

# IgA-Dominant Glomerulopathy and Thrombotic Microangiopathy After Chemotherapy



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## INTRODUCTION

The treatment of cancer has undergone much advancement in the past few decades as a consequence of development and proliferation of more potent and targeted chemotherapeutics. Despite the positive progress in cancer therapy and improvements in patient survival, nephrotoxicity remains a major inherent adverse effect of many anticancer drugs and the results can be devastating.<sup>1</sup> Furthermore, chemotherapeutics often unmask the presence of quiescent, subclinical chronic renal disease and exacerbate the clinical course and severity of preexisting renal conditions.<sup>2</sup> The renal effects of chemotherapeutics are widespread, often potentiate renal failure, and the problem may be underestimated.<sup>2</sup>

The kidney is vulnerable to injury by anticancer agents because it receives a large proportion of the cardiac output and is responsible for metabolism and excretion of many toxic substances.<sup>3</sup> Every compartment of the kidney is vulnerable to injury by chemotherapeutics, including the renal vasculature, the glomerulus, and the tubulointerstitium.<sup>3</sup> Underlying comorbid conditions in combination with cancer therapy can create a more serious situation than cancer therapy alone<sup>2</sup>; therefore, understanding of the modifiable and unmodifiable underlying risk factors for renal injury and the nephrotoxic potential of cancer therapies is critical for successful treatment and minimization of renal injury and failure. Herein, we describe a unique constellation of renal injury as a consequence of chemotherapy. We provide the clinical background, details of cancer diagnosis, management, histopathologic findings at biopsy, and patient outcome with emphasis on underlying comorbid conditions and potential mechanisms of injury.

## CASE PRESENTATION

### Clinical History

A 63-year-old white female presented with acute kidney injury that was rapidly progressing for 3 months with proteinuria and gross hematuria. Her past history was notable for uncontrolled hypertension, questionable history of scleroderma (clinically unconfirmed at our institution), and stage IV breast cancer (mucinous adenocarcinoma) with extensive gastrointestinal and hepatic metastases requiring partial hepatectomy, distal pancreatectomy, cholecystectomy, and splenectomy. She was treated with 16 cycles of gemcitabine and paclitaxel. Her chemotherapy course was complicated by *Clostridium difficile* colitis, bleeding duodenal ulcers, hypertensive urgency, and appearance of proteinuria. At presentation, she was found to have worsening hypertension (162/71 mm Hg, ultimately requiring 3 agents for control), and nephrotic range proteinuria (approximately 4 g/d). Urinalysis showed 1+ blood, 2+ protein, and she was noted to have a creatinine of 2.46 mg/dl (creatinine levels at 3, 2, and 1 months before biopsy were 0.71, 1.05, and 1.60 mg/dl, respectively), estimated glomerular filtration rate of 20 ml/min, glucose of 91 mg/dl (reference range 70–99), hemoglobin of 9.0 g/dl, platelet count of 787,000/mm<sup>3</sup>, and blood pressure of 153/70 mm Hg (day of biopsy). Routine serologic workup was significant for positive antinuclear antibodies (>1:640), negative anti-neutrophil cytoplasmic antibody (immunofluorescence), and normal myeloperoxidase, proteinase 3, and complement levels. Liver function tests were significant for elevated alkaline phosphatase (411 U/l; reference range 35–140) and elevated aspartate transaminase (62 U/l; reference range 0–32) and alanine transaminase (48 U/l; reference range 0–33). Viral serologies were

**Table 1.** Laboratory parameters at time of biopsy

Creatinine, mg/dl	eGFR, ml/min	Proteinuria, mg/24 h	Urine analysis	Complement	Serologies	Glucose, mg/dl	Alk. Phos., U/l	AST/ALT, U/l
2.46	20	4,000	2+ protein 1+ blood	C3, C4 normal	ANA+, dsDNA-, ANCA-, MPO-, PR3-, HBsAg-, HCAb-, HIV-	91	411	62/48

Alk. Phos., alkaline phosphatase; ALT, alanine transaminase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate transaminase; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B virus surface antigen; HCAb, hepatitis C virus antibody; MPO, myeloperoxidase; PR3, proteinase 3.

negative. She was started on an angiotensin receptor blocker given her proteinuria and hypertension; however, it was discontinued given a persistently rising creatinine. The clinical laboratory findings are summarized in Table 1.

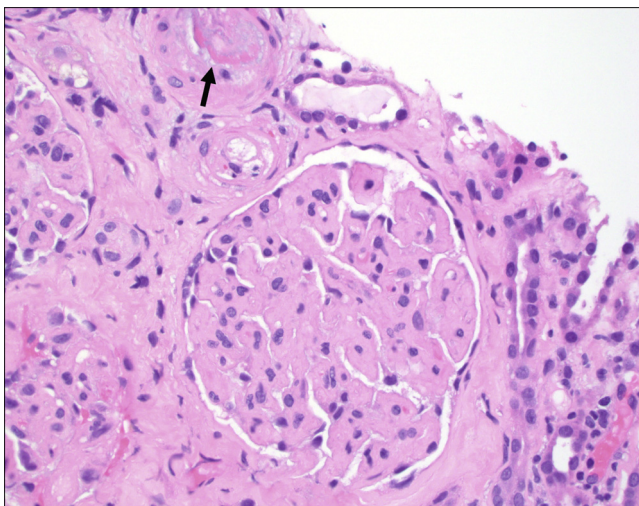
### Renal Biopsy Findings

The biopsy contained 26 glomeruli, 5 of which were globally sclerotic. Glomeruli showed diffuse thickening of capillary walls (Figure 1). Glomerular capillary loops were severely narrowed with global endotheliosis. Prominent mesangiolytic with numerous schistocytes in the mesangium was seen. Scattered glomerular capillary fibrin thrombi were noted. A single arteriole showed a large fibrin thrombus. There was moderate interstitial fibrosis and tubular atrophy (20%–30%). Immunofluorescence studies showed IgA-dominant granular staining of mesangial areas and peripheral capillary walls (IgG: 0; IgA: 2+; IgM: 1+; C3: 2+; C1q: 0; kappa: 1+; lambda: 1+ [scale: 0–3+]) (Figure 2). Electron microscopy revealed the presence of diffuse endothelial cell swelling with lifting of the endothelial cell off of the underlying glomerular basement membranes. In many areas, new basement membrane material deposition along with mesangial cell interposition was seen (Figure 3). Rare subendothelial deposits

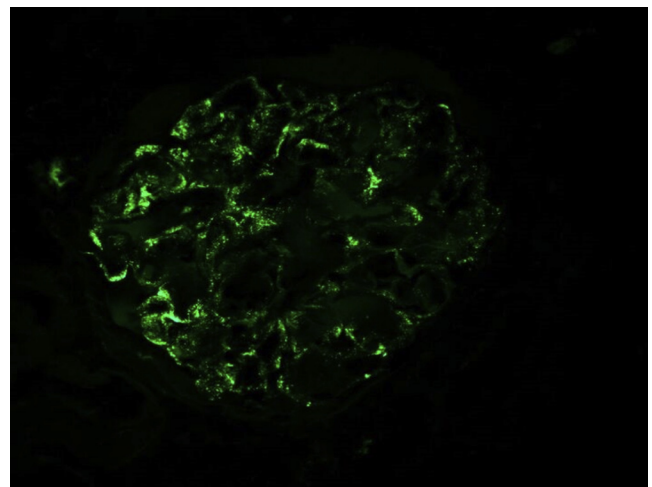
(low density), and frequent mesangial deposits (high density) were seen. No substructure was identified to any of the deposits.

### Post Biopsy Course

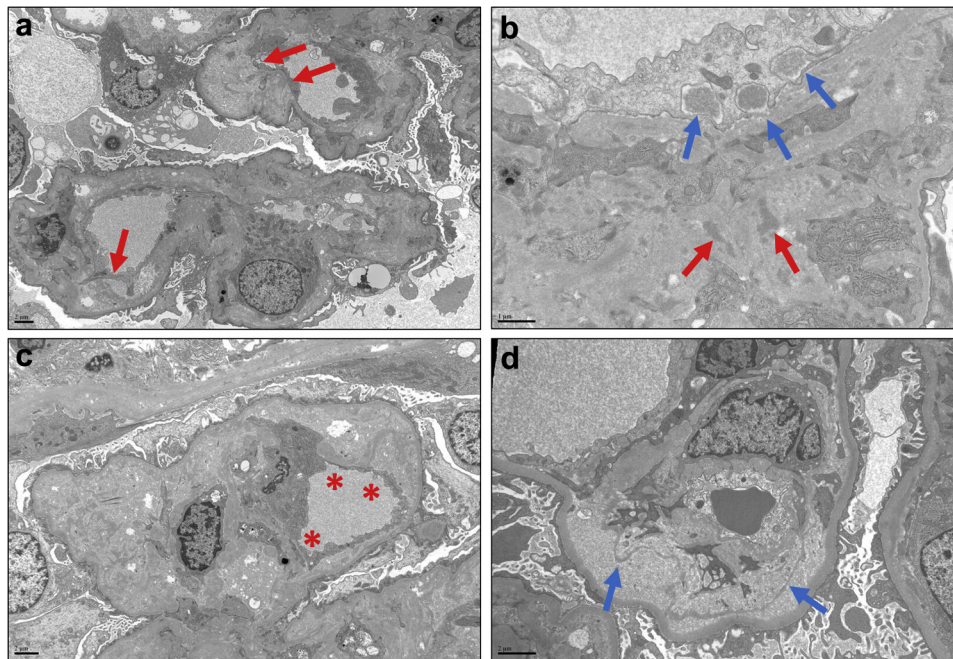
A diagnosis of “IgA-dominant immune complex-mediated glomerulopathy with thrombotic microangiopathy” was rendered. Gemcitabine was stopped 2 months before biopsy and chemotherapy was switched to liposomal doxorubicin. Unfortunately, the patient’s renal function continued to decline and the patient developed end-stage renal disease. She had a brief course of steroids while awaiting the final pathology report, and required admission for intravenous diuresis given massive anasarca due to her underlying nephrotic syndrome and renal failure. Eculizumab and rituximab were considered in the management of her gemcitabine-induced thrombotic microangiopathy (TMA) based on a limited number of case reports and case series<sup>4,5</sup>; however, the patient’s clinical status continued to deteriorate. Ultimately, the patient was started on dialysis, which was unfortunately poorly tolerated. Due to worsening clinical status and poor prognosis, the patient’s goals of care were switched to comfort care and hospice 4 months after renal biopsy.



**Figure 1.** Glomerular capillaries show diffuse thickening of peripheral capillary walls with global endothelial cell swelling (endotheliosis). An adjacent periglomerular arteriole is occluded by a fibrin thrombus (black arrow) (hematoxylin and eosin, original magnification  $\times 400$ ).



**Figure 2.** Granular staining of mesangial regions and peripheral capillary walls (IgA fluorescein isothiocyanate, original magnification  $\times 400$ ).



**Figure 3.** (a) Glomerular capillaries show diffuse subendothelial widening. (b) Immune deposits are seen in the mesangium (red arrows) and in subendothelial locations (blue arrows). (c) Endothelial cell swelling and separation from the basement membrane with mesangial cell interposition with marked narrowing of the capillary lumen (red asterisk). (d) Formation of new basement membrane material (blue arrows). (Uranyl acetate, transmission electron microscopy.)

## DISCUSSION

The patient described showed an unusual pattern of renal injury following chemotherapy with gemcitabine. The pattern of injury was characterized by an atypical pattern of IgA deposition superimposed on TMA. The differential diagnosis for glomerular diseases with an IgA-dominant pattern of staining by immunofluorescence includes IgA nephropathy (primary and secondary), IgA-dominant infection-associated glomerulonephritis (*Staphylococcus* associated), hepatic glomerulopathy, atypical anti-glomerular basement membrane disease, and rare forms of IgA-dominant membranoproliferative glomerulonephritis (Table 2).<sup>6-9</sup> The subepithelial nature of some of the deposits raised the strong possibility of an IgA-dominant infection-associated glomerulonephritis. Infection-associated glomerulonephritis often can occur in patients in whom obvious infection is not evident (occult infection). In our patient, however, there was extensive radiographic and clinical workup for occult infection, and no evidence of infection was found.

An underlying quiescent primary IgA nephropathy exacerbated by initiation of drug or other environmental stimuli was also considered in the differential diagnosis. The currently accepted theory of pathogenesis of primary IgA nephropathy is that of a confluence of genetic and environmental factors in a “multi-hit” model of injury.<sup>10</sup> Currently, there are no reliable biomarkers to confirm or rule out the

possibility of IgA nephropathy, and this diagnosis was always a consideration in our case. However, our case demonstrated a highly unusual distribution of immune deposits that are not typical of conventional IgA nephropathy, including deposits within the sub-endothelial spaces and the mesangium.

Secondary IgA nephropathy is less common than primary IgA nephropathy and is encountered in a wide variety of systemic illnesses, including disorders of the liver, skin, intestine, respiratory tract, infectious and autoimmune disease, neoplastic disorders, and iatrogenic etiologies.<sup>9-11</sup> The commonest form of secondary IgA nephropathy is chronic liver disease.<sup>12</sup> The pathogenic mechanisms are thought to be secondary to increased IgA production, production of abnormal IgA, and impaired IgA clearance (hepatocytes and Kupffer

**Table 2.** Teaching points

### Differential diagnosis for glomerular diseases with an IgA-dominant staining pattern:

1. IgA nephropathy/Henoch–Schönlein purpura
2. Secondary IgA nephropathy (e.g., chronic liver disease, celiac disease, inflammatory bowel disease, gastrointestinal bleed)
3. IgA-dominant *Staphylococcus*-associated infectious glomerulonephritis
4. Atypical anti-glomerular basement membrane disease
5. Rare forms of immune complex-mediated glomerulonephritis, such as IgA-dominant membranoproliferative glomerulonephritis, those occurring after acute mucosal injury, and drug or toxin exposure

### Proposed mechanisms of glomerular IgA immune complex deposition:

1. Mucosal injury secondary to metastatic disease, chemotherapeutics, radiation, and surgery
2. Increased mucosal permeability secondary to chemotherapy
3. Decreased IgA clearance secondary to liver dysfunction

cells both express IgA receptors).<sup>12</sup> It is possible that the ongoing liver injury in our patient contributed to the pattern of renal injury seen. The patient had significant metastatic disease to the liver with abnormalities in liver function tests that even required partial hepatectomy. Therefore, it is possible that metastatic liver disease may have contributed to decreased IgA clearance and elevations in circulating IgA levels that subsequently initiated immune complex formation and deposition in glomeruli.

Secondary IgA nephropathy is also commonly seen in cases with mucosal damage, particularly of the gastrointestinal, respiratory, and urothelial tracts, where most IgA synthesis occurs as frontline immunity against microbial intrusion.<sup>11,13</sup> Paraneoplastic IgA nephropathy has been most commonly associated with cancers of the gastrointestinal and respiratory tracts<sup>14</sup> and may be explained by increased levels of circulating IgA due to mucosal injury. Furthermore, chemotherapy and radiation are well-known causes of significant oral and gastrointestinal mucosal injury,<sup>15</sup> and this injury also may cause increased levels of circulating IgA, which may then form peripheral IgA immune complexes. Indeed, a potential mechanism was described whereby increased circulating IgA levels were produced by malignant invasion of IgA-rich mucosae, thereby leading to formation of glomerular deposits.<sup>16</sup>

Interestingly, our patient had extensive gastrointestinal metastatic disease requiring surgical and chemotherapeutic management, both of which independently contributed to mucosal injury. Widespread metastatic disease in our patient required extensive abdominal resections, including distal pancreatectomy and cholecystectomy (and partial hepatectomy with splenectomy). It is possible that a combination of liver dysfunction and mucosal damage caused by malignancy and subsequent treatments may have produced an environment whereby excess circulating IgA resulted in the formation of peripheral immune complexes that then deposited within glomeruli at clinically significant levels.

TMA is a well-documented sequela of chemotherapeutic agents, with gemcitabine as one of the most frequently cited.<sup>17,18</sup> However, we have noted similar patterns of injury in at least 2 additional patients at our institution with the use of other chemotherapeutic agents, and with newer anti-vascular endothelial growth factor inhibitors, such as bevacizumab in particular (data not shown). The implicated mechanisms of renal injury after vascular endothelial growth factor inhibitors deserves further discussion here, as it implicates a larger group of chemotherapeutics in this pattern of injury, and helps elucidate the pathologic

mechanisms at play. An IgA-dominant glomerulopathy in a bevacizumab-treated patient was first suggested in a case report by Roncone *et al.*<sup>19</sup> Similar to our patient, the authors demonstrated bright diffuse granular glomerular capillary wall and mesangial staining for IgA. Interestingly, the IgA-dominant staining was not present in the patient's biopsy before initiation of bevacizumab therapy, arguing that the presence of IgA staining was a *de novo* effect of bevacizumab. However, the authors could not exclude the possibility that concurrent administration of other medications (i.e., interferon- $\alpha$ ) may have also contributed. Since then, the finding of IgA-dominant glomerular deposition in conjunction with thrombotic microangiopathy was reported in 4 patients treated with anti-vascular endothelial growth factor therapy.<sup>20–22</sup> More recently, Yahata *et al.*<sup>22</sup> reported a single case in which hematuria was an initial symptom, followed by later development of proteinuria in a patient treated with bevacizumab for metastatic rectal cancer. Interestingly, immunofluorescence analysis demonstrated mesangial-predominant IgA deposition, and electron microscopy showed numerous hemispherical paramesangial electron-dense deposits. It is notable that no cases of bevacizumab-related IgA-dominant glomerulopathy without thrombotic microangiopathy have been published, suggesting that the two may be related and that IgA deposition alone may be subclinical. The mechanism of IgA deposition in bevacizumab-related nephropathy is incompletely understood, especially since not all patients with bevacizumab-induced thrombotic microangiopathy develop concomitant IgA deposition. It must be noted that Yahata *et al.*<sup>22</sup> demonstrated that serum levels of IgA increased after bevacizumab administration, and decreased steadily over the course of 25 months of follow-up.

The presence of renal complications such as TMA in association with IgA nephropathy has been well established in the literature. Chang and colleagues<sup>23</sup> identified 10 patients in which microscopic and/or ultrastructural evidence of TMA was present concomitantly with IgA nephropathy. Their study suggested that the occurrence of TMA in the setting of IgA nephropathy is not uncommon, and when present, is found in advanced stages of IgA nephropathy with severe proteinuria and severe hypertension. The authors concluded that the presence of severe hypertension was likely secondary to disease progression in long-standing IgA nephropathy, and was likely the driving factor behind development of TMA. A larger study of 128 patients with IgA nephropathy found that 53% had lesions of TMA and that among those with TMA, 71% had a clinical history of uncontrolled hypertension.<sup>24</sup> Interestingly, the lesions of TMA

could be seen in normotensive patients (4% of those with TMA) with mild disease and near-normal morphology, further arguing that advanced parenchymal lesions and severe hypertension are not the sole causes of TMA in cases of IgA nephropathy, and that additional, as yet unknown, pathogenic mechanisms are at play.<sup>24</sup> In our patient, light microscopic evidence of arteriolar thrombi suggest that uncontrolled hypertension may have contributed to a more severe form of TMA. Furthermore, our patient also had a questionable history of scleroderma (clinically unconfirmed at our institution), a connective tissue disorder known to predispose to development of TMA,<sup>25</sup> which in combination with gemcitabine and severe hypertension may have contributed to development of severe TMA.

In summary, we describe a case demonstrating an unusual pattern of glomerular IgA deposition that cannot be attributed to classic or typical IgA nephropathy or IgA-dominant infection-associated glomerulonephritis superimposed on TMA. The overall findings suggest that IgA deposition and TMA, occurring secondary to multiple mechanisms of injury, may have together contributed to the development of clinically significant renal dysfunction necessitating biopsy. Specifically, this patient had widely advanced metastatic cancer with evidence of gastrointestinal involvement, liver dysfunction, and mucosal injury, all of which may have contributed to increased circulating levels of IgA and its deposition in the glomerulus (Table 2). The superimposed TMA was likely due to the antineoplastic agents (gemcitabine); and additional factors such as connective tissue disease (scleroderma) and severe hypertension also likely contributed. Our case report may help to identify patients at risk for this unique type of renal injury, namely those with malignancies with any combination of liver metastases, mucosal injury, and treatment with agents known to cause endothelial damage (i.e., gemcitabine and vascular endothelial growth factor inhibitors). Additional studies are warranted to determine a potential link between IgA deposition and TMA in this setting.

## DISCLOSURE

All the authors declared no competing interests.

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