THE NEPHROLOGY FELLOWSHIP PROGRAM AT INDIANA UNIVERSITY MEDICAL CENTER

The nephrology fellowship program at Indiana University Medical Center is designed to provide trainees with the knowledge and skills necessary for them to function as nephrology subspecialists with adequate research experience to enable them to assume a faculty position at the conclusion of their fellowship.

The usual fellowship program entails a 3-yr training period with at least 12 months devoted to clinical training and the remainder devoted primarily to research. In some cases, a 2-yr period of training is offered. The majority of the clinical months are performed during the first year. Trainees attend a weekly outpatient nephrology clinic and participate in weekend call on a regular basis throughout their fellowship. There are generally two to three trainees in each of the 3 yr of fellowship.

Clinical training is obtained by caring for patients with renal and fluid and electrolyte disorders in both inpatient and outpatient settings in three hospitals and outpatient clinics located on one campus. A population of approximately 300 chronic dialysis patients and active acute dialysis, continuous venovenous hemofiltration, and renal transplantation programs, as well as a nephrology intensive care unit provide trainees with extensive experience in practical and theoretical aspects of all forms of chronic and acute renal replacement therapy. Many trainees spend an elective month on the pediatric nephrology service.

Research training is obtained by the trainees' participation in ongoing laboratory and clinical research programs under the direction of the nephrology faculty. These include the physiology, biochemistry, and molecular biology of diverse renal cell functions and clinical projects including ones dealing with solute, drug, and water transfer across artificial membranes. Some trainees obtain advanced graduate degrees during their fellowship.

An integral part of the trainees' education involves attendance at regularly scheduled didactic, clinical, biopsy, and research conferences and journal clubs. All trainees attend at least one major nephrology meeting each year.

Hematuria in Bone Marrow Transplant Patients

Dawn M. Sabau

Hematuria is a common problem in bone marrow transplant recipients. Etiologies include cyclophosphamide toxicity, graft-versus-host disease, and viruses such as BK (polyomavirus), cytomegalovirus, and adenovirus. A case of adenovirus-associated hematuria is reported in this article. The causes of this clinical entity are reviewed, and possible therapies are presented.

CASE REPORT

A 24-yr-old white man was admitted to Indiana University Medical Center on February 10, 1991, for an allogeneic bone marrow transplant. The patient had been diagnosed in October of 1989 as having acute myelogenous leukemia (Philadelphia chromosome positive), which had been treated with four courses of daunarubicin, vincristine, and prednisone. He remained in remission until November of 1990, at which time he relapsed and was treated with vincristine, intrathecal methotrexate, cytosine arabinoside, and etoposide without sustaining a remis-
A bone marrow aspirate showed 66% blasts. Admitting BUN was 13 mg/dL, creatinine was 1.1 mg/dL, and urinalysis was unremarkable. In preparation for his allogeneic transplant, he received 1,375 rads of total body irradiation, etoposide (on hospital days 6 and 7), and cyclophosphamide (on hospital days 8 and 9) with forced alkaline diuresis and sodium 2-mercaptopethane sulfonate (mesna). He was given prophylactic trimethoprim/sulfamethoxazole, norfloxacin, fluconazole, penicillin, acyclovir and allopurinol. Antithymocyte immunoglobulin and methylprednisolone were given as prophylaxis for graft-versus-host disease.

On hospital day 7, 4 days before his anticipated bone marrow infusion and while granulocytopenic, the patient became febrile during a blood product infusion. He was empirically treated with ceftazidime and amikacin for 48 h. The antibiotics were discontinued when blood cultures failed to grow any organisms. However, the fever returned and the antibiotics were restarted on hospital day 12. Vancomycin was added to his therapy on day 18, after an untreatable Streptococcus species grew from a blood culture. With the bone marrow starting to engraft, all antibiotics except vancomycin were stopped by day 30. On day 34, the patient developed hematuria, which resolved with bladder irrigation. At this time, his BUN was 18 mg/dL, creatinine was 0.6 mg/dL, white blood cell count was 500 cells/mm³, with an absolute granulocyte count of 370 and a platelet count of 24,000/mm³, and coagulation studies were within normal limits. A urinalysis showed proteinuria (not quantitated), gross blood, and no white blood cells; urine cultures were sent. The patient developed a rash on day 40 that was confirmed on biopsy to be consistent with graft-versus-host disease. Hematuria recurred the following day, and a nephrology consultation was requested because his BUN and creatinine had increased to 22 and 1.2 mg/dL, respectively. The urology service also evaluated the patient and performed a cystoscopy and retrograde pyelography. The bladder was erythematous with blood clots and punctate hemorrhages consistent with cystitis. The right ureteral orifice was visualized but could not be cannulated because of edematous mucosa. There was frank hemorrhaging from the left ureteral orifice. A retrograde pyelogram revealed edematous mucosa, pertureteral extravasation of contrast during injection, and multiple filling defects along the entire length of the ureter consistent with ureteritis or air injected during the study. Although the upper tract was not dilated, the mucosa in the renal pelvis was edematous. The urologist's impression was that the findings were consistent with chemical or viral cystitis and upper tract inflammation. The patient was treated with continuous bladder irrigation with some improvement. However, by day 51, his urine output decreased significantly. Renal ultrasonography showed bilateral hydronephrosis, and open-ended stents were placed in both ureters. The patient did poorly after the procedure and required continued mechanical ventilation. He developed a postobstructive diuresis; his weight decreased from 66.8 to 64 kg, and his BUN and creatinine decreased from 81 and 3.8 mg/dL on day 53 to 29 and 1.6 mg/dL, respectively, on day 57. The stents were removed on day 58, and percutaneous nephrostomy tubes were placed on day 59. The same day, results of a urine culture sent 10 days earlier returned positive for adenovirus type 11 and IV ribavirin was then administered on a compassionate-use protocol. The patient's overall status continued to deteriorate, and his oxygen requirements increased. On day 61, a bronchoalveolar lavage was performed, specimens from which subsequently grew adenovirus type 11. The nephrostomy tubes required repeated irrigation because of obstruction with clots, and by day 64, the left tube clotted off completely. The patient's urine output continued to decrease; his azotemia worsened, and he required dialysis for control of extracellular fluid volume. In spite of significant reductions in the patient's weight after dialysis on day 64, he required emergent dialysis for respiratory distress that was presumed to be secondary to volume overload early the following morning. The patient's respiratory status deteriorated further, and he died a few hours later. A postmortem examination was not allowed by the family.

**DISCUSSION**

The term "hemorrhagic cystitis" is frequently used in the literature when the syndrome of painless micturition, urinary frequency, and severe hematuria with or without renal insufficiency is described in bone marrow transplant recipients. In our patient, as well as others with hematuria after bone marrow transplantation, hemorrhagic cystitis is only a part of this clinical entity that causes significantly more morbidity than isolated hemorrhagic cystitis.

Hematuria is frequently observed in bone marrow transplant patients. Ambinder et al. found an incidence of 20% in a review of 502 patients who underwent bone marrow transplantation (1). Several causes are known, and each tends to occur at a different point in therapy (Table 1).

**Cyclophosphamide** causes hemorrhagic cystitis (2). Injury to the uroepithelium occurs from acrolein, which is a hydroxylated metabolite of the drug. Hemorrhagic cystitis secondary to cyclophosphamide occurs soon after the drug is given (usually within 3 days of administration). Fortunately, toxicity to the uroepithelium has become less frequent because of prophylactic treatment with simultaneous forced alkaline diuresis and IV mesna. This combines with
TABLE 1. Etiologies and expected time of onset of hematuria in bone marrow transplant recipients

<table>
<thead>
<tr>
<th>Cause of Hematuria</th>
<th>Onset of Hematuria</th>
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<tbody>
<tr>
<td>Cyclophosphamide (2)</td>
<td>0–7 days after chemotherapy</td>
</tr>
<tr>
<td>Graft-Versus-Host Disease (2)</td>
<td>17–51 days after transplantation (median, 27 days)</td>
</tr>
<tr>
<td>Viruses (5)</td>
<td>11–106 days after transplantation (median, 55 days)</td>
</tr>
</tbody>
</table>

Table 2. Renal and urologic manifestations of adenovirus-associated hematuria in bone marrow transplant recipients

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Hematuria (Microscopic or Gross)</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Urinary Tract Obstruction</td>
<td>Urinary Tract Obstruction</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>Acute Renal Failure</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Nephritis</td>
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Acrolein in the urine to decrease its toxicity to the uroepithelium (2,3).

Graft-versus-host disease also causes hematuria. Graft-versus-host disease occurs when immunocompetent cells (T lymphocytes) in a bone marrow graft recognize the recipient tissues as "foreign." Clinically, this is manifested as diffuse cell-mediated epithelial injury, involving the skin, intestine, liver, lungs, and frequently, the uroepithelium (2,4). It tends to occur after bone marrow engraftment but may develop as early as 3 days after transplantation (4).

Several viruses also cause hematuria. Viral infections generally present after engraftment of the bone marrow, frequently in patients with graft-versus-host disease (5). Causes include polyomavirus (BK) and cytomegalovirus (6). Adenovirus, especially types 11, 34, and 35, has also been described as a cause of uroepithelial injury. In the first report of isolated adenovirus hemorrhagic cystitis by Numazaki et al. in 1968 (7), the authors tested 11 children who presented with polyuria, dysuria, and hematuria for a viral etiology. Adenovirus type 11 was isolated from the urine of nine of the patients, and all had a significant rise in antibody titers to this virus. These cases were self-limited and resolved in 2 wk. However, none of the children were immunocompromised.

Injury to the bladder epithelium causes significant morbidity if bleeding is profuse and/or urinary tract obstruction occurs. Uroepithelial injury as an isolated entity without renal parenchymal involvement may lead to renal insufficiency if an obstruction develops and persists for an extended period. Hiraoka et al. (8) described a patient after bone marrow transplantation with hematuria, hydronephrosis, and bilateral ureteral obstruction. No stones or anatomic abnormalities were found, but adenovirus type 11 grew from a urine culture. Electron microscopic examination of the urine sediment revealed 80-nm viral particles in the degenerating cells, consistent with adenovirus. The authors concluded that the virus had caused diffuse uroepithelial injury, leading to hemorrhage and obstruction (8).

Viral infections may affect the renal parenchyma as well as the uroepithelium (Table 2). Levy et al. (9) reported a patient who received an autologous bone marrow transplant after recurrent Wilms' tumor that was not treatable by further surgery. She developed hematuria 60 days after bone marrow transplantation. On postmortem examination, the remaining portion of her right kidney was hypertrophied, with hydronephrosis, pericapsular fibrosis, cortical tubular necrosis, and hemorrhage, as well as adenovirus inclusions (9). Shields et al. (10) reviewed adenovirus infections in 1,051 bone marrow transplant patients. Adenovirus was isolated in 51 patients, and 13 patients (27.7%) had positive urine cultures for the related types 11, 34, and 35. The first isolates were obtained from these patients an average of 43 days after transplantation. Five patients subsequently had cultures of the renal parenchyma that were positive for adenovirus, and four of these developed renal insufficiency. Two patients had histologic evidence of viral invasion in the kidney, with viral inclusions, tubular necrosis, interstitial inflammation, and hemorrhage.

Shields et al. (10) also evaluated several risk factors that might predispose patients to adenovirus infections, including the illness for which the transplant was performed, age, and prophylaxis against graft-versus-host disease, but none of these differed from patients who were not infected. The only risk factor identified was the presence of moderate to severe graft-versus-host disease (10). Miyamura et al. (5) performed a prospective study of 50 bone marrow transplant recipients. They evaluated 137 urine specimens collected 30, 60, and 100 days after transplant. Twelve patients had hemorrhagic cystitis (clinical signs and symptoms with hematuria), and eight excreted adenovirus type 11 at the onset of cystitis. Of the remaining negative 129 specimens, only 3 were collected during a hemorrhagic episode. Factors associated with the development of adenovirus-induced or associated hemorrhagic cystitis included female gender, seropositivity for adenovirus before bone marrow transplantation, and acute graft-versus-host disease. They also found that adenovirus-associated hematuria developed later in the patient's course and lasted longer than idiopathic hemorrhagic cystitis (median onset, 55 days; median duration, 42 days in patients with adenovirus-induced hematuria versus 25 and 11 days, respectively, in
patients with hemorrhagic cystitis of undetermined cause (5).

Manifestations of adenovirus infections in bone marrow transplant patients most likely represent reactivation of latent virus. Shields et al. (10) could not find a common source of adenovirus infection nor any benefit from laminar air-flow rooms in preventing the disease. Graft-versus-host disease disrupts the integrity of epithelia and probably makes it more susceptible to viral infection (2).

Currently, there is little specific therapy available for adenovirus infections (Table 3). Management of urinary tract obstruction with continuous bladder irrigation, ureteral stents, and nephrostomy tubes may preserve renal function if the primary insult is to the uroepithelium. Immunoglobulin with high titers against adenovirus has been used to treat adenovirus infections in immunocompromised patients, but there are few data on this therapy. Dagan et al. (11) reported the possible efficacy of immunoglobulin in a patient with combined immunodeficiency and adenovirus-associated pneumonia. However, the patient reported by Levy et al. (9) with adenovirus infection after bone marrow transplantation for Wilms' tumor died in spite of treatment with this therapy.

Ribavirin has in vitro activity against adenovirus (12), and the aerosolized form of the drug has been used to treat respiratory syncytial virus pneumonia (13). Intravenous ribavirin was used successfully by Cassano (12) to treat a patient with adenovirus cystitis after bone marrow transplantation. However, his case involved isolated cystitis; invasion of other organs and renal insufficiency were not found. His patient had graft-versus-host disease and developed hemorrhagic cystitis 36 days after bone marrow transplantation. Adenovirus was cultured from two urine specimens taken 7 days apart. The patient received 9 days of iv ribavirin on a compassionate-use basis. By 5 days after the initiation of treatment, urine cultures became negative for adenovirus and the cystitis resolved by the seventh day of therapy. Cassano advocated performing a controlled clinical trial of iv ribavirin in these patients (12).

In summary, hematuria is associated with a significant amount of morbidity and mortality in bone marrow transplant patients. Early in the treatment course, isolated hemorrhagic cystitis is generally caused by cyclophosphamide toxicity to the uroepithelium; later, graft-versus-host disease with or without concomitant viral infection may be implicated. Current management includes irrigation of the urinary tract to prevent obstruction, analgesia, and relief of obstruction if it develops.

It is difficult to discern the cause of subacute urinary tract hemorrhage on the basis of clinical grounds only, because both graft-versus-host disease and viral infections tend to occur later in the treatment course. When diffuse epithelial injury occurs after a bone marrow transplant, treatment is directed toward graft-versus-host disease, a well-recognized cause. In spite of therapy, however, moderate to severe graft-versus-host disease is almost always fatal (2). There currently is no proven effective therapy for adenovirus infections, but ribavirin is a promising prospect, especially if given earlier in the course of treatment before multiple organ systems are involved. More information is also needed on the efficacy of iv immunoglobulin. Hematuria due to adenovirus may herald severe, and usually fatal, disseminated adenovirus infection in bone marrow transplant recipients, as was observed in our patient. Therefore, cultures of the urine, stool, sputum, and throat may be helpful in clarifying the clinical picture. As specific therapy for adenovirus becomes available, it will be important to differentiate this cause of diffuse epithelial injury from graft-versus-host disease in order to guide treatment.

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REFERENCES

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"Richards had remarked that the major credit should not come to him, but rather it should go to the many investigators who carried out the bulk of the actual work. True enough, perhaps, but one of the rough spots of modern medical research is that many young men, interested, willing and competent, come and go through our laboratory portals, spending at the most two or three years in research before launching into a career in which they are all too frequently engulfed by other professional or administrative duties. It can be no other way because clinical medicine needs them, and the clinical and preclinical research departments cannot always contain them. Despite its disadvantages this system of transient apprentices continues to produce a large fraction of both our medical researchers and our good clinicians. As for credit, however, through these twenty years someone had to maintain continuity, esprit de corps, high standards of performance, perspective, critical acuity, and courage when the going was particularly rough; and, probably in many instances, to reduce complicated series of data to a comprehensible paper. Like Ludwig, Richard's name is on every paper in the small type that reads From the Laboratory of Pharmacology of the University of Pennsylvania."