Immunoglobulin A Nephropathy Associated with Mesothelioma

Adewale Fawole, MD; Hamed Daw, MD; Harris Taylor, MD; Arash Rashidi, MD

ABSTRACT
Immunoglobulin A nephropathy (IgAN) has been identified in patients with various malignancies. Although membranous glomerulonephritis and minimal change disease have been described in patients with mesothelioma, to our knowledge IgAN associated with mesothelioma has not been reported. We present a case of IgAN, characterized by progressive deterioration of renal function from normal and confirmed by kidney biopsy. Despite improvement of renal function following treatment with cyclophosphamide and prednisone, the patient succumbed to acute respiratory failure 8 months later. We conclude that IgAN may be a potential complication of mesothelioma.

INTRODUCTION
Adult patients with cancer are at risk of developing acute renal failure from various causes including volume depletion, hypercalcemia, tumor lysis syndrome, chemotherapy, or accompanying paraneoplastic syndromes. Immunoglobulin A nephropathy (IgAN), once thought to be rare in patients with cancers, has now been described in association with renal cell carcinomas, lymphoma, and small cell lung carcinoma as well as membranous glomerulonephritis and minimal change disease.1-3 We describe what is, to our knowledge, the first case of IgAN associated with renal failure in a patient with mesothelioma; membranous glomerulonephritis and minimal change disease have already been described in patients with mesothelioma.4,5

CASE REPORT
A 65-year-old man was admitted to hospital in February 2010 with chief complaints of progressive shortness of breath, dry cough and right-sided chest discomfort during the preceding 3 weeks. Past medical history was significant for diabetes mellitus, hypertension and dyslipidemia. He had a 20-pack per year history of cigarette smoking prior to quitting 25 years previously. In addition, he experienced prolonged exposure to asbestos while working with the Navy and in the boiler industry. On physical examination he was dyspneic at rest. There was mediastinal shift to the left and dull percussion notes with absent breath sounds and vocal fremitus in his right hemithorax. The rest of the examination was normal. Complete blood count and serum electrolytes were normal. Serum creatinine (SCr) was 0.83 mg/dL. X-ray and computed tomographic scan of the chest showed a massive right pleural effusion. Following drainage of 4.8 liters of bloody pleural effusion, a talc pleurodesis to prevent recurrent effusion was performed. Histopathologic examination of a right parietal pleural biopsy revealed epithelioid mesothelioma (Figures 1A and 1B). Positron emission tomographic scan demonstrated direct right chest wall invasion by tumor, mediastinal adenopathy, and bilateral calcified pleural plaques.

At his office visit in April 2010, the patient’s SCr was 1.0 mg/dL. Treatment with carboplatin and pemetrexed was initiated. After 5 cycles of carboplatin/pemetrexed, he was switched to gemcitabine in July 2010, because of poor clinical and radiologic response. One week after starting gemcitabine, SCr had risen to 1.5 mg/dL. He was readmitted to hospital for pneumonia and worsening renal function in August 2010, 4 weeks after commencement of gemcitabine. At this time his SCr was 2.9 mg/dL. Urinalysis showed microscopic hematuria and proteinuria with a spot urinary protein to creatinine ratio of 1.96 mg/mg. Serum C3 and C4 levels were 143 mg/dL (normal [nl] 90-180 mg/dL) and 35 mg/dL ([nl] 10-40 mg/dL), respectively. Tests for antinuclear antibody, antineutrophil cytoplasmic antibody, hepatitis B surface antigen and hepatitis C virus antibody were negative. Serum and urine protein electrophoresis were negative for monoclonal gamopathy. White blood cell count was 7.6k/µL ([nl] 3.7-11.0k/µL), hemoglobin 9.3 g/dL ([nl] 13.0-17.0 g/dL) and platelet count 452 k/µL ([nl] 150-400 k/µL). The peripheral blood smear was normal with no schistocytes. The rapid progression
Figure 1. Histologic Findings in Lung Biopsy (A, B) and Kidney Biopsy (C-F) Specimens

A. Epithelioid mesothelioma (arrow) on the surface of a fibrous pleural plaque (arrow head) (hematoxylin and eosin stain, magnification x 100) B. Epithelioid mesothelioma with ovoid nuclei, irregular nuclear membranes, prominent nucleoli, high mitotic activity, and abundant pink cytoplasm in a haphazard growth pattern (hematoxylin and eosin stain, magnification x 400) C. Mesangial hypercellularity (hematoxylin and eosin stain, magnification x 400) D. Acute tubular injury (hematoxylin and eosin stain, magnification x 400) E. Co-dominant moderate staining with IgA in mesangium (immunofluorescence stain, magnification x 400) F. Electron microscopy shows mesangial and subendothelial electron dense deposits (Electron micrograph, magnification x 4400).
small cell lung carcinoma. However, to our knowledge in some patients with renal cell carcinomas, lymphoma, and reports have described biopsy-proven paraneoplastic IgAN and proteinuria necessitated a kidney biopsy. Light micros -

sures were withdrawn and he died shortly thereafter.

respiratory failure. According to his wishes, life support mea -

readmitted for the last time in late October 2010 with acute to creatinine ratio from 1.96 mg/mg to 1.7 mg/mg. He was early October 2010 his renal function had improved with gemcitabine was continued. At his subsequent office visit in and prednisone 60mg daily for treatment of his IgAN while IgAN and acute tubular injury.

were mildly thickened. These results were consistent with IgAN and acute tubular injury.

The patient was begun on cyclophosphamide 125mg daily and prednisone 60mg daily for treatment of his IgAN while gemcitabine was continued. At his subsequent office visit in early October 2010 his renal function had improved with SCr falling from 2.9 to 2.2 mg/dl and spot urine protein to creatinine ratio from 1.96 mg/mg to 1.7 mg/mg. He was readmitted for the last time in late October 2010 with acute respiratory failure. According to his wishes, life support measures were withdrawn and he died shortly thereafter.

DISCUSSION
Primary IgAN is an immune-complex mediated glomerulo -nephritis of unknown etiology characterized by the deposit -ion of IgA in the glomerular mesangium demonstrable on immunohistological examination of the kidneys. Secondary causes of IgAN include diseases of the liver, intestine, human immunodeficiency virus infection, and neoplasias. Case reports have described biopsy-proven paraneoplastic IgAN in some patients with renal cell carcinomas, lymphoma, and small cell lung carcinoma.1-3 However, to our knowledge IgAN associated with mesothelioma has not been described previously. We believe that the IgAN in our patient is likely due to mesothelioma although chance association remains possible. Gemcitabine initially was suspected as the cause of renal failure based on previous reports of gemcitabine-induced thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.5-9 However, thrombocytosis and absence of typical red cell changes on peripheral smear negated this possibility. To our knowledge, gemcitabine is not known to cause IgAN which has, however, been described in patients with malignancies. More importantly, the improvement in his renal function while he continued to receive gemcitabine, cyclophosphamide, and prednisone made gemcitabine an unlikely cause of his renal insufficiency.

The exact pathogenesis of IgAN remains unknown. As in primary IgA nephropathy,10 no specific antigen has been consistently identified in the circulating IgA-containing immune complexes and the kidney biopsies of patients with paraneoplastic IgAN. Mimura et al11 found IgA and interleukin-6 in the plasma cells and lymphocytes around the renal cell carcinoma in their 3 patients. They believed that these infiltrating cells produced the IgA deposits in the glomerular mesangium. Mak et al12 proposed a direct link between a B-cell lymphoma of mucosa-associated lymphoid tissue and simultaneously diagnosed IgAN in their patient. As demonstrated in Table 1, temporal relationships exist between the occurrence of IgAN and diagnosis of associated malignancies. IgAN has been diagnosed both concomitant with and after the diagnosis of cancer.2,13 Our patient developed hematuria and proteinuria with renal failure 6 months following diagnosis of mesothelioma.

Because of our patient’s deteriorating renal function, he received treatment with cyclophosphamide and prednisone with appreciable improvement in renal function before succumbing to respiratory failure.

CONCLUSION
We believe this is the first report of mesothelioma and coexisting IgAN and that it expands the number of cancers associated with paraneoplastic IgAN.

Table 1. Reports of Immunoglobin A Nephropathy (IgAN) Associated with Neoplasias

<table>
<thead>
<tr>
<th>Author</th>
<th>Age / Gender</th>
<th>Diagnosis</th>
<th>Interval between neoplasia and IgAN diagnosis / Treatment given</th>
<th>Clinical course of IgAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherubini et al2</td>
<td>44 years / Male</td>
<td>Hodgkin’s lymphoma</td>
<td>1 year / MPL, PS, MOPP, ABVD and dialysis</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Bergmann et al13</td>
<td>60 years / Female</td>
<td>Hodgkin’s lymphoma</td>
<td>2 weeks / MPL, PS, CY, BEACOPP</td>
<td>Remission</td>
</tr>
<tr>
<td>Yacoub et al3</td>
<td>55 years / Male</td>
<td>Small cell lung carcinoma</td>
<td>Simultaneous / Dialysis and carboplatin</td>
<td>End stage renal disease</td>
</tr>
<tr>
<td>Mak et al12</td>
<td>62 years / Male</td>
<td>B cell lymphoma</td>
<td>Simultaneous / Chlorambucil</td>
<td>Remission at 20 months</td>
</tr>
</tbody>
</table>

Abbreviations: MPL, methylprednisone; PS, prednisone; MOPP, nitrogen mustard, oncovin, procarbazine, prednisone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; CY, cyclophosphamide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; etoposide.
Acknowledgments: The authors wish to thank Dr Andres Chiesa-Vottero and Dr Mark Malaragno for preparing the pathology photomicrographs.

Financial Disclosures: None declared.

Funding/Support: None declared.

REFERENCES
