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Kidney Biopsy Teaching Case

Chronic Ifosfamide Toxicity: Kidney Pathology and Pathophysiology

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Ifosfamide is a nitrogen mustard alkylating agent used as both a first-line and a salvage chemotherapeutic agent in the treatment of testicular germ cell tumors, various sarcomas, carcinomas, and some lymphomas. A well-known complication of ifosfamide therapy is transient acute kidney injury. However, in a minority of patients, the reduction in kidney function is progressive and permanent, sometimes occurring long after exposure to ifosfamide. Scattered reports have described the pathologic findings in kidneys permanently affected by ifosfamide toxicity. We present the findings of an illustrative case and review the pathology and molecular mechanisms of long-term ifosfamide toxicity with implications for personalized medicine.
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INDEX WORDS: Ifosfamide; tubular toxicity; chemotherapy-related injury; chronic kidney injury; drug toxicity.

INTRODUCTION

Chemotherapeutic agents used for the treatment of malignant neoplasms frequently induce collateral kidney injury. Two widely used oxazaphosphorine nitrogen mustards, ifosfamide and its related compound cyclophosphamide, are known to cause both acute and chronic kidney injury. Ifosfamide is particularly notorious for sporadically causing irreversible kidney injury. We describe the histologic findings of chronic ifosfamide-induced kidney injury and possible pathophysiologic mechanisms underlying these changes.

CASE REPORT

Clinical History and Initial Laboratory Data

A 22-year-old man was first given the diagnosis at age 17 years of stage IIB classic Hodgkin lymphoma. He received multiple rounds of chemotherapy, including ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine), GVD (gemcitabine, vinorelbine, and doxorubicin), and DHAP (dexamethasone, cytarabine, and cisplatin), but his disease was refractory to treatment. He underwent autologous stem cell transplantation and haploidentical allogeneic stem cell transplantation at age 18 years. Prophylaxis for graft-versus-host disease included tacrolimus, which was limited to 10 days around the time of the allogeneic stem cell transplantation.

Two years later, the patient experienced a skin rash that initially was attributed to graft-versus-host disease and empirically treated with tacrolimus for 5 days, after which tacrolimus therapy was discontinued. Trough tacrolimus levels ranged from 1.2-8.6 ng/mL during this course.

The patient's lymphoma relapsed 3 years later and failed to respond to salvage therapies with bendamustine and brentuximab vedotin. At age 21 years, he underwent salvage chemotherapy with ifosfamide (2 cycles) administered with sodium-2-mercaptoethane sulfonate (MESNA) in preparation for a donor lymphocyte infusion. After receiving the donor lymphocyte infusion, his disease relapsed, prompting plans for a third stem cell transplantation. To prepare for this, he received 3 additional cycles of ifosfamide with MESNA. After each cycle of ifosfamide, the patient's serum creatinine concentration increased, reflecting kidney function deterioration, but returned to a new (elevated) baseline (Fig 1A). Each cycle was associated with severe thrombocytopenia, and the first 2 cycles were associated with a mild elevation in serum lactate dehydrogenase level (Fig 1B). After the final cycle, his serum creatinine concentration increased progressively to 3 mg/dL (corresponding to estimated glomerular filtration rate calculated with the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation of ~40 mL/min/1.73 m^2). This was accompanied by proteinuria quantitated by a spot urine protein-creatinine ratio of 5.5 g/g (2+ on urinalysis). An albumin-creatinine ratio of 511.8 mg/g indicated substantial nonalbumin proteinuria. These findings prompted a kidney biopsy 12 weeks after completion of this last cycle of therapy.

Kidney Biopsy

The biopsy specimen showed renal cortex with 17-20 glomeruli, of which 3 were globally sclerosed. One glomerulus had a hilar thrombus (Fig 2A) and another had mesangiolysis (Fig 2B), both features of thrombotic microangiopathy (TMA). Focal nodular hyalinosis also was present, suggesting that the glomerular and vascular findings were attributable to calcineurin-inhibitor (tacrolimus) toxicity. Isometric tubular epithelial cytoplasmic vacuolization, a feature of acute calcineurin-inhibitor toxicity, was not present. The remaining glomeruli were unremarkable. The most prominent finding was diffuse and severe acute tubular injury (Fig 2C and D). Several tubular segments were extensively denuded of epithelial cells, and many of the surviving cells demonstrated nuclear atypia, including nucleomegaly and hyperchromasia. These atypical-appearing cells prompted consideration of possible viral infection, but immunostains did not detect the presence of polyomavirus or cytomegalovirus. In addition to the acute tubular injury, there was diffuse tubulointerstitial inflammation and interstitial edema. This active inflammatory infiltrate made it difficult to

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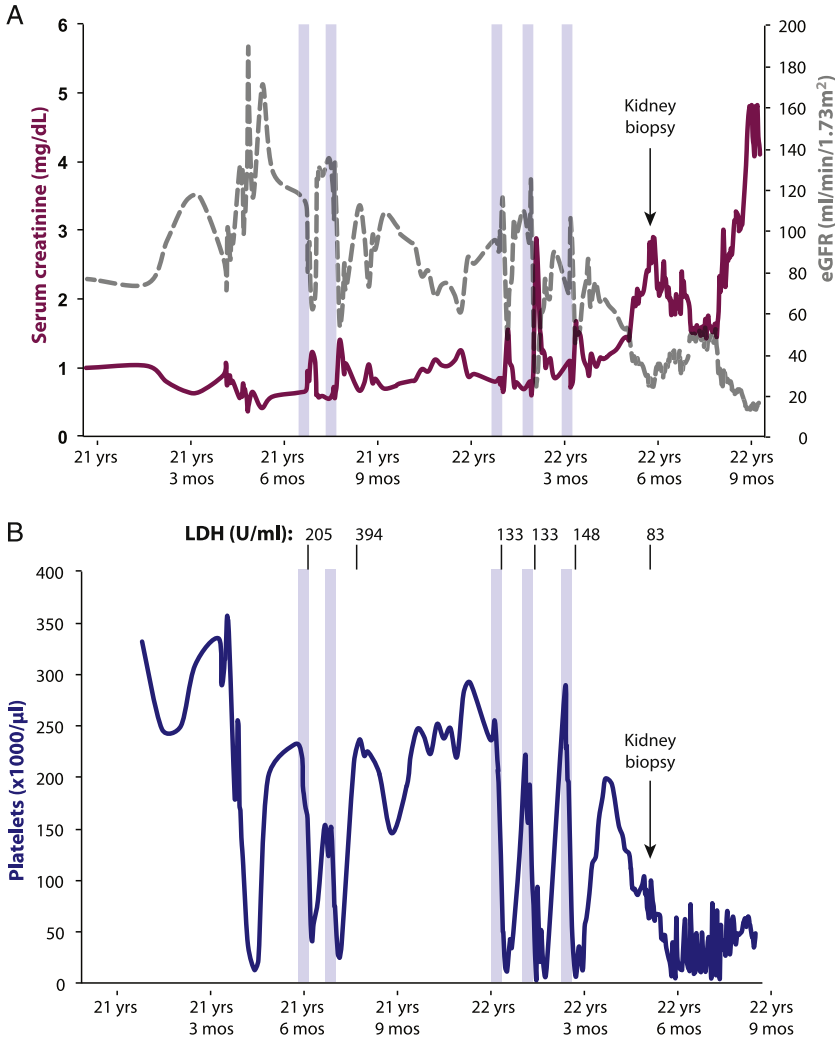

Figure 1. (A) Time course of the patient's decline in kidney function. The patient's serum creatinine levels are plotted as a function of age (solid line, adult reference range, 0.51-1.18 mg/dL). Estimated glomerular filtration rate is plotted along the right axis (dashed line). Vertical gray bars below the time course indicate ifosfamide treatments. (B) The patient's platelet count during the same period is plotted. Serum lactate dehydrogenase levels in U/mL are shown at indicated time points (reference range, 80-190 U/mL).

accurately assess the degree of chronic parenchymal injury. Immunofluorescence microscopy study findings were unremarkable. Electron microscopy did not show immune deposits, abnormal mitochondrial forms within tubular epithelial cells, or viral particles. Glomeruli were not present in the electron microscopic sample to evaluate for acute endothelial injury.

Diagnosis

Based on the biopsy findings, a diagnosis of diffuse acute tubular injury with tubulointerstitial nephritis was rendered. The epithelial cytologic atypia was noted, and association of tubular injury to the patient's treatment with ifosfamide was suggested. The degree of interstitial fibrosis was deemed difficult to assess accurately due to extensive interstitial inflammation and edema. With this caveat, chronic tubulointerstitial injury was estimated to be mild. Focal TMA involving glomeruli was noted. Focal nodular arteriolar hyalinosis, a feature associated with calcineurin-inhibitor toxicity, also was described.

Clinical Follow-up

After the biopsy, stem cell transplantation was postponed temporarily and the patient was aggressively volume resuscitated. However, this maneuver resulted in only modest improvement in kidney function, as detected by a small reduction in serum creatinine concentration. Four months later, he was restarted on tacrolimus therapy as part of preparative conditioning for stem cell transplantation, but developed fevers and septic shock. His kidney function declined precipitously, which was attributed to hypovolemic injury superimposed on chronic tubular injury and diminished kidney reserve. His serum creatinine concentration has remained highly elevated and he currently is preparing for renal replacement therapy.

DISCUSSION

In most patients, ifosfamide-induced decreased kidney function is temporary, and kidney function appears to normalize upon cessation of therapy. However, long-term analysis of adult survivors of pediatric malignancies treated with ifosfamide has shown permanently decreased kidney function, comparable in magnitude to unilateral nephrectomy.[1] Rarely, the ifosfamide-related kidney injury is progressive, leading to end-stage kidney disease. Potential risk factors for persistent nephrotoxicity in children include high cumulative dose, younger age at presentation, and reduced kidney mass (eg, prior nephrectomy).[2-6] There are fewer data for risk factors in adults, but older age and concurrent treatment with cisplatin appear to increase the risk for persistent decreased