Specific Renal Tubular Dysfunction and Associated Fluid and Electrolyte Disorders

RENAL TUBULAR DYSFUNCTION IN MALIGNANCY

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor-induced inappropriate hormone concentrations</td>
<td>Hypercalcemia, Hypoposphatemia</td>
</tr>
<tr>
<td>PTH-like substances</td>
<td></td>
</tr>
<tr>
<td>Excess ADH</td>
<td>Hypernatremia (SIADH), Hypokalemia</td>
</tr>
<tr>
<td>Deficient ADH</td>
<td>Hyperkalemia, central DI</td>
</tr>
<tr>
<td>Adrenocortical excess</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Adrenocortical insufficiency</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Tumor products or metabolites</td>
<td>Hypokalemia, Fanconi's syndrome</td>
</tr>
<tr>
<td>Lysozyme (AML)</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin light chains (MM)</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Hypercalcemia (MM, osseous metastases)</td>
<td>Urinary concentrating defect, Multiple transport defects, Hypouricemia</td>
</tr>
<tr>
<td>Reabsorptive urate transport inhibitor (Hodgkin's, solid tumors)</td>
<td></td>
</tr>
<tr>
<td>Intrinsic</td>
<td></td>
</tr>
<tr>
<td>Amyloid deposits in collecting ducts (MM)</td>
<td>Nephrogenic DI</td>
</tr>
<tr>
<td>Partial intrarenal obstruction (MM cast nephropathy)</td>
<td>Nephrogenic DI</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>SIADH</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Fanconi's syndrome</td>
</tr>
<tr>
<td>Vincristine</td>
<td>SIADH</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Hypoposphatemia, Fanconi's syndrome</td>
</tr>
</tbody>
</table>

**FIGURE 5-35**

Renal tubular dysfunction. Specific tubular dysfunction may be encountered in association with the four major causes listed.

Normal renal tubular function is controlled by a delicate balance of humoral mediators. Thus, a tumor-induced inappropriate concentration of a hormone that normally contributes to the modulation of this balance may result in a profound disturbance of tubular function, thereby causing impairment of fluid and electrolyte balance as well as other homeostatic defects. A tumor product appears to be the basis for renal phosphate loss in some cases, in that the resultant hypophosphatemia regresses when the tumor is removed [75]. Hypernatremia occurs frequently in the patient with cancer; it is frequently caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Bronchogenic carcinoma is the most frequent cause of this syndrome. A number of other tumors have also been reported to cause SIADH. Disappearance of the syndrome on removal of the tumor or improvement following successful chemotherapy has been observed frequently [76]. Cancer is a common cause of central diabetes insipidus; metastatic lesions have been reported to cause 5% to 20% of all cases, with breast cancer being the primary malignancy in more than half the cases reported [77]. Adrenocortical steroid excess may be associated with malignancies and often manifests with hypokalemia and metabolic alkalosis due to excessive mineralocorticoid effect in the distal nephron. Adrenal insufficiency may develop owing to metastatic lesions of the adrenal glands, producing hyperkalemia and hyponatremia due to mineralocorticoid deficiency and affecting tubular transport at the same site.

Hypercalcemia is the most common setting in which tumor products or metabolites can cause specific tubular defects. In this case, profound tubular dysfunction is observed involving impairment of bicarbonate or sodium transport, urinary concentration, hydrogen ion secretion, or the renal handling of potassium, phosphorus, or magnesium [35]. Massive lysozymuria may be associated with renal damage, leading to kaliuresis and hypokalemia [78]. Elevations of lysozyme levels are seen with acute myelogenous leukemia. In this setting, proximal tubular defects in urate, phosphate, and amino acid reabsorption have also been noted [79]. Isolated hypouricemia has been reported in patients with advanced Hodgkin’s disease; these patients have increased renal clearance of urate despite decreased serum urate levels. An abnormal urate clearance was corrected by successful treatment of the underlying Hodgkin’s disease, suggesting a humoral basis for this tubular defect. Hypouricemia, in association with other types of proximal tubular dysfunction, has been associated with a variety of solid tumors. In multiple myeloma, the proliferation of abnormal plasma cells produces large quantities of a variety of immunoglobulins. These may produce changes in tubular function, which result from tubular reabsorption of the freely filtered low-molecular-weight tumor products. These in turn interfere with normal metabolism of proximal tubular cells after their reabsorption. This toxicity produces Fanconi’s syndrome, which is a complex proximal tubulopathy associated with multiple reabsorption defects, and renal tubular acidosis, which may be of the proximal or distal variety.

Intrinsic renal lesions produced by cancer may cause nephrogenic diabetes insipidus, in which the kidney is unresponsive to the action of antidiuretic hormone (ADH), with resultant formation of inappropriately dilute urine. This may be seen in multiple myeloma, in which causative intrinsic lesions could include intratubular obstruction by myeloma proteins or amyloid deposition in collecting ducts.

Various antineoplastic agents produce a wide array of tubular dysfunction, with defective reabsorptive transport of magnesium constituting the defect of greatest clinical significance. AM L — acute myelogenous leukemia; DI — diabetes insipidus; MM — multiple myeloma; PTH — parathyroid hormone.
Malignancy in the Renal Transplant Patient

**Cancer of the skin and lips**
- Squamous cell carcinoma
- Basal cell carcinoma
- Malignant melanoma
- Malignant lymphoma
- Non-Hodgkin's lymphoma
- Reticulum cell sarcoma
- B-cell lymphoproliferative syndromes (Epstein-Barr virus)

**Kaposi's sarcoma**
- Cutaneous form
- Visceral and cutaneous form

**Genitourinary cancer**
- Carcinoma of the native kidney (acquired cystic kidney disease)
- Carcinoma of the transplanted kidney
- Renal cell carcinoma
- Malignant melanoma
- Carcinoma of the urinary bladder (cyclophosphamide associated)
- Uroepithelial tumors (associated with analgesic abuse)

**Gynecologic cancer**
- Carcinoma of the cervix
- Ovarian cancer

**FIGURE 5-36**
Malignancy in the renal transplant patient. In patients with end-stage renal disease with an adequately functioning renal allograft, there is an increased incidence of malignancy at various sites [80]. The most common form of malignancy is skin cancer. Its incidence may be as high as 24% in countries such as Australia where excessive exposure to the sun occurs. Other forms of cancer also occur with increased incidence in the transplant recipient. Malignant lymphoma, especially at extranodal sites (such as the central nervous system), occurs with increased frequency. Women with renal transplants have been observed to have an increased incidence of cervical cancer. Kaposi's sarcoma can account for 5% to 10% of posttransplant neoplasms. This tumor may be confined to the skin or may involve the viscera.

Several factors contribute to the increased risk of cancer in the immunosuppressed renal transplant recipient. These include loss of immune surveillance, chronic antigenic stimulation, oncogenic potential of the immunosuppressant agents, and viral infections leading to neoplasia. Epstein-Barr virus has been implicated in the polyclonal B-cell lymphoproliferative disease in these patients. Lymphoproliferative disorders have been noted to occur after a median period of 56 months when azathioprine and prednisone are used as immunosuppressive therapy. After the introduction of cyclosporine, lymphoproliferative disorders develop sooner, with a median interval of only 6 months [81].

The prognosis for patients with skin cancer remains good. Preventive measures such as avoiding sun exposure, utilization of sun-blocking creams, and careful periodic skin examinations are important. Patients with Kaposi's sarcoma confined to the skin may have remission rates of up to 50% with cessation of immunosuppression or with chemotherapy. Patients with Kaposi's sarcoma involving the viscera or with other lymphoproliferative disorders do poorly, with a more rapid course than seen in nontransplant patients with malignancy. Even those patients responding to chemotherapy tend to have only short remissions and a poor outcome.

**FIGURE 5-37**
Malignant lymphoma in the transplanted kidney. A 55-year-old man with end-stage renal disease due to diabetic nephropathy received a cadaveric renal transplant. He was managed with prednisone, azathioprine, and antilymphocyte globulin (ALG). The allograft functioned poorly despite therapy a week later with OKT3.

Results of a percutaneous renal biopsy were suspicious for a lymphoproliferative disorder in the renal allograft. He had a transplant nephrectomy 5 weeks after the original surgery. Pathologic study of the allograft showed extensive infiltration of the interstitium, renal pelvis, and blood vessels with large round and ovoid lymphocytes with many nucleoli and scant cytoplasm, diagnostic of a malignant lymphoma. Special studies revealed the lymphoid cells to be polyclonal in nature, and the patient's serologic testing was positive for Epstein-Barr virus. Immunosuppression was stopped, and therapy with ganciclovir was started.
References
