Use of steroid therapy in immunoglobulin A-dominant poststaphylococcal glomerulonephritis

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glomerulonephritis; IgA-dominant; Staphylococcus; steroids

Abstract
Staphylococcal immunoglobulin A (IgA)-dominant infection-related glomerulonephritis (IgA-IRGN) is an emerging clinical entity seen in immunocompromised hosts. Antibiotics are the mainstay of treatment and the role of steroids is controversial. We present a review of literature and our recommendations on the use of steroids in the management of IgA-IRGN.

Introduction

Nasr and colleagues introduced the term “immunoglobulin A (IgA)-dominant postinfectious glomerulonephritis” in the year 2003. The causative infection is often ongoing at the time of diagnosis, hence, the term IgA-dominant infection-related glomerulonephritis (IgA-IRGN) is preferable. IgA-IRGN may be caused by Staphylococcus including methicillin-resistant Staphylococcus aureus (MRSA), Streptococcus, and Gram-negative bacteria with variable sites of infection and has a predilection for elderly, diabetic, and immunocompromised hosts. Most of the case reports have been reported from the US, Japan, and Taiwan. Diabetic patients with evidence of end organ damage such as nephropathy, neuropathy, and peripheral vascular disease are at great risk of development of skin ulcers with superimposed bacterial infection explaining the increased incidence of IgA-IRGN in this population. There are only a few case reports that focus on the treatment of this entity. The role of steroids has been controversial with regard to its indications, timing, and long-term complications including relapse of infection. The purpose of this article is to review the literature regarding the role of steroids in the management of this emerging clinical entity.

Pathogenesis

Koyama et al found that the serum levels of IgA and IgA immune complexes were higher in patients with post-MRSA glomerulonephritis than in patients without nephritis. They speculated that staphylococcal enterotoxins may behave as superantigens that can bind directly to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. The enterotoxin-MHC class II complex then binds to the T-cell receptor which results in massive T-cell activation with cytokine burst, leading to B-cell
activation and immune complex formation in renal tissue. A new S. aureus envelope antigen termed "probable adhesin" has been proposed to induce IgA formation.\(^7\) Cell wall components of several strains of Gram-negative bacteria have also been administered in mice experimental models to induce glomerular IgA and complement 3 (C3) deposition.\(^8\)

Clinical and histologic features that favor IgA-IRGN over IgA nephropathy include initial presentation in older age, acute renal failure at presentation, intercurrent culture-documented staphylococcal infection, hypocomplementemia, diffuse endocapillary hypercellularity with prominent neutrophil infiltration on light microscopy, stronger staining for C3 than IgA and lack of lambda predominance on immunofluorescence, and the presence of subepithelial humps on electron microscopy.\(^1,9–11\)

**Role of steroids**

Due to lack of good quality trials, there is no robust data for the use of steroids in IgA-IRGN. Given the immune-mediated pathophysiology involving the interaction of the host immune system with bacterial superantigens, the anti-inflammatory and immunomodulatory effects of steroids may be of therapeutic value.\(^12\) The dilemma lies in risk of flare up of underlying infection, especially in an immunocompromised host.

Okuyama et al\(^13\) suggest considering steroid use, only in patients in whom the MRSA infection has definitely been cured and whose glomerulonephritis symptoms do not improve for weeks. Even in such instances, they advise simultaneous antibiotic treatment. Kapadia et al\(^12\) proposed similar recommendations for crescentic IRGN. We described successful treatment of staphylococcal IgA-IRGN with steroids alone in a patient who presented 6 weeks after the onset of infection, at which time there was no evidence of active infection.\(^14\) Chen and Wen\(^15\) reviewed 10 cases of MRSA-associated crescentic IgA-IRGN. In addition to antibiotic treatment, steroids were administrated to five patients. All patients achieved partial recovery of renal function, however, two patients succumbed to infectious complications (sepsis and cerebral bacterial embolism), 4 months after initiation of steroid therapy. The authors echoed the suggestion given by Okuyama et al.\(^13\)

Several authors\(^16,17\) do not support the use of steroids in staphylococcal IgA-IRGN. They have suggested that steroids should be avoided because of the increased risk of worsening of the infections and that this type of glomerulonephritis may respond to antibiotic treatment alone in most cases. One explanation for this suggestion could be the

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Age (y)/sex</th>
<th>Origin of infection</th>
<th>Antibiotics</th>
<th>Renal outcome</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamashita et al(^22)</td>
<td>1</td>
<td>58/M</td>
<td>Pneumonia</td>
<td>Given</td>
<td>Improved HD after 2nd deterioration</td>
<td>Alive</td>
</tr>
<tr>
<td>Nagaba et al(^17)</td>
<td>2</td>
<td>54/M</td>
<td>Abdominal abscess</td>
<td>Given</td>
<td>Improved</td>
<td>Died from sepsis</td>
</tr>
<tr>
<td></td>
<td>23/M</td>
<td></td>
<td>Skin abscess</td>
<td>Given</td>
<td>Not improved</td>
<td>Died from cerebral hemorrhage</td>
</tr>
<tr>
<td>Pola et al(^23)</td>
<td>1</td>
<td>30/NA</td>
<td>Septic arthritis</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Kai et al(^14)</td>
<td>1</td>
<td>48/M</td>
<td>Pneumonia</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Satoskar et al(^16)</td>
<td>1(^a)</td>
<td>56/F</td>
<td>Endocarditis</td>
<td>Given</td>
<td>Partial improvement</td>
<td>NA</td>
</tr>
<tr>
<td>Hashimoto et al(^25)</td>
<td>1</td>
<td>28/F</td>
<td>Delivery procedure</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Hoshino et al(^26)</td>
<td>1</td>
<td>59/F</td>
<td>Lung abscess</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Okuyama et al(^13)</td>
<td>1</td>
<td>48/M</td>
<td>Mediastinal abscess</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Wehbe et al(^17)</td>
<td>1(^b)</td>
<td>73/M</td>
<td>Pleural effusion</td>
<td>Given</td>
<td>Dialysis dependent</td>
<td>NA</td>
</tr>
<tr>
<td>Chen and Wen(^15)</td>
<td>1</td>
<td>57/M</td>
<td>Septic arthritis</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Kapadia et al(^12)</td>
<td>1</td>
<td>39/M</td>
<td>Psoas abscess</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Koo et al(^28)</td>
<td>1(^c)</td>
<td>76/M</td>
<td>NA</td>
<td>Not given</td>
<td>Dialysis dependent</td>
<td>Died due to pneumonia</td>
</tr>
<tr>
<td>Worawichawong et al(^29)</td>
<td>4(^d)</td>
<td>46/M</td>
<td>Skin lesions</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
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<tr>
<td></td>
<td>59/M</td>
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<td>Bloody diarrhea</td>
<td>Given</td>
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<td>Alive</td>
</tr>
<tr>
<td></td>
<td>74/M</td>
<td></td>
<td>Diabetic foot ulcer</td>
<td>Given</td>
<td>Dialysis dependent</td>
<td>Died due to pneumonia</td>
</tr>
<tr>
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<td>86/F</td>
<td></td>
<td>Cellulitis</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Handa et al(^11)</td>
<td>1</td>
<td>57/F</td>
<td>Atopic dermatitis</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
<tr>
<td>Eswarappa et al(^14)</td>
<td>1</td>
<td>70/M</td>
<td>Pneumonia</td>
<td>Given</td>
<td>Improved</td>
<td>Alive</td>
</tr>
</tbody>
</table>

HD = hemodialysis; NA = not available.

\(^a\) One out of the eight patients studied was treated with steroids.

\(^b\) One out of the two patients studied was treated with steroids.

\(^c\) One out of the seven patients studied was treated with steroids.

\(^d\) Four out of the seven patients were treated with steroids.
prolonged persistence of staphylococcal antigens and the corresponding antibodies in host circulation despite appropriate therapy. The decision to treat elderly patients with immunosuppressive therapy is more challenging than treating poststreptococcal glomerulonephritis in children, because the infection is frequently active at the time of renal presentation and coexistent diabetes. The best available data come from a retrospective observational study of 109 elderly patients with bacterial IRGN, 46% of whom had staphylococcal IgA-IRGN. Among the 98 patients with available data, 22 patients with an elevated serum creatinine with or without crescents were treated with glucocorticoids for variable periods of time. Three patients had a complete remission, 12 patients had a persistent elevation in serum creatinine, seven patients progressed to end-stage renal disease (ESRD), and four patients died. No correlation was observed between glucocorticoid therapy and renal outcomes. Similar lack of benefit has also been noted in other observational studies of patients with bacterial IRGN. Published cases of staphylococcal IgA-IRGN treated with steroids and their outcomes are summarized in Table 1.

On the basis of the absence of proven benefit and the potential risks in this population, Nasr et al. recommend that immunosuppressive therapy should not be used in most adults with staphylococcal IgA-IRGN and that active infection should be eradicated using antibiotics, with surgery, if indicated. Based on the data reviewed and our experience, we suggest that a meticulous evaluation including a thorough clinical examination and investigation (chest radiograph, abdominal ultrasonogram, echocardiogram, appropriate cultures) should be performed in all cases of IgA-IRGN to rule out active infection before initiating steroids. Steroids may be considered in IgA-IRGN in the following conditions: (1) histologic evidence of >30% glomeruli with crescents or severe acute interstitial nephritis or diffuse proliferative glomerulonephritis pattern of injury with associated persistent or progressive renal dysfunction; (2) those who do not respond to antibiotic therapy alone with associated lack of improvement or a progressive decline in renal function even after 6 weeks of starting antibiotics; and (3) those with nephrotic-range proteinuria. Concomitant use of antibiotic therapy is strongly recommended.

We suggest using a short course of intravenous pulse steroid therapy (500 mg to 1 g/1.73 m² methylprednisolone once daily) for 3 days, particularly for patients with rapidly progressive renal failure. This may be followed by oral prednisolone 0.5 mg/kg/d tapered over 3 weeks. Oral steroids may suffice in other conditions mentioned above.

Limitations of our review include use of retrospective data, low patient numbers, and lack of data on optimal dose and duration of steroids.

In conclusion, patients with IgA-IRGN remain at risk for chronic kidney disease and ESRD in cases of incomplete resolution of the inflammatory process. The risks of using steroids should be carefully balanced against potential benefits.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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References


