Remission of Posttransplant Lymphoproliferative Disorder after Interferon Alfa Therapy

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Abstract. Posttransplant lymphoproliferative disorder (PTLD) is one of the major complications of immunosuppressive therapy. PTLD is strongly associated with the Epstein-Barr virus (EBV). It is believed that EBV-infected B cells proliferate in an unchecked manner due to suppression of cytotoxic T cells and elevation of B cell-promoting cytokines. There is no consensus on the treatment of PTLD other than reduction of immunosuppressive therapy. We report a case of PTLD with monoclonal B cells confined to the lymph nodes. The patient did not initially respond to reduction of immunosuppression, oral acyclovir, and intravenous immunoglobulin injection. She subsequently responded when subcutaneous injections of interferon alfa (5 million U) were given three times a week. The patient received a 3-mo course of interferon and remained in remission 12 mo after treatment. Her graft function was well maintained, and cyclosporin A was restarted 2 mo after achieving remission. The clinical manifestations, risk factors, pathogenesis, and treatment of PTLD, as well as 12 previously reported cases of PTLD treated with interferon, were reviewed. On the basis of the results presented here, it appears that interferon alfa may be useful in treating PTLD and that there is a need for further clinical trials. (J Am Soc Nephrol 8: 1483–1490, 1997)

Malignancy is one of the major complications of immunosuppressive therapy used after transplantation. These malignancies are unique in both type and frequency when compared with the general population. Of the various types of malignancies that occur, the posttransplant lymphoproliferative disorders (PTLD) make up a large portion. PTLD are usually of B cell origin and are associated with Epstein-Barr virus (EBV) infection (1,2). For many years, it has been debated whether the antiviral agents play a role in the treatment of PTLD (3,4). We present a case of PTLD in which interferon alfa appeared to have an important beneficial effect in inducing a complete remission.

Case Presentation
In December 1994, a 65-yr-old white woman presented with night sweats, a 6-lb weight loss over 1 mo, and the abrupt development of a right supraclavicular mass. The patient developed end-stage renal disease secondary to vasculitis-related rapidly progressive glomerulonephritis in 1988. She subsequently received a cadaveric renal transplant that was 3/6 HLA-matched. This transplant was complicated by two episodes of acute rejection that were effectively treated with prednisone and OKT3. The patient was then maintained on triple immunosuppression therapy (cyclosporin A, azathioprine, and prednisone) until 1992, when she eventually lost the graft secondary to chronic rejection. In January 1994, she underwent a second cadaveric transplantation, which was a 6/6 HLA match. She did not receive antilymphocyte preparation as inductive therapy or prophylactic antiviral therapy. She experienced no rejections and was maintained on the triple immunosuppression therapy with cyclosporin A (7 mg/kg per d), azathioprine (2 mg/kg per d), and prednisone (15 mg daily).

Other significant features of her past medical history included dysplastic nevus syndrome, basal cell carcinoma, atrial fibrillation, and osteoarthritis. The patient’s other medications included metoprolol (100 mg), digoxin (0.125 mg), aspirin (325 mg), dipyridamole (25 mg), trimethoprim/sulfamethoxazole (160/800 mg), sulfa1icate (4 g), and iron sulfate (325 mg), all taken daily, and an estrogen patch twice weekly.

The patient smoked two packs of cigarettes per day. Her father was deceased secondary to lymphoma, and her mother was deceased secondary to breast cancer.

A physical examination revealed an elderly female with cushingoid facies. Her BP was 150/76 mmHg, pulse rate 80/min, respiratory rate 18/min, and temperature 37°C. A soft 3×3-cm movable mass was found in the right supraclavicular area. There was no other cervical, axillary, or inguinal adenopathy. The skin was noted to be thinning and contained numerous purpura. Other examinations were not remarkable.

Laboratory findings initially revealed blood urea nitrogen 8.2 mmol/L, creatinine 124 µmol/L, white blood cells (WBC) 7.3 × 10⁹/L, hemoglobin 10.9 g/L, hematocrit 32.3%, platelets 197 × 10⁹/L, and normal liver function tests. Epstein-Barr viral serology was as follows: IgG against viral capsid antigen > 1:20,480, early antigen 1:20, Epstein-Barr nuclear antigen >
Computed tomography (CT) scans of the neck, chest, abdomen, and pelvis revealed right supraclavicular, mediastinal (Figure 1A), para-aortic (Figure 1C), and right inguinal lymphadenopathy. A CT scan of the head revealed mild cerebral atrophy without evidence of tumor.

The patient underwent an excisional biopsy of the right supraclavicular mass. The tumor had a "starry-sky" appearance with single-cell necrosis and numerous mitoses (Figure 2A). Large monomorphic tumor cells exhibited irregular nuclear profiles, large predominantly single nucleoli, chromatin condensation, and scant eosinophilic cytoplasm (Figure 2B). Occasional Dutcher bodies were seen. In situ hybridization to the EBV-encoded small RNA (EBER) was strongly positive (Figure 2C). Immunophenotyping studies with the biotin-avidin method and antigen retrieval demonstrated late B cell lineage with expression of cytoplasmic IgG, kappa (Figure 2D). Double labeling of the node with EBER and monoclonal antibodies against B cell or T cell markers showed that the EBER was strongly expressed in both the neoplastic B cells and a minority of admixed T cells. These findings led to the diagnosis of plasmacytoid B cell lymphoma. A bone marrow biopsy revealed a hypocellular marrow without evidence of lymphoma.

Immediately after the diagnosis, the patient's immunosuppression was decreased. Azathioprine was decreased to 100 mg daily, and cyclosporin A was discontinued. Prednisone was continued at 15 mg daily. In addition, the patient was given acyclovir (400 mg three times daily initially and 600 mg three times daily 2 wk later), along with intravenous immunoglobulin (25 g twice a week for 1 wk and then once weekly). One month later, due to lack of response, interferon alfa (5 million U, subcutaneously, three times...
a week) was started. Regression of the adenopathy was found 20 d after the initiation of interferon therapy. Intravenous immunoglobulin was discontinued. Also noted was an increase in the serum creatinine to 141 μmol/L and a decrease in WBC to 2.0 × 10⁹/L. Azathioprine was discontinued, and the prednisone dosage was increased to 40 mg daily.

Four months after initial diagnosis, CT scans showed resolution of mediastinal and para-aortic adenopathy (Figure 1, B and D). Interferon alfa was discontinued, cyclosporin A was restarted at 75 mg twice a day, and the prednisone dose was decreased to 25 mg/d. Ten months after the initial diagnosis, the patient remained in remission as evaluated by CT of the chest. Acyclovir was then discontinued. A follow-up at 16 mo showed that the serum creatinine level was stable at 124 μmol/L and WBC counts were above 5.0 × 10⁹/L. Her immunosuppressive therapy included cyclosporin A (250 mg) and prednisone (15 mg), each given daily, with cyclosporin A levels in the 40 to 50 ng/dl range.

Discussion
Clinical Manifestations

PTLD is the most common malignancy and constitutes 21% of tumors in transplant patients, excluding nonmelanoma skin cancers and in situ carcinoma of the uterine cervix (5). The clinical presentation of PTLD is extremely variable. The common signs and symptoms of PTLD in renal transplant patients are fever (52%), lymphadenopathy (28%), tonsillitis or pharyngitis (28%), intestinal perforation or obstruction (20%), central nervous system symptoms (16%), and weight loss (8%). The major difference between renal and nonrenal transplant patients is that pulmonary symptoms are rare in the former, but common in the latter, particularly in heart and heart-lung transplant patients (6). The severity of PTLD ranges from infectious mononucleosis, i.e., fever, sore throat, and lymphadenopathy, to sepsis and multiple organ failure. The common sites of PTLD in renal transplant patients are lymph nodes (32%), kidney (32%), small intestine (32%), central nervous system (24%), bone marrow (20%), liver (20%), and large intestine (16%). Involvement of the allograft varies depending on the organ transplanted. Lungs were involved in 80% of heart-lung transplants, whereas one-third of patients with renal transplants developed lymphomas, as did those undergoing liver and bone marrow transplants (6). Because of the extremely variable presentation of PTLD, a high index of suspicion is necessary to make the diagnosis (2).
Pathogenesis

The role of EBV in the pathogenesis of PTLD has been well established. In situ hybridization studies have demonstrated that virtually all PTLD have detectable EBV genomes within the transformed B cells (7). When EBV infects B lymphocytes, it results in either full viral replication and B cell lysis or partial viral gene expression associated with cell transformation. Cell transformation is associated with B cell activation and continuous proliferation. Under normal circumstances, these transformed B cells are suppressed or destroyed by cytotoxic T cells. In individuals with either acquired or congenital immunosuppression, these transformed B cells may escape the destruction by cytotoxic T cells. In addition, immunosuppression may enhance the expression and release of cytokines such as interleukin (IL)-4, IL-6, and IL-10, which promote the proliferation of EBV-infected B cells (8,9). The viral genome is maintained in B cells as a circular episome and produces nine viral proteins that are responsible for the maintenance of the transformed B cells and for further viral replication. These B cells proliferate in an uncontrolled manner, producing a polyclonal proliferation. Over time, as these cells continue to divide, mutations collect within them. Those cells with certain critical mutations begin to overgrow the population of slower-growing cells, thus producing oligoclonal and then eventually monoclonal proliferations (7,10). This concept of progression along a continuum from polyclonal to monoclonal is supported by the observation of a case with transition from polyclonal to monoclonal PTLD (10) and a case of severe combined immunodeficiency disease-associated lymphoma with monoclonal, oligoclonal, and polyclonal lesions from various locations (7).

Risk Factors

The risk factors for developing PTLD in transplant patients can be divided into two categories: immunosuppression and EBV infection (Table 1). The incidence of PTLD is closely related to the total burden of immunosuppression. For instance, the cumulative dose of OKT3 is related to the incidence and onset of PTLD after cardiac transplantation (11). Patients who received 75 mg or less had an incidence of 6.2% and a mean interval from transplantation to diagnosis of PTLD of 11 mo, whereas patients who received more than 75 mg had an incidence of 35.2% with a mean interval of 1.5 mo. The high incidence of PTLD in these OKT3-treated patients may be related to T cell activation and cytokine release induced by OKT3. A high total burden of other immunosuppression commonly required in cardiac transplant patients may be another contributing factor (8). The high incidence and early onset of PTLD in OKT3-treated patients, however, was not confirmed by others (12).

The incidence of PTLD varies with the type of transplant. It is much higher in heart and heart-lung transplant patients than in other organ recipients because of the need for higher doses of immunosuppression. Nalesnik et al. (13) reported from the Pittsburgh-Denver series that the incidence of PTLD was 1% for renal transplantation, 1.8% for cardiac transplantation, 2.2% for liver transplantation, and 4.6% for heart-lung transplantation. In a literature review by Cohen (6), the overall incidence of PTLD was found to be 1 to 3% in bone marrow, kidney, or liver transplant recipients, and 5 to 13% in heart or heart-lung transplants.

With the introduction of new immunosuppressive agents, PTLD appears to occur more often and earlier compared with the conventional therapy with azathioprine. Penn (5) reported that the interval from transplantation to the onset of PTLD was 48 mo in the azathioprine/cyclophosphamide group, 15 mo in the cyclosporin A group, and 7 mo in the OKT3 group. The percentage of lymphoma occurring within 4 mo of transplantation is 11, 32, and 68%, respectively, for these three groups. Lastly, PTLD accounts for 11% of total tumors in the azathioprine group, 32% in the cyclosporin A group, and 64% in the OKT3 group. Tacolimus, or FK506, another new and powerful immunosuppressive agent, has been used increasingly for solid organ transplantation. Cox et al. (14) reported their experience of PTLD in young children who received tacolimus after liver transplantation. In children under 5 yr of age, tacolimus is associated with a higher incidence of EBV infection (38% versus 13%) and PTLD (19% versus 3%) when compared with cyclosporin A. These findings are probably related to a greater intensity of immunosuppression for patients on tacolimus than those on cyclosporin A.

As for EBV infection per se, both pretransplant EBV seronegativity and donor EBV seropositivity are risk factors for PTLD. Cockfield et al. (15) reported that the incidence of PTLD was significantly higher in EBV-seronegative patients than in EBV-seropositive recipients (23.1% versus 0.7%). Similar results were reported by Walker et al. (16). Both groups found that the population most at risk is that receiving potent antilymphocyte preparations in the setting of primary EBV infection. Transmission of donor EBV in transplanted organs can cause PTLD in EBV-seronegative recipients. Haque et al. (17) recently reported such transmission in one cardiac and in one pulmonary transplant recipient. Fortunately, PTLD, except those in bone marrow transplant recipients, are predominantly of host origin (18).

Table 1. Risk factors for development of PTLD

<table>
<thead>
<tr>
<th>Immunosuppression</th>
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<tbody>
<tr>
<td>total burden of immunosuppression</td>
<td></td>
</tr>
<tr>
<td>type of organ transplant</td>
<td></td>
</tr>
<tr>
<td>immunosuppressive agents</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus infection</td>
<td></td>
</tr>
<tr>
<td>pretransplant seronegativity</td>
<td></td>
</tr>
<tr>
<td>donor seropositivity</td>
<td></td>
</tr>
</tbody>
</table>

Treatment

Therapy for PTLD includes the following: measures to improve immune function, tumor removal, radiation therapy, chemotherapy, and antiviral therapy. Treatment of PTLD certainly should involve reduction of immunosuppression as the initial step of therapy. However, such treatment carries the risk
of allograft rejection and is not feasible in cardiac or hepatic transplant patients (19).

In the earlier literature, cytotoxic chemotherapy and radiation therapy were reported as ineffective for PTLD. Cohen (6) reported that the survival rate for transplant patients treated with cytotoxic chemotherapy was 23%, and with radiation therapy it was 20%. However, these poor results may reflect the fact that chemotherapy and radiation therapy were usually given after patients failed to respond to reduction of immunosuppression. Recently, Lien et al. (20) reported a case of PTLD with multiorgan involvement that was treated successfully with radiation therapy and a protocol designated for high-grade lymphoma, i.e., proMACE-cytaBOM: prednisone, Adriamycin, Cytoxan, etoposide, arabinoside cytosine, bleomycin, Oncovin, and methotrexate. Subsequently, Swinnen et al. (21) reported that using the same protocol, 6 of 8 patients with monoclonal PTLD after cardiac transplantation achieved complete remission. The major side effects are neutropenic sepsis and subclinical cardiotoxicity due to Adriamycin. Another group reported a high remission rate of PTLD, using the CHOP protocol (cyclophosphamide, doxorubicin, vincristine, and prednisone) in four patients after heart or lung transplantation (22). These results suggest that the patients with widespread monoclonal PTLD may be treated as nontransplant-related, high-grade lymphomas.

Because EBV plays a critical role in the pathogenesis of PTLD, it has been suggested that antiviral therapy may be effective in the treatment of PTLD. Acyclovir has been noted to be effective in a few cases, especially those with a histology indicative of B cell hyperplasia. However, the concomitant reduction in immunosuppression that accompanies almost all PTLD treatment regimens makes it difficult to assess the efficacy of acyclovir alone. Our patient received a 10-mo course of acyclovir, which may not be effective for curing PTLD but may be of value in preventing further EBV infection (23).

Another modality for treating PTLD is anti-B cell monoclonal antibodies. Leblond et al. (24) reported their experience of treating 12 PTLD patients with anti-B cell monoclonal antibodies in a single center. Immunosuppressive therapy was reduced in most of those patients. Four of five patients with polyclonal PTLD and four of seven patients with monoclonal PTLD achieved complete remission. Only one of the responders received additional chemotherapy and surgical resection. They concluded that this therapy seemed to be effective for PTLD, even in monoclonal forms, but other approaches would be necessary to improve survival further.

**Table 2. Characteristics of patients with posttransplant lymphoproliferative disorders treated with interferon alfa**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Type of Transplant</th>
<th>EBV</th>
<th>Site</th>
<th>Clonality</th>
<th>Histology</th>
<th>Other Therapy</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36/M</td>
<td>Bone marrow</td>
<td>+, S/I</td>
<td>LN, Lung</td>
<td>Mono</td>
<td>Polymorphic</td>
<td>Acy, Ig</td>
<td>DWD</td>
<td>27,28</td>
</tr>
<tr>
<td>2</td>
<td>30/F</td>
<td>Bone marrow</td>
<td>+, S/I</td>
<td>LN, Lung</td>
<td>Poly</td>
<td>Polymorphic</td>
<td>Acy, Ig</td>
<td>CR</td>
<td>27,28</td>
</tr>
<tr>
<td>3</td>
<td>4/M</td>
<td>Liver</td>
<td>+, S/I</td>
<td>SI</td>
<td>Poly</td>
<td>Polymorphic</td>
<td>Surg, Acy, Ig</td>
<td>CR</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>14/M</td>
<td>Kidney</td>
<td>NA</td>
<td>LN, BM</td>
<td>Mono</td>
<td>Immunoblastic</td>
<td>Acy</td>
<td>PR, DWD</td>
<td>30,31</td>
</tr>
<tr>
<td>5</td>
<td>56/F</td>
<td>Heart</td>
<td>+, S/I</td>
<td>LN, SI</td>
<td>Mono</td>
<td>Polymorphic</td>
<td>Acy</td>
<td>CR</td>
<td>30,31</td>
</tr>
<tr>
<td>6</td>
<td>14/F</td>
<td>Liver</td>
<td>+, S/I</td>
<td>LN, CNS</td>
<td>Mono</td>
<td>Polymorphic</td>
<td>Acy, Ig, CT, RT</td>
<td>CR</td>
<td>30,31</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>Kidney</td>
<td>NA</td>
<td>ELR</td>
<td>Mono</td>
<td>Polymorphic</td>
<td>Acy</td>
<td>CR</td>
<td>30,31</td>
</tr>
<tr>
<td>8</td>
<td>6/M</td>
<td>Heart/Lung</td>
<td>+, I</td>
<td>Lung</td>
<td>Mono</td>
<td>Polymorphic</td>
<td>Acy</td>
<td>PR</td>
<td>30,31</td>
</tr>
<tr>
<td>9</td>
<td>NA</td>
<td>Heart</td>
<td>+, S</td>
<td>LN</td>
<td>Mono</td>
<td>Immunoblastic</td>
<td>Ig</td>
<td>CR</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
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<td>Heart</td>
<td>+, S</td>
<td>SI</td>
<td>Mono</td>
<td>Immunoblastic</td>
<td>Surg, Ig</td>
<td>CR</td>
<td>32</td>
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<tr>
<td>11</td>
<td>NA</td>
<td>Heart</td>
<td>−, S</td>
<td>Heart</td>
<td>Mono</td>
<td>Immunoblastic</td>
<td>Surg, Ig, CT</td>
<td>PR, DWD</td>
<td>32</td>
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<tr>
<td>12</td>
<td>11/M</td>
<td>Lung</td>
<td>+, S/I</td>
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<td>Polymorphic</td>
<td>Acy</td>
<td>CR</td>
<td>33</td>
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<tr>
<td>13</td>
<td>65/F</td>
<td>Kidney</td>
<td>+, S/I</td>
<td>LN</td>
<td>Mono</td>
<td>Immunoblastic</td>
<td>Acy, Ig</td>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

*EBV, Epstein-Barr virus; Ref., reference; S, serology; I, in situ hybridization; LN, lymph nodes; Mono, monoclonal; Acy, acyclovir; Ig, intravenous immunoglobulin; DWD, death with disease; Poly, polyclonal; CR, complete remission; SI, small intestine; Surg, surgical resection; NA, not available; BM, bone marrow; PR, partial remission; CNS, central nervous system; CT, chemotherapy; LI, large intestine; RT, radiation therapy; ELR, extralymphoreticular system.*
In a total of 13 cases, four received cardiac transplantation, three kidney, two liver, two bone marrow, one lung, and one heart and lung. At the time of diagnosis, most of the patients were EBV-positive by serology or in situ hybridization. Three patients had lymph node involvement only, seven had extranodal involvement, and three had both. Two patients had polyclonal PTLD, 1 was unknown, and 10 were monoclonal. Eight patients had polymorphic B cell lymphoma, four had immunoblastic lymphoma, and one had plasmacytoid lymphoma. Immunosuppressive therapy was reduced in most of these patients. Other treatments in addition to interferon include: acyclovir, intravenous immunoglobulin, radiation therapy, and surgical resection. Eight patients experienced complete remission and all of them survived at the time of reporting without loss of grafts. Three had partial remission, two of whom died with disease 3 and 7 mo after diagnosis. Two patients died within 1 mo of diagnosis; one died of dissemination of PTLD and the other of cytomegalovirus pneumonitis without progression of pulmonary PTLD.

Because the patients who received interferon alfa for PTLD are heterogeneous and because the number of patients is small, it is difficult to determine whether interferon causes the resolution of PTLD. However, several subjects (patients 2, 3, 9, 12, and 13) had a documented response shortly after the administration of interferon with or without intravenous immunoglobulin. Therefore, the beneficial effects of interferon can be established based on the temporal relationship. Patients with only lymph node involvement (three of three achieved remission) and patients with polyclonal lymphoma (two of two achieved remission) tended to respond to interferon. These observations remain to be confirmed by further studies. The beneficial effects of interferon for PTLD are supported by the observations of interferon alfa in the treatment of PTLD may, in part, be due to the inhibition of type 2 helper T cells. These T cells release cytokines such as IL-4, IL-6, and IL-10, which promote B cell proliferation (8,9). Patients with PTLD have low serum levels of interferon alfa (9). Faro et al. (33) reported that the mRNA abundance of IL-4 and IL-10 was markedly elevated in the bronchoalveolar lavage cells in a patient with pulmonary PTLD (Table 2, patient 12). During therapy with interferon alfa, the patient’s IL-4 and IL-10 mRNA decreased significantly, coinciding with clinical and histological improvement. Because these results were derived from a single patient, further studies are needed to confirm this speculation.

In conclusion, the pathogenesis of PTLD is multifactorial and its treatment is still controversial. We reported a case of a monoclonal PTLD that did not respond to treatment until the initiation of interferon alfa therapy. The patient has been in remission with good graft function since completing the therapy with interferon alfa and is currently maintained on a cyclosporin A and prednisone immunosuppressive regimen. We believe that further clinical trials regarding the safety and efficacy of interferon alfa for the treatment of PTLD are warranted.

Acknowledgment

We thank Dr. Lisa M. Rimsza for performing in situ hybridization studies.

References

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Overview of the Nephrology Training Program at the University of Arizona Health Sciences Center

The University of Arizona offers both 2-yr clinical training and 3-yr research training tracks in nephrology. These programs are designed to prepare physicians for careers in clinical practice or academic medicine. Extensive training in all aspects of clinical nephrology, dialysis, hypertension, and transplant nephrology is provided. The research program provides a variety of opportunities, and disciplines include renal physiology, molecular biology, cell biology, immunohistochemistry, and biochemistry. National Institutes of Health- and industry-funded research is ongoing in areas of gene therapy, osmoregulation, renal calcium channels, microcirculation, and diabetic nephropathy.

Fellows rotate through the University Medical Center, Tucson Veterans Administration Medical Center, and Kino Community Hospital. The renal transplant program at the University Medical Center averages 35 kidney and simultaneous kidney-pancreas transplants per year and continues to grow. The renal section directs three outpatient dialysis facilities with approximately 100 hemodialysis and 30 peritoneal dialysis patients. An extensive hypertension outpatient service is provided at the Tucson Veterans Administration Medical Center. Outpatient activities include the longitudinal management of the fellow’s own renal patients for 2 or 3 yr. Because of our geographic location, we are exposed to most of the ethnic groups of North America, as well as a Hispanic population, and therefore have experience with a wide variety of pathologies. Skills are developed in all aspects of dialysis, renal biopsy, dialysis catheter placement, and management of renal transplant recipients. The educational activities include weekly renal grand rounds and journal clubs/research conferences and monthly renal pathology and renal radiology conferences. Fellows are actively involved in teaching medical students and house staff who rotate through the renal service.

Fellows who decide to take the research track have 2 yr of protected research time after 1 yr of clinical training, thus providing training in basic or clinical research. This program allows for the acquisition of the scientific techniques and skills necessary to conduct independent research and pursue an academic career.