Background and Objectives: Hematopoietic cell transplantation is a common treatment option for a variety of hematopoietic malignancies. As a result of the use of total body irradiation and/or chemotherapeutic agents, renal dysfunction often ensues. Many pharmacologic agents, such as cyclosporine and high-intensity conditioning regimens, have been linked with thrombotic microangiopathy. In addition, an association between membranous nephropathy and graft-versus-host disease has been reported in this clinical setting.

Design, Setting, Participants, and Measurements: A study of autologous and allogeneic hematopoietic cell transplantation patients with renal dysfunction was conducted to document the spectrum of renal manifestations. The pathology files at the University of Washington and University of Chicago Medical Centers were reviewed, and 20 patients with a kidney biopsy after hematopoietic cell transplantation were identified. The histologic findings were correlated with relevant clinical information.

Results: A wide spectrum of renal diseases could be classified into four categories: (1) Complications related to hematopoietic cell transplantation (conditioning regimen, immunosuppression, or posttransplantation complications), (2) podocytopathy, (3) membranous nephropathy, or (4) recurrence or persistence of original hematologic disease. Pathologic diagnoses included thrombotic microangiopathy, polyoma virus nephropathy, acute kidney injury/acute tubular necrosis, acute and chronic interstitial nephritis, minimal-change disease, “tip” variant of focal segmental glomerulosclerosis, membranous nephropathy, amyloidosis, and myeloma cast nephropathy. Membranous nephropathy, minimal-change disease, and amyloidosis were common causes of severe proteinuria. Because of the conditioning regimens, posttransplantation complications, and potential nephrotoxic agents used during hematopoietic cell transplantation, it was difficult to attribute the subsequent renal dysfunction to specific factors.

Conclusions: The renal biopsy remains essential for diagnosing the underlying injury that can affect one or more compartments of the kidney in this unique clinical setting.

scopic evaluation. The tissue sections were approximately 2 \( \mu m \) in thickness. Hematoxylin and eosin, periodic acid-Schiff, and Jones methenamine silver stains on three-level sections and a Masson trichrome stain for one-level section were obtained on all specimens. Standard procedures for direct immunofluorescence (IF) microscopy were used in all cases to detect deposition of IgG, IgA, IgM, C3, C1q, fibrinogen, \( \kappa \) and \( \lambda \) light chains, and albumin. The intensity of immunofluorescence staining was semiquantitatively scored on a scale of 0 to 4, as described previously (21). Standard procedures for electron microscopy (EM) were applied to evaluate renal specimens using a Philips 410LS or CM10 electron microscope. Clinical data were reviewed and extracted from the medical charts. Clinical information obtained during the 2 wk before the renal biopsy included age, type of transplant, date of transplantation, conditioning regimen, medications, GVHD status, weight, BP, presence of edema, serum creatinine and albumin, and urinalysis including 24-h collection for protein when available. Treatment that was instituted after review of the renal biopsy was also obtained when available. The relevant clinical information was correlated with the histopathologic findings. This study was approved by the University of Washington Medical Center, Fred Hutchinson Cancer Research Center, and University of Chicago Medical Center institutional review boards.

**Results**

**Clinical Data**

The clinical characteristics of all 20 patients are summarized in Table 1. The median age at presentation was 52 yr (range 37 to 72 yr). Patients presented at an average of 19 mo after transplantation (range 1.5 to 60 mo). Acute elevations in
serum creatinine were the primary presentation in nine patients. The remaining 11 patients presented with nephrotic-range proteinuria, seven of whom had severe proteinuria in the range of 11 to 26 g/d. In the 17 patients for whom data were available, the median serum creatinine was 2.5 mg/dl (range 1.1 to 6.0 mg/dl). Serum albumin ranged from 1.5 to 3.9 mg/dl with a median of 2.1 mg/dl, and 75% of patients had edema before their renal biopsy. Half of the patients had GVHD around the time of their renal biopsy. Patients 5 and 16 have been previously reported in detail (22,23). The original hematologic malignancies included multiple myeloma \((n = 7)\), acute myeloid leukemia \((n = 5)\), non-Hodgkin lymphoma \((n = 3)\), amyloidosis \((n = 2)\), Hodgkin lymphoma \((n = 1)\), acute lymphoblastic leukemia \((n = 1)\), and chronic lymphocytic leukemia \((n = 1)\). Six patients underwent autologous HCT, and the remaining patients underwent either an allogeneic or an autologous followed by an allogeneic HCT. Many patients were treated with prednisone ± cyclosporine ± an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Patients 5 and 16 went on to dialysis, and patients 3, 4, and 12 died. Limited clinical follow-up information was available for the remaining patients.

**Renal Biopsy Findings**

**TMA.** Glomerular capillary thrombi and mesangiolysis, which are characteristic features of TMA, were present in patients 1, 3, and 4. Focal to diffuse duplication of the glomerular basement membranes (GBM) was seen in all four TMA cases. Patient 1 had small arteries and arterioles that were occluded by eosinophilic thrombotic material (Figure 1A) and prominent hyalinosis in some vessels. One small artery was occluded by lipid-laden macrophages. Adventitial hyaline nodules characteristic of calcineurin inhibitor toxicity were noted in some arteries and arterioles. Many of the proximal tubules demonstrated loss or attenuation of the brush borders. The first renal biopsy of patient 2 had intact glomeruli demonstrating mesangial expansion with a spongiform appearance and focal areas of mesangiolysis. Some of these mesangial areas showed hypercellularity. Most glomerular capillary walls were thickened with focal duplication of the GBM. Intracapillary or arterial thrombi were not identified. A second renal biopsy 3 yr later demonstrated persistent mild mesangial expansion of the glomeruli and focal duplication of the GBM in one glomerulus. Red cell fragments were interposed between the duplicated GBM. The arterioles showed focal subendothelial hyalinosis. Patient 3 had two glomeruli with prominent foam cell infiltration in several capillaries, duplicated basement membranes, and prominence of the adjacent visceral epithelial cells (Figure 1B). This biopsy also showed focal features of polyomavirus infection (Table 2).

**Polyomavirus Nephropathy.** Patients 3, 5, 6, and 7 initially presented with elevated serum creatinine. The SV40 (Lee Biomolecular Co., San Diego, CA) immunohistochemical stain in patient 3 was positive in only three tubules with focally prominent tubulitis and no histologically identifiable viral cytopathic effect. The predominant finding in this case was TMA and intimal arteriopathy (see previous paragraph). The remaining three cases showed diffuse interstitial inflammation with frequent tubulitis, which was often more prominent in the medulla. Marked nuclear enlargement and intranuclear inclusions were seen in many tubular epithelial cell nuclei (Figure 2A) and focally in parietal epithelial cells, which was confirmed by SV40 immunohistochemical studies. BK virus was detected by PCR in blood and urine samples for all four patients. The additional presence of tubular basement membrane (TBM) deposits was observed by both IF (Figure 2B) and EM in patient 5 (Table 2).

**Acute Kidney Injury/Acute Tubular Necrosis.** Patients 8 and 9 demonstrated severe acute kidney injury characterized
Table 2. Summary of renal biopsy findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Light Microscopy</th>
<th>IF and/or IHC</th>
<th>EM</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% GS, mesangial thickening + mesangiolysis, duplicated GBM, few glomerular capillary, arterial, and arteriolar thrombi, arteriolar hyalinosis with adventitial hyaline nodules</td>
<td>IF: Negative</td>
<td>Prominent subendothelial space widening, extensive podocyte FPE</td>
<td>Acute and chronic TMA, arteriolar hyalinosis suggestive of calcineurin inhibitor toxicity, acute kidney injury</td>
</tr>
<tr>
<td>2, first biopsy</td>
<td>30% GS, mesangial expansion + many duplicated GBM</td>
<td>IF: Negative</td>
<td>Focal podocyte FPE without other abnormalities</td>
<td>Chronic TMA</td>
</tr>
<tr>
<td>2, second biopsy</td>
<td>60% GS, duplicated GBM</td>
<td>IF: Negative</td>
<td>Focal subendothelial space widening, focal podocyte FPE</td>
<td>Chronic TMA</td>
</tr>
<tr>
<td>3</td>
<td>&lt;10% GS, duplicated GBM, mesangiolysis, focal foam cells and leukocytes, and glomerular capillary thrombosis, diffuse IF/TA, infiltration of intima by leukocytes in one artery</td>
<td>IF: Negative; IHC: SV40 positive in tubular epithelial cells of three tubules</td>
<td>Focal subendothelial space widening</td>
<td>Acute and chronic TMA, intimal arteritis, polyoma virus infection</td>
</tr>
<tr>
<td>4</td>
<td>Many glomerular capillary and arteriolar thrombi, loss of proximal tubular brush borders, mild arterial intimal fibrosis</td>
<td>IF: No glomerular staining, granular TBM staining for IgG (1 to 2+), C3 (3+), and k and λ (trace to 1+); IHC: SV40+</td>
<td>No glomerular abnormalities, electron-dense particles in tubular epithelial cell cytoplasm, consistent with virions, TBM electron dense deposits</td>
<td>PVN with TBM deposits</td>
</tr>
<tr>
<td>5</td>
<td>Normal glomeruli, patchy interstitial inflammation with tubulitis, nuclear atypia and intranuclear inclusions in many tubules</td>
<td>IF: Negative; IHC: SV40 positive in many tubular epithelial cell nuclei</td>
<td>No significant abnormalities</td>
<td>PVN</td>
</tr>
<tr>
<td>6</td>
<td>Normal glomeruli, diffuse interstitial inflammation with frequent tubulitis and viral cytopathic effect in tubular epithelial cells</td>
<td>IF: Negative</td>
<td>No significant abnormalities</td>
<td>PVN</td>
</tr>
<tr>
<td>7</td>
<td>Normal glomeruli, diffuse interstitial inflammation with abundant viral cytopathic effect in peritubal and epithelial cells</td>
<td>IF: Negative</td>
<td>No significant abnormalities</td>
<td>PVN</td>
</tr>
<tr>
<td>8</td>
<td>Normal glomeruli, vacuolated tubular epithelial cells with attenuated brush borders</td>
<td>IF: Negative</td>
<td>No significant abnormalities</td>
<td>Acute kidney injury/acute tubular necrosis</td>
</tr>
<tr>
<td>9</td>
<td>Normal glomeruli, vacuolated tubular epithelial cells with attenuated brush borders and sloughed cells</td>
<td>IF: Negative</td>
<td>No significant abnormalities</td>
<td>Acute kidney injury/acute tubular necrosis</td>
</tr>
<tr>
<td>10</td>
<td>10% GS, focal ischemic glomerular changes, diffuse interstitial inflammation with tubulitis in preserved tubules, attenuation of the proximal tubular brush borders, diffuse IF/TA</td>
<td>IF: No significant staining of glomeruli, tubular casts stain for both k and λ</td>
<td>No significant abnormalities</td>
<td>Acute and chronic interstitial nephritis</td>
</tr>
<tr>
<td>11</td>
<td>10% GS, many ischemic glomeruli, diffuse IF/TA, mild intimal fibrosis, and focal disruption of the internal elastic lamina, fibrocellular intimal expansion with near complete occlusion of an artery</td>
<td>IF: Granular to confluent staining for IgG and k and λ (k &lt; λ) in 10 to 15% of TBM, no glomerular staining</td>
<td>Extensive podocyte FPE, many small TBM electron-dense deposits</td>
<td>MCD, arteriopathy, TBM deposits</td>
</tr>
<tr>
<td>12</td>
<td>Normal glomeruli, mild IF/TA, vacuolated and swollen tubular epithelial cells with blebbing of proximal tubular brush borders</td>
<td>IF: ND; no glomeruli available</td>
<td>Extensive podocyte FPE without electron-dense deposits</td>
<td>MCD, acute kidney injury/acute tubular necrosis</td>
</tr>
<tr>
<td>13</td>
<td>Normal glomeruli, patchy and mild IF/TA, mild intimal fibrosis of arteries and focal arteriolar hyalinosis</td>
<td>IF: Negative</td>
<td>Extensive podocyte FPE, mesangial matrix accumulation</td>
<td>MCD, mild arterionephrosclerosis</td>
</tr>
<tr>
<td>14</td>
<td>5% GS, one glomerulus with foam cells at the glomerular tip</td>
<td>IF: Negative</td>
<td>Focal podocyte FPE</td>
<td>FSGS, tip variant</td>
</tr>
<tr>
<td>15</td>
<td>Normal glomeruli, mild IF/TA, prominent attenuation/loss of proximal tubular brush border</td>
<td>IF: Granular cw staining for IgG (3+), IgM (trace), C3 (2+), k (3+), and λ (2 to 3+)</td>
<td>Subepithelial podocyte deposits, extensive podocyte FPE</td>
<td>MN, acute kidney injury</td>
</tr>
<tr>
<td>16</td>
<td>20% GS, 20% SS, thickened GBM with rarefactions, diffuse IF/TA</td>
<td>IF: Granular cw staining for IgG (1 to 2+), k and λ (1 + both)</td>
<td>Subepithelial + intramembranous electron-dense deposits with microsporidal substructural organization, extensive podocyte FPE</td>
<td>MN with atypical features</td>
</tr>
<tr>
<td>17</td>
<td>10% GS, normal glomeruli, diffuse IF/TA</td>
<td>IF: Granular cw staining for IgG (2+), C3 (1+), k and λ (1+ for both)</td>
<td>Segmental small subepithelial and rare mesangial electron-dense deposits</td>
<td>MCD, minimal-change disease</td>
</tr>
<tr>
<td>18</td>
<td>40% GS, acellular eosinophilic amorphous deposits in mesangial areas, cw, and arterioles (Congo red positive), diffuse IF/TA</td>
<td>IF: No glomeruli present; interstitial amorphous deposit IF staining for λ only</td>
<td>Numerous fibrils in mesangial areas, cw, and arterioles measuring 9 to 10 nm in thickness; Extensive podocyte FPE</td>
<td>Amyloidosis, AL type</td>
</tr>
<tr>
<td>19</td>
<td>45% GS; acellular eosinophilic deposits in mesangial areas, cw, and arterioles (Congo red positive), diffuse IF/TA</td>
<td>IF: λ (2+), C3 (1+) only in amorphous glomerular and vascular deposits</td>
<td>Numerous fibrils in mesangial areas and cw measuring 9 to 10 nm in thickness, variable podocyte FPE</td>
<td>Amyloidosis, AL type</td>
</tr>
<tr>
<td>20</td>
<td>20% GS, normal glomeruli, diffuse IF/TA, many tubular casts with fractured edges and multinucleated cellular reaction</td>
<td>IF: Dull confluent staining of GBM for k in sclerotic glomeruli, strong k staining of tubular casts</td>
<td>Extensive podocyte FPE, thick TBM with focal granular deposits</td>
<td>Myeloma cast nephropathy with features of light-chain deposition disease</td>
</tr>
</tbody>
</table>

*a* cw, capillary wall; EM, electron microscopy; FPE, foot process effacement; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GS, global glomerulosclerosis; IF, immunofluorescence; IF/TA, interstitial fibrosis and tubular atrophy; IHC, immunohistochemistry; MCD, minimal-change disease; MN, membranous nephropathy; ND, not done; PVN, polyoma virus nephropathy; SS, segmental glomerulosclerosis; SV40, simian virus 40; TBM, tubular basement membrane; TMA, thrombotic microangiopathy.
by the loss or attenuation of the proximal tubular brush borders (Figure 3). There were no significant glomerular alterations or interstitial inflammation. Patient 8 revealed focal subendothelial hyalinosis of the arterioles, and patient 9 showed mild intimal fibrosis of the arteries. Patients 1, 12, and 15 also had a minor component of acute kidney injury but had other primary histopathologic features (Table 2).

**Interstitial Nephritis.** Patient 10 had a moderate interstitial mononuclear cell inflammatory infiltrate with a few scattered eosinophils and frequent tubulitis in many well-preserved tubules. One small artery had mucoid intimal change with duplication of the internal elastic lamina, and the other arteries were normal. This patient’s medication list included acyclovir, phenytoin, aspirin, citalopram, loratadine, omeprazole, metoprolol, calcitriol, and thalidomide, but the precise cause of interstitial nephritis remains uncertain (Table 2).

**Podocytopathy.** Patients 11, 12, and 13 had 38, seven, and nine glomeruli available for evaluation, respectively. Although the possibility of FSGS as a result of sampling could not be
entirely excluded, the prominent podocyte injury with extensive foot process effacement (Figure 4) that was observed by EM in all three cases along with the absence of segmentally sclerotic glomeruli was most characteristic of MCD. Patient 11 showed additional findings of prominent fibrocellular intimal expansion with near occlusion of a small artery and focal disruption of the internal elastic lamina. IF microscopy demonstrated granular staining of 10 to 15% of the TBM for IgG and κ and λ light chains in patient 11, which was confirmed by the presence of electron-dense deposits in the TBM. Patient 14 had one glomerulus that revealed foam cells within a few capillaries at the urinary pole, diagnostic of the glomerular “tip” variant of FSGS (Figure 5). EM showed only focal foot process effacement of the podocytes (Table 2).

MN. Patients 15 to 17 demonstrated granular IF staining of the capillary walls for IgG and κ and λ light chains, with focal C3 staining in two cases typical of MN. The glomeruli in patient 15 had no significant alterations, and characteristic subepithelial “spikes” were not present by light microscopy. Patient 16 had glomeruli showing prominent GBM thickening with subepithelial spikes and frequent rarefactions seen with the silver stain (Figure 6). Two glomeruli had segmental sclerosis. EM revealed subepithelial and intramembranous deposits with microspherular substructural organization and extensive podocyte foot process effacement. Patient 17 had intact glomeruli without significant morphologic alterations. Segmental and small subepithelial electron densities were seen by EM. The findings were consistent with an early stage of MN (Table 2).

Recurrence or Persistence of Original Hematologic Disease
Amyloidosis of the AL (λ light chain) subtype was identified in both patients 18 and 19. Significant proteinuria in patient 19 persisted even after HCT. Both biopsies demonstrated significant global glomerulosclerosis, and many glomeruli showed ischemic features and irregular scarring. Amorphous eosinophilic glomerular deposits were predominantly mesangial in location. Some capillary walls and arterioles demonstrated similar eosinophilic material, which was confirmed by Congo red stains to be amyloid. IF staining for both cases demonstrated λ light chain staining only in the glomeruli and vessels for patient 19 and interstitium for patient 18, which did not contain glomeruli in the tissue that was available for IF microscopy. Diffuse interstitial fibrosis and tubular atrophy were present in both biopsies of which patient 18 had aggregates of interstitial foam cells. EM confirmed the presence of randomly arranged, nonbranching fibrils that measured up to 10 nm in thickness. Focal to extensive podocyte foot process effacement was present in these two cases. Patient 20 demonstrated prominent intratubular casts with a fractured appearance and giant cell reaction, consistent with myeloma cast nephropathy. IF microscopy showed confluent staining of the intratubular casts and GBM for κ light chains only, which confirmed the diagnosis of myeloma cast nephropathy and suggested the additional diagnosis of light-chain deposition disease. Small granular electron-dense deposits characteristic of light-chain deposition disease were identified by EM along the TBM but not GBM. There was diffuse interstitial fibrosis and tubular atrophy with focally prominent interstitial inflammation. The small arteries showed moderate intimal fibrosis, and some arterioles demonstrated prominent subendothelial hyalinosis.

Discussion
Renal dysfunction in HCT patients can be arbitrarily separated into early and late manifestations and has been well reviewed (1,24). The differential diagnosis of early renal dysfunction includes infection, tumor lysis syndrome, sinusoidal obstruction syndrome leading to hepatorenal syndrome, TMA, amphotericin toxicity, and acute kidney injury/acute tubular necrosis.
Livery of radiation to the marrow of patients with multiple myeloma (28). Given the presence of GBM alterations with focal duplication, the first renal biopsy findings are best classified as a thrombotic microangiopathic injury process, although the initial biopsy did not demonstrate significant subendothelial space widening in one glomerulus that was available for EM. A follow-up biopsy 3 yr later demonstrated focal duplication of the GBM in one glomerulus without overt thrombi in capillaries or arterioles. We observed similar renal biopsy findings in other patients who were treated with $^{166}$Ho-DOTMP (29), but it is unclear whether this particular agent or other factors may be contributing to the histopathologic changes in the kidney.

Polyoma virus nephropathy (PVN) is a common complication of immunosuppression that affects up to 8% of renal transplant patients (30). In the nonrenal transplant setting, rare cases of PVN in the native kidney have been described in pancreas, lung, heart, and HCT patients (23,31–34). Our study adds three cases to the medical literature and suggests that PVN may not be such an uncommon manifestation in HCT patients. In our series, patient 11 had MCD and demonstrated TBM immune complex deposition. Although TBM immune complex deposition without glomerular involvement is best described in the setting of systemic lupus erythematosus, Sjögren syndrome, and drug-induced interstitial nephritis (35), this finding recently was described in PVN (36). We speculate that the TBM immune complex deposition in our patient could represent the resolution of a previous polyoma virus infection.

MN is the most common form of immune complex–mediated glomerulonephritis (GN) that has been described in the setting of HCT. More than 40 cases of MN have been reported in the English medical literature (3–12,19,37–46). Reddy et al. (44) and Terrier et al. (46) represent the two largest series with five cases of MN each. Most cases of MN have been associated with acute and/or chronic GVHD. Of note, two of our three cases of MN were associated with GVHD, although we had limited clinical information regarding the GVHD status in one patient. The pathogenic mechanism of idiopathic MN and MN secondary to HCT is largely unknown. Only one antigen, neutral endopeptidase, has been specifically identified in the pathogenesis of MN (47), which we previously demonstrated is not the antigenic target of MN in our HCT patient (22). In addition, IgA nephropathy, membranoproliferative GN, and other unclassified immune complex–mediated GN have been described (45,48–50). The precise relationship of these immune complex–mediated glomerular injuries to HCT, GVHD, or the therapeutic regimen remains unclear.

Non–immune complex–mediated glomerular injuries in HCT patients include MCD, FSGS, and pauci-immune crescentic GN (13–20,42–44,51–53). The finding of FSGS has been reported in non-HCT patients with IFN therapy and high-dosage chemotherapy for chronic myeloid leukemia (54), which provides evidence that high-dosage chemotherapy alone may be sufficient to result in severe podocyte injury. The pathogenesis of MCD remains elusive and has been considered to be a T cell–mediated injury. Although direct podocyte toxicity from various therapeutic agents could be a contributing factor, most patients present with MCD several months after HCT, frequently when there is a decrease in immunosuppressive med-
ications or acute or chronic GVHD (43). Although MCD has been associated with a variety of hematologic malignancies, particularly Hodgkin lymphoma, two of the three cases in our study were in the setting of multiple myeloma, which has not previously been associated with MCD. Stevenson et al. (19) reported two HCT patients, one of whom had MCD that presented with nephrotic syndrome shortly before the relapse of the underlying hematologic malignancy. The authors suggested that a clinical relapse should be considered in HCT patients without overt evidence of GVHD.

The six patients who underwent autologous HCT had renal dysfunction as a result of TMA, PVN, interstitial nephritis, and amyloidosis. The first three entities could be classified as complications of the therapeutic agents and/or immunosuppression. Although this is based on a small number of patients, neither a podocytopathy nor an immune complex-mediated disease process was encountered in these patients after autologous HCT.

**Conclusions**

A wide spectrum of renal pathologic findings can be observed in HCT patients. Either severe proteinuria or acute elevations in serum creatinine were common presentations in our study, which can be due to MN, MCD, FSGS, and amyloidosis for the former and TMA, PVN, acute kidney injury, and interstitial nephritis for the latter. Renal biopsies are necessary to establish the underlying cause of renal dysfunction in HCT patients. Once the underlying pathology is known, therapies can be tailored to target the specific disease process and to prevent progression to ESRD.

**Disclosures**

None.

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Access to UptoDate on-line is available for additional clinical information at [http://www.cjASN.org/](http://www.cjASN.org/)