risk factors which predispose patients with RA or ITP to develop leukocytoclastic vasculitis...
### Table 1. Cases of glomerulonephritis associated with SPA immunoadsorption

<table>
<thead>
<tr>
<th>Case</th>
<th>Indication for Prosorba</th>
<th>Number of SPA treatments</th>
<th>Concurrent medications</th>
<th>Clinical presentation</th>
<th>Renal biopsy</th>
<th>Treatment</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>43-year-old female</td>
<td>Rheumatoid arthritis</td>
<td>3</td>
<td>Azathioprine, prednisone</td>
<td>Nephrotic syndrome, depressed C3, C4 glomerulonephritis</td>
<td>Membranoproliferative glomerulonephritis</td>
<td>Cessation of Prosorba, pulse soludmedrol and cytoxan</td>
<td>Yes</td>
</tr>
<tr>
<td>42-year-old female</td>
<td>Rheumatoid arthritis</td>
<td>3</td>
<td>Leufluonamide, prednisone, benadryl</td>
<td>Palpable purpura, glomerulonephritis 3000 mg of proteinuria</td>
<td>Diffuse proliferative glomerulonephritis Weak IgG, 1+IgA (no glomeruli in tissue stained for IgM, C1q, C3)</td>
<td>Cessation of Prosorba, steroids</td>
<td>Yes</td>
</tr>
<tr>
<td>72-year-old female</td>
<td>Rheumatoid arthritis</td>
<td>11</td>
<td>Prednisone</td>
<td>Nephrotic range proteinuria, glomerulonephritis, acute renal failure, depressed C4 normal C3</td>
<td>Diffuse proliferative glomerulonephritis 1+IgG, 2+IgM, 2-3+IgA, 2+ C3, -Cq</td>
<td>Cessation of Prosorba, pulse soludmedrol, mycophenolate mofetil, plasmapheresis^a</td>
<td>Yes</td>
</tr>
<tr>
<td>57-year-old female</td>
<td>Rheumatoid arthritis</td>
<td>9</td>
<td>Methotrexate anti-TNF-α therapy, minocycline</td>
<td>Palpable purpura leukocytoclastic vasculitis</td>
<td>Crescentic glomerulonephritis with faint mesangial IgG staining</td>
<td>Pulse cytoxan and pulse soludmedrol</td>
<td>Yes</td>
</tr>
<tr>
<td>60-year-old male</td>
<td>Rheumatoid arthritis, systemic lupus nephritis</td>
<td>9</td>
<td>Failed therapy with multiple disease modifying agents</td>
<td>Palpable purpura, acute oliguric renal failure requiring dialysis.</td>
<td>Treated as GN by consulting nephrologist^b</td>
<td>Pulse cytoxan and pulse soludmedrol</td>
<td>Yes</td>
</tr>
<tr>
<td>64-year-old female [8]</td>
<td>Autoimmune thrombocytopenic purpura</td>
<td>2</td>
<td>None</td>
<td>Palpable purpura, fever, arthritis, haematuria renal failure skin biopsy: leukocytoclastic vasculitis</td>
<td>None performed</td>
<td>Cessation of prosorba, high-dose steroids</td>
<td>Yes</td>
</tr>
<tr>
<td>39-year-old female [14]</td>
<td>Autoimmune thrombocytopenic purpura</td>
<td>2</td>
<td>Intravenous immune globulin</td>
<td>Urticarial rash, purpura, fever, arthralgias, haematuria encephalopathy, renal failure, skin biopsy negative for vasculitis</td>
<td>None performed</td>
<td>High-dose steroids, cessation of prosorba</td>
<td>Yes</td>
</tr>
</tbody>
</table>

^aThe use of fresh frozen plasma during plasmapheresis was at the discretion of the attending nephrologists for reasons unrelated to GN as the patient had just undergone renal biopsy.

^bA secondary analysis was also performed in which patient N5 of Table 1, who had both SLE and RA, was excluded from analysis. The relative risks for developing GN and/or leukocytoclastic vasculitis were still significantly increased among patients who have only RA vs patients with ITP.
Acute glomerulonephritis occurring during immunoadsorption

Table 2. Incidence of leukocytoclastic vasculitis, glomerulonephritis (GN), and concurrent leukocytoclastic vasculitis/glomerulonephritis (GN) in patients with RA and ITP during Prosorba® treatments

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>ITP</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytoclastic vasculitis*</td>
<td>7 (1.75)</td>
<td>20 (0.2)</td>
<td>8</td>
<td>3–21</td>
<td>0.00005</td>
</tr>
<tr>
<td>GN*</td>
<td>5 (1.25)</td>
<td>2 (0.02)</td>
<td>62.9</td>
<td>10–453</td>
<td>0.00002</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis and GN*</td>
<td>3 (0.75)</td>
<td>1 (0.01)</td>
<td>75</td>
<td>7–1869</td>
<td>0.00021</td>
</tr>
</tbody>
</table>

*Comparison of the incidences of Prosorba®,-associated GN and leukocytoclastic vasculitis among patients with RA vs ITP was performed using 2 × 2 contingency tables and either chi-squared analysis (with Yates’ correction for continuity) or Fisher’s exact test. Fisher’s exact test was used when the expected number in the cells was small. Statistical analysis was performed using the NCSS statistical program (NCSS, Jerry Hintze, Salt Lake City, UT).

**Cases of leukocytoclastic vasculitis include both those with and those without GN. Similarly, cases of GN include both those with and those without leukocytoclastic vasculitis. Thus, for example, the total number of RA patients having leukocytoclastic vasculitis only, GN only, or both leukocytoclastic vasculitis and GN is 12.

**Absolute attribution of cases of leukocytoclastic vasculitis to administration of SPA cannot be made, as nearly all patients had alternative potential aetiologies. For example, leukocytoclastic vasculitis is a recognized complication of RA. Cases of leukocytoclastic vasculitis included in this table all had their onset concurrent with administration of SPA.

**Comparison of the incidences of Prosorba®-associated GN and leukocytoclastic vasculitis among patients with RA vs ITP was performed using 2 × 2 contingency tables and either chi-squared analysis (with Yates’ correction for continuity) or Fisher’s exact test. Fisher’s exact test was used when the expected number in the cells was small. Statistical analysis was performed using the NCSS statistical program (NCSS, Jerry Hintze, Salt Lake City, UT).

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Also predisperse them to develop GN in association with SPA immunoadsorption. While an association between SPA and the development of GN in no way implies a causal relationship, it does suggest the need for future prospective studies and clinical vigilance in the use of SPA.

Although the pathogenesis of GN in association with SPA is unclear, several mechanisms are plausible. Perfusion of plasma through SPA columns results in neutrophil activation, complement activation, and increased T-helper-cell activity [4,6,9,10–14].

Complement activation can lead to recruitment and activation of leucocytes and platelets, resulting in an intense inflammatory cascade [6,9–11]. Moreover, studies have shown that minute quantities of soluble SPA-silica can leak out of the SPA column, yielding plasma concentrations from 0.23 to 70 mcg/ml [11].

These circulating SPA-silica particles may combine with circulating IgG, either free or antigen-complexed, to form SPA-induced circulating immune complexes. Finally, removal of immune complexes may abrogate important negative feedback mechanisms on pathogenic B cell clones and lead to increased production of free undesired antibody, thereby potentially leading to a paradoxical worsening of disease [4,6,9].

In summary, our report highlights the potential for patients undergoing SPA immunoadsorption to develop GN. We recommend screening patients for the presence of renal disease with routine urinary studies and chemistries prior to and during therapy with SPA immunoadsorption.

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References


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