Paraneoplastic IgA nephropathy and IgA vasculitis in mesothelioma

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ABSTRACT

Immunoglobulin A (IgA) vasculitis and IgA nephropathy have been associated with underlying malignancies when present in adult populations. To date, we have found only two previously reported cases of IgA vasculitis and one IgA nephropathy case associated with mesothelioma, with our patient being the fourth. Our case describes a patient with biopsy proven IgA nephropathy and IgA vasculitis with known malignant mesothelioma who presented with features of lower extremity purpura, leukocytoclastic rash, and dialysis-dependent acute kidney injury (AKI).

Keywords: Acute kidney injury, Crescentic IgA nephropathy, Henoch–Schönlein purpura, IgA nephropathy, IgA vasculitis, Mesothelioma

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular pathology worldwide, regardless of age [1, 2]. It is diagnosed by the presence of IgA deposition in the mesangium of the glomerulus, often accompanied by other immunoglobulins or complement on histological examination [3]. Prognosis is dependent on multiple clinical and pathologic markers, but 10-year survival can be as high as 90% [4, 5].

Immunoglobulin A vasculitis (IgAV), formerly called Henoch–Schönlein purpura, is the most common vasculitis in pediatric populations [1]. It is characterized by nonthrombocytopenic palpable purpura with the presence of abdominal pain, arthritis, leukocytoclastic vasculitis on biopsy, and renal disease [6–8]. The renal manifestations in both IgAN and IgAV share multiple pathophysiologic mechanisms, including abnormal IgA1 O-glycosylation. The overall mechanism of injury, however, remains poorly defined, and despite this overlap there is considerable heterogeneity in outcomes among IgAN and IgAV [9, 10].

Immunoglobulin A vasculitis in adults is much less common than in pediatrics, with an incidence of 0.1–1.8 per 100,000 individuals compared to 3–26 per 100,000 in children [6, 11, 12]. It also tends to have a worse prognosis in adults compared to children, including higher rates of progression to end stage renal disease, more frequent
relapses, and higher incidence of life-threatening extra-
renal complications [13, 14].

Immunoglobulin A nephropathy and IgAV are both 
associated with many systemic illnesses, including liver 
disease, ankylosing spondylitis, and inflammatory bowel 
disease [15–18]. An increasing body of literature has 
described IgAN and IgAV as a finding in malignancy, 
particularly with lung involvement [19–22]. Here we 
describe a case of biopsy proven IgAN and IgAV in the 
setting of recent mesothelioma diagnosis with a literature 
review of mesothelioma associations with both disorders.

CASE REPORT

A 74-year-old Caucasian man presented with 
recently diagnosed stage IIIb malignant desmoplastic 
mesothelioma by histology (immunohistochemistry 
positive for CK-AE1/3, CK5/6, calretinin, D240, EMA, 
and CK7) requiring right thoracotomy and decortication 
due to a trapped lung. At the time of mesothelioma 
diagnosis, he had a creatinine of 0.8 mg/dL and no red 
blood cells (RBCs) on urine analysis. His other past 
medical history was relevant for grade II clear cell renal 
carcinoma treated with partial nephrectomy 11 years 
prior, with no evidence of recurrence, and coronary artery 
disease with coronary artery bypass grafting five years 
previously. His chronic medications included 
atorvastatin, felodipine, and metoprolol.

Three weeks after diagnosis, he presented to the 
emergency department for a purpuric rash and was found 
to have an AKI, with a creatinine of 1.7 mg/dL and 50+ RBC 
on urine analysis. A skin biopsy showed leukocytoclastic 
vasculitis with IgA deposition on immunofluorescence. He 
was discharged on prednisone 40 mg daily. Upon 
outpatient follow-up with his oncologist the patient was 
found to have a worsening AKI (creatinine 2.1 mg/dL). A planned course of carboplatin and pemetrexed was 
postponed due to concern for further nephrotoxicity.

On physical examination, he appeared to be in no 
acute distress although his oxygen saturation was 92% on 
2 L of oxygen via nasal cannula. His blood pressure was 
150/75 mmHg, heart rate 78 beats/minute, respiratory 
rate 20 breaths/minute, and his temperature was 36.2°C. He 
appeared slightly pale and had coarse crackles at the 
bilateral lung bases. He had bilateral small purpuric 
lesions on his lower extremities extending up to the thighs.

His abdominal and joint examination was unremarkable.

His blood work was relevant for blood urea nitrogen of 
39 mg/dL (6–23 mg/dL), creatinine of 2.07 mg/dL, 
potassium 3.3 mg/dL (3.5–5.1 mg/dL), white blood cell 
count 20.25 K/uL (4–10.4 K/uL), hemoglobin 10.6 g/dL 
(13–17 g/dL), and a platelet count of 364 K/uL (150–350 
K/uL). Urine analysis showed glucose 100 mg/dL, large 
amount of hemoglobin (via pseudoperoxidase activity; 
normal: none), protein >300 mg/dL, positive nitrites, 
and trace leukocyte esterase. Urine white blood cells were 
5–9 cells/HPF and RBCs were 50+ cells/HPF. The urine 
protein to creatinine ratio was 8.91 and a 24-hour urine 
collection revealed nephrotic range proteinuria of 8.45 g.

Renal ultrasound demonstrated increased echogenicity of the left kidney and simple cysts in the 
upper pole. The right kidney was unremarkable in size, 
echogenicity, or other pathology.

During his hospital course, the patient underwent a renal biopsy (Figure 1) due to rising creatinine in the setting 
of gross hematuria and nephrotic range proteinuria. 
Biopsy showed asynchronous mesangial and segmental 
endocapillary proliferation with focal subcircumferential epithelial crescents. One-third of the glomerular tufts 
were globally sclerotic. Mesangial deposition of IgA and 
codominant C3 was noted by immunofluorescence as 
well as mesangial electron densities by ultrastructural 
examination, which supported a diagnosis of IgA 
nephropathy with an Oxford criteria (MEST-C of M1, S0, 
E1, T0, C1).

The initiation of pulse steroids was delayed until the 
fifth day of his hospitalization due to concern for acute pneumonia. His creatinine continued to rise to 4.52 mg/
dL and he received pulse methylprednisolone 1000 mg

Figure 1: Renal histology in IgAV, (A) mild global mesangial cellular proliferation and segmental endocapillary proliferation (arrows) resulting in closure of capillary loops [Periodic acid–Schiff (PAS) × 500]. (B) Mesangial cellular proliferation and segmental tuft necrosis with associated fibroepithelial crescent (arrow). Crescents were present in a minority of tufts (PAS × 500). (C) Granular IgA deposition in mesangial stalks; there was codominant staining for C3 (immunofluorescence, IgA, ×500).
in two weeks, and prednisone was tapered to 20 mg daily. His oncologist held further chemotherapy given the stability of his mesothelioma on follow-up thoracic imaging.

DISCUSSION

Immunoglobulin A nephropathy and IgAV are classically described as primary pathologies, but an increasing body of literature has recognized them as secondary to other systemic processes, including malignancy [18, 19, 23]. Our patient had biopsy confirmed IgAN and IgAV in the setting of a recent diagnosis of mesothelioma and distant history of clear cell renal carcinoma.

Our patient presented with gross hematuria, nephrotic range proteinuria without nephrotic syndrome, and an AKI which rapidly progressed toward dialysis dependency. This severe presentation is considerably uncommon for primary IgAN and IgAV [2, 24], which raised suspicion for secondary nephropathy etiologies or other glomerulonephropathies, including minimal change disease and membranous nephropathy.

Tissue diagnosis confirmed IgAN and IgAV, with the kidney biopsy showing mesangial hypercellularity (>50% (M1) and endocapillary hypercellularity (E1) without evidence of segmental glomerulosclerosis (S0), tubular atrophy (T0), or crescent formation (C1) [25]. This categorization would generally correspond with a favorable overall IgAN prognosis via classic Oxford criteria with probable immunosuppression responsiveness. Our patient had poor improvement with immunosuppression therapy and instead developed rapid progression toward dialysis dependency. This may be due to lack of validation of the Oxford classification in adults with concomitant IgAV or those with secondary IgAN, or the presence of crescents, which tends to predict worse outcomes [26, 27]. Alternatively, IgAN progression is variable overall and our patient may have fallen in the minority cohort who does develop progressive end stage renal disease [28].

Immunoglobulin A nephropathy is uncommonly recognized as a paraneoplastic disorder in solid tumors, with the strongest associations in renal cell carcinoma and lung cancers [23, 29, 30]. While our patient had a distant history of clear cell renal carcinoma, the timing of IgAN development with his diagnosis of mesothelioma, in addition to the absence of evidence of renal cell carcinoma recurrence, makes paraneoplastic development secondary to malignant pleural mesothelioma much more likely. Immunoglobulin A nephropathy association with mesothelioma, in particular, has previously been scarcely described in only one other case, with our patient adding to the literature [31].

Adult-onset IgAV has a well-described association, with lung malignancy and it is considered the most common solid tumor associated with IgAV [19, 32–50]. Squamous cell carcinoma subtype represents the majority of these cases, followed by adenocarcinoma and small cell carcinoma, and this may represent a slight overrepresentation compared to the general incidence of lung cancer in the United States [32, 47, 49, 51]. To date, we are aware of only two prior cases of IgAV associated with mesothelioma, with our patient being the third reported case [48, 50].

Comparing our patient with previously described IgAN and IgAV cases associated with malignant pleural mesothelioma demonstrates a number of trends. All cases demonstrated initial responsiveness to immunosuppression, usually with prednisone, but without any consistent trend in dosing [31, 48, 50]. Unfortunately, progression of renal disease occurred in our patient and two of the three total IgAN and IgAV cases previously described [31, 50]. The deterioration of renal function observed in our patient is similar to IgAV cases reported in the elderly, who tend to have higher rates of progressive renal insufficiency compared to those diagnosed at a younger age [52]. Renal prognosis, even in the elderly, remains favorable, though in aggressive malignancy-associated IgAV, this trend would be difficult to detect, as most patients succumb to their malignancy prior to resolution of the nephritis [53]. Unfortunately, there are no large prospective or randomized clinical trials that have confirmed these observations in IgAV and malignancy [24].

Mesothelioma outcomes were more difficult to compare as the timing of diagnosis varied greatly and none of the cases opted for treatment of the mesothelioma. The average life expectancy of malignant pleural mesothelioma without treatment is around 12 months [54]. At eight months follow-up after mesothelioma diagnosis, two of the three case reports culminated in death [31, 50]. Our patient remains dialysis dependent at approximately five months postmesothelioma diagnosis.

Our case report adds to the growing evidence detailing the association between two rare disorders in adults. This analysis is limited given the extremely few case reports in the English literature and lack of large-scale trials that have involved IgAV or IgAN in association with malignancy. Our findings support the need for heightened awareness when making a diagnosis of IgAV and maintaining a high clinical suspicion for underlying malignancy meriting appropriate cancer screening in these patients. Further studies are needed to more
clearly delineate the association between IgAV, IgAN, and underlying malignancy, in particular mesothelioma. Future investigations that focus on the pathophysiologic links between cancer development and IgA-related renal disease can help elucidate potential risk factors for development, diagnostic modalities, and, ultimately, evidence-based treatments.

CONCLUSION

Adult onset IgAV and IgAN are increasingly recognized as potential paraneoplastic syndromes. Detection of these disorders should prompt aggressive malignancy screening in this patient population as outcomes are likely to be poor and treatment of secondary IgAV and IgAN differs from primary variants.

REFERENCES


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Korey Bartolomeo – Design of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Said Al Zein – Conception of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
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Catherine Abendroth – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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