Chapter 6: Glomerular Diseases and Cancer

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INTRODUCTION

Glomerular diseases are associated with many solid and hematologic malignancies. Additionally, many chemotherapeutic agents and post–stem cell transplant–associated glomerular lesions have been described. These glomerular lesions are most likely due to abnormal products produced by tumor cells, although the exact pathogenesis is unclear. The treatment of these cancer-associated glomerulopathies is primarily targeted at treating the underlying malignancy. This chapter will review glomerular diseases associated with cancer, chemotherapy, and hematopoietic stem cell transplantation (HSCT).

SOLID TUMOR–ASSOCIATED GLOMERULAR DISEASES

Membranous nephropathy

Membranous nephropathy (MN) is the most common glomerular pathology (Figure 1, A and B) described in patients with solid tumors (1,2). In a review of 240 patients with biopsy proven MN, Lefaucheur *et al.* (3) reported a prevalence of malignancy of 10%. Only about half of these patients had symptoms related to cancer at the time of their kidney biopsy. Also, most of these patients were diagnosed with malignancy within a year of MN diagnoses. Review of case series shows a reported prevalence of as low as 1% to as high as 22% (2).

Classically, the solid tumors most commonly associated with MN are lung, bronchus, and gastric cancers, followed by renal cell, prostate, and thymoma (2). Other cancers reported with MN are colorectal, pancreatic, esophageal, and hepatic carcinomas.

Differentiating primary MN from secondary MN associated with malignancy can be difficult. Our suspicion for a secondary glomerular disease should be high in a patient with known cancer who has presence of proteinuria or nephrotic syndrome. Also development of proteinuria within a year of diagnosis of cancer should raise the suspicion of secondary form of glomerulopathy. Studies have reported risk factors like age >65 years and history of smoking for >20 pack-years for paraneoplastic MN (3). Review of relevant studies (3–7) has suggested certain parameters, which can help differentiate primary from secondary MN, the latter being associated with cancer. These features are summarized in Table 1 (8).

In addition to these findings, one should have a high index of suspicion for malignancy when a patient with MN is evaluated. It is reasonable to perform routine age- and sex-appropriate screening for malignancy, once other known causes of secondary MN have been excluded. In patients with high risk of lung cancer, low-dose chest computed tomography should be considered. The risk of cancer persists for ≥ 5 years from the time of kidney biopsy (9). This is most likely due to slow-growing malignancy, use of cytotoxic therapy for MN, or increased surveillance. Therefore, close medical follow-up is needed even if the cancer is not detected on initial screening at the time of MN diagnosis.

The possible mechanisms by which solid tumors may be associated with MN include the following (10):

1) *In situ* immune complex formation: Antibodies are formed against a tumor antigen, which is localized in the sub epithelial location or to a podocyte antigen that is identical or similar to the tumor antigen.

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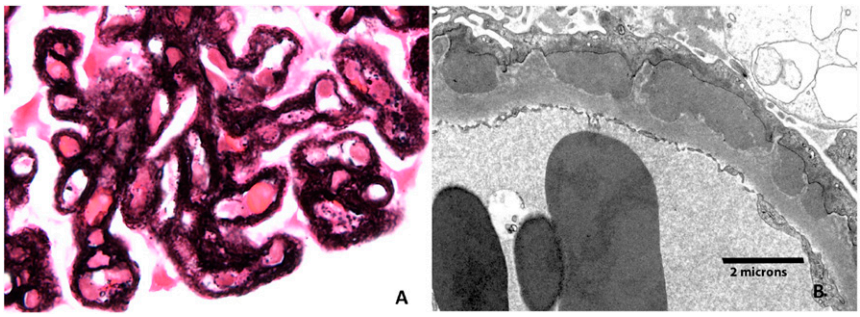

Figure 1. Membranous nephropathy. (A) Light microscopy showing immune complex deposits. Note the thickened basement membrane, which stains black while deposits within it stain pink, giving a variegated appearance to the capillary wall. Silver [periodic acid silver methamine (PASM)] stain; 60×, original magnification. (B) Electron microscopy showing immune complex deposits in a subepithelial location, between effaced podocyte foot processes (top) and the basement membrane (bottom).

2) Tumor antigens may form circulating immune complexes that are subsequently trapped in glomerular capillaries.
3) External factors such as infections with oncogenic viruses or altered immune function that can cause both the malignancy and MN.

Other glomerular diseases

Minimal change disease (MCD) has been reported in association with solid tumors like lung, colorectal, renal cell cancers, and thymoma. Rarely, pancreatic, bladder, breast, and ovarian cancers have also been associated (2). Focal segmental glomerular sclerosis (FSGS) has been observed with renal cell carcinoma, thymoma, and rarely with lung, breast, and esophageal cancers (2). A membranoproliferative glomerular nephritis (MPGN) pattern of injury has been described with lung, kidney, and stomach cancer (2).

Mustonen *et al.* (11) reported the first known association between IgA nephropathy and solid tumors of the respiratory tract, buccal mucosa, and nasopharynx. Renal cell carcinoma is the most frequently reported solid malignancy associated with IgA nephropathy (12). Treatment of underlying cancer improved the IgA nephropathy (11).

Rarely, both solid and hematologic malignancies have been associated with adult Henoch-Schönlein purpura (HSP) (13,14). Endocapillary glomerulonephritis is the most commonly seen lesion on kidney biopsy in adults with HSP (15). Older age and male sex were identified risk factors for cancer-associated HSP (14).

Crescentic glomerulonephritis (CGN) has been associated with renal cell, gastric, and lung cancers (2).

Thrombotic microangiopathy (TMA) has been associated with mucin-producing gastric, lung, and breast cancers (16). In these patients, ADAMTS13 activity is not impaired, and they respond poorly to plasmapharesis (17).

The exact mechanism of these solid tumor malignancy associations with glomerular disease is poorly understood. There have been animal studies (18) done to help us understand the pathomechanisms involved.

This animal study suggested that T-cell response might be critical in the development of paraneoplastic glomerular disease. Th1 (T-helper type 1)-predominant responses have been associated with proliferative and crescentic forms of GN and Th2 (T-helper type 2) type responses with a membranous pattern of injury (19). Cancer-associated MCD might be related to vascular endothelial growth factor (VEGF) production (20). Overexpression of VEGF leads to a collapsing variant of FSGS, and underexpression is associated with a TMA pattern of injury (21,22).

Thymoma-associated glomerular disease

MCD is the most common glomerular disease associated with thymoma (23). The prevalence of thymoma associated glomerulopathy is ~2% (23). Other glomerular lesions

Table 1. Differences between primary and tumor-associated secondary MN

Compared feature	Primary MN	Solid tumor–associated MN
History	Younger age, no history of smoking	Age >65 years, smoking >20 pack-years
Serologic markers	Presence of circulating anti-PLA2R autoantibodies in serum	Absence of anti-PLA2R autoantibodies
Histopathologic clues on kidney biopsy	Predominance of glomerular IgG4 deposition Enhanced glomerular PLA2R staining Presence of less than eight inflammatory cells per glomeruli	Predominance of glomerular IgG1/IgG2 deposition Normal glomerular PLA2R staining Presence of greater than eight inflammatory cells per glomeruli

IgG, immunoglobulin G; MN, membranous nephropathy; PLA2 R phospholipase A2. Reprinted with permission from reference 73.

Table 2. Glomerular diseases associated with solid tumors and hematologic malignancies (23)

Malignancy	Glomerular diseases reported
Lung cancer[a]	MN, MCD, MPGN, IgAN, FSGS, CGN, TMA
Colon cancer	MN, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA, CGN, IgAN, MCD, FSGS, MPGN
Prostate cancer	MN, CGN
Breast cancer	MN, FSGS, MPGN, TMA
Esophageal cancer	MPGN, FSGS
Gastrointestinal stromal tumor	AAA
Gastric cancer	MPGN, CGN, TMA
Spleen sarcoma	AAA
Head and neck cancer	MN, IgAN
Wilms' tumor	MN, MPGN
Teratoma	MN
Ovarian cancer	MN, MCD
Cervical cancer	MN
Endometrial cancer	MN
Tongue cancer	IgAN
Mesothelioma	MCD
Melanoma	MN, MPGN
Skin cancers (basal and squamous cell)	MN
Pheochromocytoma	MN
Thymoma	MCD, FSGS, CGN, MPGN
Hodgkin disease	MCD, MN, MPGN, IgAN, FSGS, CGN, AAA, Anti-GBM
Non-Hodgkin's disease	MN, MCD, MPGN, IgAN, FSGS
CLL	MN, MCD, MPGN, FSGS, CGN
AML	MN, FSGS
CML	MN, MCD, MPGN
MGUS	MPGN
T-cell leukemia	FSGS

[a]Includes small-cell, non–small-cell, squamous cell, and bronchogenic cancers. AAA, AA amyloidosis; AML, acute myelogenous leukemia; CGN, Crescentic glomerulonephritis; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; FSGS, focal segmental global sclerosis; GBM, glomerular basement membrane; IgAN, IgA nephropathy; MCD, minimal change disease; MGUS, monoclonal gammopathy of unclear significance; MN, membranous nephropathy; MPGN, membranoproliferative glomerular nephritis; TMA, thrombotic microangiopathy. Reprinted with permission from reference 23.

described are MN, FSGS, CGN, and lupus-like nephritis (24). MN is associated with thymoma of epithelial origin. MCD is associated with thymoma with lymphocyte predominance. The pathogenesis of thymoma-associated MN seems to be similar to solid tumor–associated MN, and thymoma-associated MN is likely related to T-cell dysfunction (24). Studies (25–27) have suggested a major role of T cells, especially the Th2 subtype, in thymoma-associated nephrotic syndromes.

Table 2 summarizes the various solid tumors seen with solid tumors.

HEMATOLOGIC MALIGNANCIES–ASSOCIATED GLOMERULAR DISEASES

Minimal change disease

MCD is classically associated with Hodgkin lymphoma (HL), more so in the mixed cellularity and nodular sclerosing types. MCD usually presents around the time of diagnosis of the malignancy (28). One case series does report diagnosis of MCD preceding the diagnosis of lymphoma by several months (29). A poor response to the treatment of MCD with corticosteroids should raise suspicion of underlying lymphoma. In the case series by Audard *et al.*, (29), the simultaneous diagnosis of HL and MCD was associated with the remission of proteinuria in response to chemotherapy.

Th2-related cytokines such as interleukin (IL)-13 have been reported to cause inflammatory response in Hodgkin disease (30), and rat studies have shown that overexpression of IL-13 induces proteinuria, hypoalbuminemia, and hypercholesterolemia (31). These kidney biopsies showed fusion of foot processes, suggesting MCD like pathology.

Membranoproliferative glomerulonephritis

Da'as *et al.* (32) reviewed 42 cases of glomerular disease with chronic lymphocytic leukemia (CLL); of these, 36 had nephrotic syndrome. The most common glomerular lesion was MPGN, followed by MN. Another case series of 13 patients with glomerular disease and either CLL or well-differentiated lymphocytic lymphoma (33) showed that the majority had an MPGN pattern of injury. Most MPGN patients had an associated cryoglobulinemia.

An MPGN pattern on kidney biopsy (Figure 2) may also be a clue to a developing of undiagnosed lymphoplasmacytic malignancy (8). Sethi *et al.* (34) reported an association between MPGN and monoclonal gammopathy of uncertain significance. They showed that patients with monoclonal gammopathy with normal bone marrow biopsies had granular immune deposits on their kidney biopsy, which correlated with their serum and urine monoclonal proteins. This study (34) also demonstrated that monoclonal gammopathy can be seen in the setting of other lymphoplasmacytic diseases, including low-grade B-cell lymphoma, CLL, and multiple myeloma. Although this direct relationship is not proven, the current observation suggests this possibility (34). More of this is discussed in the paraproteinemia chapter of the curriculum.

Glomerular diseases associated with myeloproliferative disorders

Myeloproliferative disorders include chronic myelogenous leukemia (CML), polycythemia Vera (PCV), and essential thrombocythemia. A recent study (35) of 11 patients with myeloproliferative disorders with proteinuria and renal failure showed mesangial sclerosis with hypercellularity in all patients, segmental sclerosis in eight patients, features of TMA in eight patients, and intracapillary hematopoietic cells in four patients. Glomerular disorders associated with myeloproliferative disorders are usually late complications and tend to

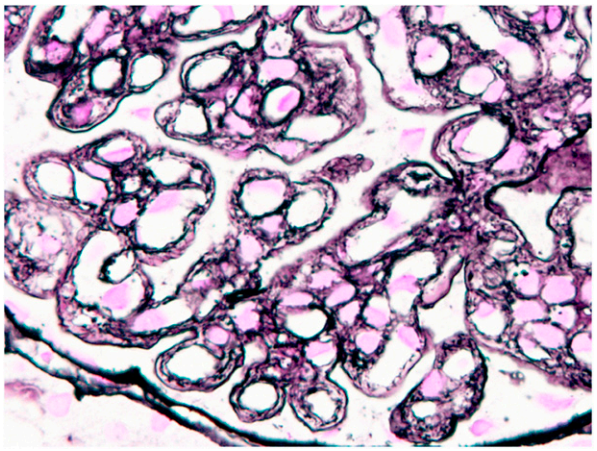

Figure 2. Membranoproliferative glomerulonephritis. Light microscopy showing basement membrane duplication and increased cells in capillary lumens. Silver (PASM) stain; 60×, original magnification.

have a poor renal prognosis, with progressive kidney injury occurring in most patients (35).

Essential thrombocythemia and PCV have been associated with FSGS and mesangial proliferative glomerular disease. The prevalence of glomerular disease in PCV and essential thrombocythemia is approximately 3%–4% (36). CML is least likely to have an association with glomerular pathology (36).

FSGS has also been reported with Hodgkin's lymphoma (28) with good response to chemotherapy.

Other glomerular diseases associated with lymphoproliferative disorders

MN has also been reported with CLL, but less commonly compared with MPGN (32). A case of IgA nephropathy has been described with cutaneous T-cell lymphoma (37).

Fibrillary glomerulonephritis (FGN) and Immunotactoid glomerulopathy (ITG) are rare groups of disorders characterized by formation of organized glomerular deposits (Figure 3, A and B). These diseases can either occur as primary condition or be secondary to systemic diseases, mainly lymphoproliferative disorders. ITG is more strongly associated with neoplasms, typically paraproteinemias and CLL, compared with FGN (38). ITG on kidney biopsy should warrant an investigation of an underlying hematologic malignancy. Treatment is directed toward underlying malignancy.

Glomerular diseases have also been associated with hemophagocytic syndrome. This syndrome is most commonly associated with Epstein-Barr virus; however, it has also been described with T-cell lymphoma (39,40). Thaunat *et al.* (40) described 11 patients with hemophagocytic syndrome who developed nephrotic syndrome. Renal biopsy showed glomerular lesions consisting of MCD, FSGS, and TMA. In the absence of a causative viral infection, hemophagocytic syndrome is often treated with immunosuppressive therapy with uncertain renal outcomes.

HEMATOPOIETIC STEM CELL TRANSPLANT–RELATED GLOMERULAR DISEASES

In HSCT patients, the kidney biopsy findings in patients with nephrotic range proteinuria include MN, MCD, and FSGS (41). Although we discuss briefly here, an entire chapter is devoted to HSCT-related kidney disease in the Curriculum.

Chronic graft-versus-host disease

MN accounts for a majority of cases of HSCT-associated glomerular disease, followed by MCD (41). When MCD occurs in such patients, it is prudent to rule out recurrence of the primary hematologic malignancy.

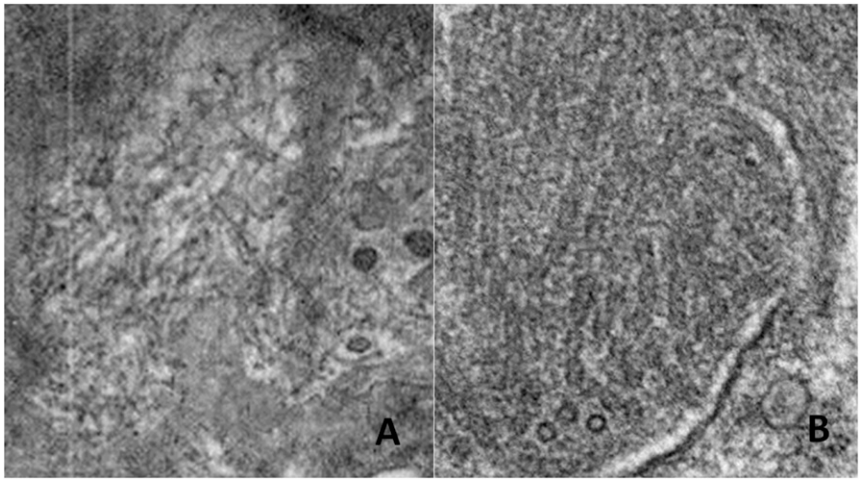

Figure 3. Fibrillary and immunotactoid glomerulonephritis. (A) Electron microscopy view of fibrillary glomerulonephritis. (B) Electron microscopy view of immunotactoid glomerulonephritis.

A review of literature by Brukamp *et al.* (41) showed a close temporal relationship between development of nephrotic syndrome shortly after cessation of immunosuppression and the diagnosis of chronic graft-versus-host disease (GVHD). Luo *et al.* (42) investigated the etiology and pathogenesis of nephrotic syndrome after allogenic HSCT. Nephrotic syndrome after allogenic SCT was associated with the occurrence of chronic GVHD.

Autologous HSCT can also develop glomerular diseases (43), although in these patients, GVHD does not occur. It is possible that there is an immune dysregulation that might be causing nephrotic syndrome secondary to induction agents or that these glomerular diseases are *de novo*. T cell–depleted HSCT recipients are highly unlikely to develop glomerular diseases. However, our knowledge about glomerular diseases in HSCT patients is incomplete, and more research is needed for complete understanding.

Thrombotic microangiopathy after HSCT

TMA after HSCT is also known as bone marrow transplant nephropathy or, in some specific cases, radiation nephropathy. A diagnosis criteria for HSCT-related TMA included >4% schistocytes in blood, *de novo* prolonged or progressive thrombocytopenia, sudden persistent increase in lactate dehydrogenase, and a decrease in serum haptoglobin (44). Studies have suggested that acute GVHD grade 2–4, hepatic GVHD, veno-occlusive disease, adenovirus infection, older age, being female, and total body irradiation of >12 Gy are risk factors for the development of TMA (45,46). TMA can also occur in T cell–depleted group of patients where calcineurin inhibitors (CNIs) and GVHD do not exist (47). Treatment of HSCT-related TMA is usually supportive, with control of hypertension and proteinuria. Plasma exchange has not proven to be effective.

CHEMOTHERAPY-ASSOCIATED GLOMERULAR DISEASE

Thrombotic microangiopathy

Mitomycin C, an alkylating agent, used to treat breast, gastric, and pancreatic cancer, can cause TMA-like syndrome. Its nephrotoxicity is dose dependent and usually appears after a cumulative dose of >40–60 mg/m^2 given over a period of several months (48).

Gemcitabine, commonly used for pancreas, urothelial, and ovarian cancers, has been shown to cause TMA (49). Cessation of these medications is shown to improve TMA. Carfilzomib is a second-generation proteasome inhibitor used for the treatment of relapsed or refractory multiple myeloma. There has been recent case reports (50,51) that reported TMA associated with the use of this agent. One of them (51) had kidney biopsy evidence of TMA (Figure 4). Treatment options include cessation of the drug with uncertain importance of therapeutic plasma exchange. Kidney biopsy–proven renal TMA has been reported by Kwa *et al.* (52) in patients receiving years of pegylated liposomal doxorubicin for recurrent ovarian cancer.

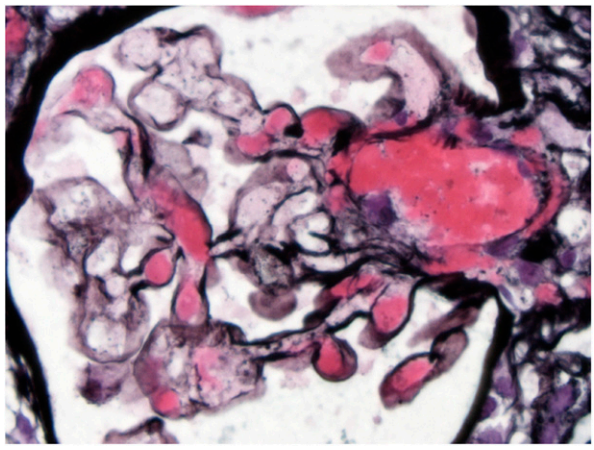

Figure 4. Thrombotic microangiopathy. Light microscopy view showing red cell thrombi in the afferent arteriole and two glomerular capillaries. Some basement membrane duplication, but without increased intracapillary cells, is also visible. Silver (PASM) stain; 60×, original magnification.

Bisphosphonate-induced glomerular injury

Pamidronate is used to treat malignancy associated bone disorders in myeloma. Markowitz *et al.* (53) showed that pamidronate causes biopsy-proven collapsing FSGS. MCD has also been reported with this agent (54).

Interferon-induced glomerular injury

Interferons (IFN)-α, -β, and -γ have been associated with moderate proteinuria (55). Markowitz *et al.* (56) reported 11 cases of collapsing FSGS that developed during treatment with IFN. IFN-α developed significant proteinuria and renal failure after a short duration of treatment. Patients treated with IFN-β developed proteinuria after a prolonged course of treatment. The authors (56) also reviewed 21 additional cases of IFN-associated glomerular disease. Thirteen of these patients had FSGS, and the rest had MCD. The mechanism of this injury is not fully understood. There is a direct effect of IFN on the podocyte by altering the cellular proliferation and cell metabolism (56). The indirect effects of IFN might be due to adaptive immune mechanism that increase macrophage activation or via 1L-6 or 1L-13 production (56).

IFN-α, when used for treatment of CML, has been reported to be associated with TMA (57,58).

Calcineurin and mammalian target of rapamycin inhibitors

CNIs can cause a rare manifestation of TMA with glomerular changes. The histology is indistinguishable from other causes of TMA (59). The only consensus on treatment is to withdraw the CNIs (60).

Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, tensirolimus, and everolimus can develop

Table 3. Glomerular toxicity associated with chemotherapeutic agents

Type of cells involved	Chemotherapy agents
Glomerular epithelial cells (podocytes)	
Minimal change disease	Interferon-α and -β, pamidronate, tyrosine kinase inhibitors, anthracyclines, mTOR inhibitors
Focal segmental glomerular sclerosis	Interferon-α and -γ, pamidronate, tyrosine kinase inhibitors, clofarabine, anthracyclines, mTOR inhibitors
Other glomerular diseases	Ipilimumab, mTOR inhibitors
Glomerular endothelial cells	
Thrombotic microangiopathy	Mitomycin-c, gemcitabine, cisplatin, carboplatin, cytarabine, lomustine, tamoxifen, bleomycin, bortezomib, carfilzomib, anthracyclines, hydroxyurea

complications including TMA and FSGS in renal transplant patients (61–63). MCD, MN, FSGS, MPGN, and IgA nephropathy have also been associated with sirolimus in the kidney transplant literature (64–66). There is speculation that sirolimus-induced proteinuria is related to collapsing FSGS associated with VEGF overexpression in podocytes.

Antiangiogenesis agents

Antiangiogenic agents are used primarily for advanced stage solid tumors, including renal cell carcinoma, non–small cell lung carcinoma, colorectal carcinoma, and gastrointestinal stromal tumors. Monoclonal antibodies against VEGF and tyrosine kinase inhibitors (TKIs) (67,68) have been observed to cause hypertension, proteinuria, and renal vascular injury, manifested by proteinuria and TMA (69). VEGF maintains normal functioning of glomerular endothelial cells, podocytes, mesangium, and peritubular capillaries. Hence, inhibition of VEGF can lead to dose-dependent proteinuria, swelling and detachment of glomerular endothelial cells, vacuolization of endothelial cells, disruption of slit diaphragms, and down-regulation of nephrin (70). Examples of anti-VEGF therapy include bevacizumab, and TKIs include sunitinib and sorafenib. In the majority of cases, proteinuria and hypertension resolve or significantly improve with cessation of this therapy (69). VEGF inhibitors are more likely to present as TMA or renal-limited TMA and TKIs as MCD or MCD/FSGS on kidney biopsy (71).

New chemotherapeutic agent–associated glomerular disease

Several new chemotherapies are now available in clinical practice. Renal toxicity of these novel agents has been increasingly reported in the last decade. Clofaribine is a purine nucleoside analog used to treat relapsed or refractory pediatric acute lymphoblastic leukemia and adult acute myelogenous leukemia. Nephrotoxicity most commonly manifests as elevation in serum creatinine. Kintzel *et al.* (72) reported AKI following exposure of clofaribine along with nephrotic range proteinuria. Unfortunately a kidney biopsy was not available. Extrapolating from animal studies, Jhaveri *et al.* (73) postulated that inhibition of ribonucleotide reductase by clofarabine might be the cause of collapsing glomerulopathy and/or kidney injury seen with this agent.

Ipilimumab is a monoclonal antibody against human cytotoxic T-lymphocyte antigen 4. It is US Food and Drug Administration (FDA) approved for unresectable or metastatic melanoma. Renal biopsy in a patient with ipilimumab-associated AKI with nephrotic range proteinuria revealed lupus nephritis with positive anti–double-stranded DNA antibodies (74). There are also case reports of acute granulomatous interstitial nephritis by this agent (75).

Anthracyclines like daunorubicin and doxorubicin have been known to cause nephrotic syndrome with renal lesions consistent with MCD, FSGS not otherwise specified (NOS), or collapsing glomerulopathy (76).

Table 3 summarizes the glomerular toxicities associated with chemotherapy agents.

Ongoing education and heightened physician awareness regarding these negative associations is central to early recognition and their successful management.

CONCLUSION

Several cancers are associated with various glomerular diseases. Membranous nephropathy remains the most common glomerular pathology reported in patients with solid tumors. Although MCD disease has been classically associated with HL, MPGN has been recognized in patients with CLL. Several reports and studies in the literature suggest that treating the cancer leads to resolution of the glomerular disease.

TAKE HOME POINTS

- Many solid and hematologic malignancies are associated with different glomerular diseases.
- Several case reports and case series of cancer-associated glomerular diseases have shown that treating the cancer may lead to resolution of the glomerular process.
- Although membranous nephropathy has been classically associated with solid malignancies, minimal change disease has been commonly described with hematologic malignancies, especially Hodgkin lymphoma.
- Membranoproliferative glomerulonephritis is increasingly being recognized to be associated with chronic hematologic malignancies such as chronic lymphocytic leukemia.
- Chemotherapy agents can also lead to glomerular diseases, the most common being TMA associated with targeted therapies.

ACKNOWLEDGMENTS

Pathology images are courtesy of James Pullman, Albert Einstein Medical Center, NY.

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REVIEW QUESTIONS

1. Which of the following statements regarding glomerular diseases seen with cancer is true?

   a. The most common glomerular pathology seen with solid tumors is minimal change disease
   b. The most common glomerular pathology seen with hematologic malignancies is membranous nephropathy
   c. The most common associated glomerular disease with GVHD is membranous nephropathy
   d. Thymoma has not been associated glomerular diseases

   Answer: c is correct. The most common glomerular pathology seen with solid tumors is membranous nephropathy (MN). Minimal change disease (MCD) is commonly seen with hematologic malignancies such as Hodgkin lymphoma. MN accounts for the majority of the cases of HSCT-associated glomerular disease. Thymoma has been associated with MCD (lymphocyte predominant) and MN (epithelial origin).

2. A primary care physician refers a 60-year-old white woman for evaluation of nephrotic range proteinuria. She presented with a 1-month history of worsening bilateral lower extremity edema. She has a history of refractory malignant melanoma. She was recently started on ipilimumab after failing standard chemotherapy. Her melanoma has responded to therapy.
   On physical examination, her BP was normal at 120/80 mmHg, and there was 3+ pitting edema of his lower extremities. The rest of the examination was unremarkable. At the time of presentation, serum creatinine was 0.9 mg/dL, serum albumin was 2.8 g/dL, total cholesterol was 290 mg/dL, and low-density lipoprotein (LDL) cholesterol was 197 mg/dL. Liver function tests and complete blood count were normal. A 24-hour urine collection revealed 8.5 g protein. A workup for secondary causes of nephrotic syndrome revealed normal complement levels. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, cryoglobulins, and human immunodeficiency virus (HIV) antibody were negative. Serum free light chains were within the normal ratio. Sonogram revealed normal-sized kidneys. A kidney biopsy reveals a proliferative glomerular disease with immunofluorescence suggestive of a full house pattern and electron microscopy showing mesangial and subendothelial deposits.
   What is the most likely diagnosis?

   a. Melanoma-induced proliferative glomerulonephritis
   b. Ipilimumab-induced lupus-like nephritis
   c. *De novo* seronegative lupus nephritis
   d. Membranoproliferative glomerulonephritis

   Answer: b is correct. Ipilimumab is a monoclonal antibody against human cytotoxic T-lymphocyte antigen 4, which is FDA approved for unresectable or metastatic melanoma. Nephrotic range proteinuria with a lupus nephritis–like picture on renal biopsy has been reported.

3. A 62-year-old white man with a long-standing history of hypertension and recent history of CLL was referred by his oncologist for evaluation of proteinuria and elevated serum creatinine. He denied any history of diabetes, hepatitis, or blood transfusion. There was no recent infection or travel history. Review of systems was significant for bilateral intermittent lower extremity swelling over the last 4 months. He denied fever, chills, dyspnea, gross hematuria, arthralgia, or rash. His current medication included amlodipine for hypertension management.
   On physical examination, his BP was elevated at 160/94 mmHg. There was mild edema of his lower extremities. The rest of the examination was unremarkable. At the time of presentation, serum creatinine was 1.5 mg/dL, and serum albumin was 3.5 g/dL. Complete blood count, liver function tests, and a lipid profile were normal. Urinalysis was significant for 10–20 RBC/hpf and 2+ proteinuria. A 24-hour urine collection revealed 1.8 g protein. A workup for secondary causes of proteinuria revealed low C3 and C4 levels. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, cryoglobulins, and human immunodeficiency virus (HIV) antibody were negative. Serum and urine immunofixation did not reveal any monoclonal immunoglobulin. Sonogram revealed normal-sized kidneys. A kidney biopsy was subsequently performed.
   What is the most likely kidney biopsy diagnosis?

   a. Membranous nephropathy
   b. Membranoproliferative glomerulonephritis
   c. Focal segmental glomerulosclerosis
   d. Acute interstitial nephritis

   Answer: b is correct. A membranoproliferative glomerulonephritis (MPGN) pattern of injury on renal biopsy has been most commonly associated with CLL, followed by MN.