A Case Series of Nephrotic Syndrome: A Harbinger of Catastrophic Oncologic Diseases

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ABSTRACT

Introduction: A cancer patient can have numerous complications involving the kidneys, ranging from acute kidney injury, chronic kidney disease, glomerulopathies, electrolyte, and acid-base disorders. It can be due to the malignancy itself or due to chemotherapeutic agents. Paraneoplastic glomerulopathy is a rare presentation of neoplastic disease.

Case discussion: We present a case series of two patients presenting with nephrotic syndrome as a paraneoplastic syndrome associated with a gynecologic tumor. Both patients responded only partially to steroids and immunosuppressive therapy. Complete remission was only achieved after treatment of primary malignancy.

Conclusion: It is critical to recognize this entity as immunosuppression may induce a flare in the tumor course and worsen outcomes. So, age-appropriate screening of malignancy should ideally be performed in any adult patient with nephrotic syndrome.

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INTRODUCTION

Neoplasms are associated with a variety of renal syndromes ranging from acute kidney injury, chronic kidney disease, electrolyte-acid base disorders, and rarely paraneoplastic glomerulopathy. Nephrotic syndrome is seen at presentation in 10–11% of malignant tumors.¹ Solid tumors are associated with membranous nephropathy (MN), and Hodgkin’s lymphoma is associated with minimal change disease (MCD). MN is the most common lesion associated with solid organ tumors, followed by MCD. The focal segmental glomerulosclerosis (FSGS) lesion observed in our case series is an uncommon presentation of solid gynecologic tumors.

CASE DESCRIPTION

Case 1

A 65-year-old female with type 2 diabetes mellitus of 5 years duration and newly detected hypertension presented with anasarca and foamy urine. Examination revealed blood pressure 140/90, bipedal edema. Fundus evaluation did not reveal hypertensive or diabetic retinopathy. Detailed investigations are listed in Table 1. Kidney biopsy revealed one sclerosed and 13 viable glomeruli. The glomerular size, cellularity, and basement membrane thickness were normal, with focal segmental sclerosis-type not otherwise specified (NOS) lesion seen involving 15–20% of glomeruli. Tubules showed severe hydropic changes. The interstitium was edematous, and the vessels were unremarkable. Immunofluorescence (IF) was negative, and a diagnosis of primary FSGS was made. The patient was initiated on prednisolone at a dose of 1 mg/kg/day. The patient achieved partial remission only after 12 weeks of therapy. Calcineurin therapy was initiated after 16 weeks in view of partial remission and side effects of steroids. An ultrasound was done after 2 weeks for abdominal distension and pain, which incidentally detected a solid mass lesion in the liver. A computerized tomography scan revealed multiple hypoechoic discrete lesions scattered in both lobes of the liver and a bulky, nodular, and inhomogeneously enhancing left ovary. A core biopsy of the liver lesion revealed metastatic adenocarcinoma with primary ovarian neoplasm. Tumor cells expressed cytokeratin 7 and paired-box gene 8. Immunosuppression was discontinued, and the patient was started on paclitaxel and carboplatin chemotherapy. The patient achieved complete renal remission after six cycles of chemotherapy. A significant reduction in the size of the ovarian and hepatic lesions was observed after 18 cycles of chemotherapy.

Case 2

A 50-year-old morbidly obese (body mass index 44.2 kg/m²) normotensive female with hypothyroidism presented with bipedal edema and frothy urine. Systemic examination was unremarkable. Detailed investigations are listed in Table 1. Kidney biopsy revealed 10 mildly enlarged normocellular glomeruli with patent capillary lumina, normal basement membrane thickness, and focal segmental sclerosis type—NOS involving 25–30% of glomeruli. The interstitium had bands of fibrous tissue and mild tubular atrophy. The vessels were unremarkable. IF was negative. A diagnosis of FSGS was made, and the patient was started on prednisolone at a dose of 1 mg/kg/day. The patient responded well to treatment and achieved remission after 6 weeks of starting therapy. The course was complicated by frequent relapses, which prompted the initiation of calcineurin therapy for steroid-sparing effect. After 5 months, the patient was diagnosed with invasive ductal carcinoma of the right breast NOS grade 3 Paget’s disease. The tumor was classified as pT2 N2 M0 and was positive for estrogen receptor (ER) and progesterone receptor (PR) but negative for HER2 receptors. Steroids and calcineurin inhibitors were stopped. Modified radical mastectomy with axillary clearance was performed, and the patient was started on adjuvant chemotherapy with epirubicin and cyclophosphamide. The patient achieved complete renal remission after 2 months of starting chemotherapy.

DISCUSSION

Paraneoplastic syndromes are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. The concept of paraneoplastic glomerulopathy was introduced in 1922 by Galloway.² Since then, nephrotic syndrome has been associated with several malignancies. MN and MCD are the most common glomerular lesions in cancer patients.³,⁴ FSGS is a relatively rare occurrence in solid organ tumors, which was seen in both of our patients. The pathogenesis of paraneoplastic glomerulopathy is not clear. However, it is probably due to the secretion of tumor cell products such as hormones, growth factors, soluble urokinase receptors, etc.

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A Case Series of Nephrotic Syndrome

Table 1: Investigations

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin (Hb)/white blood cell (WBC)/platelet</td>
<td>12.3/9,450/167,000</td>
<td>9.8/10,000/18,7000</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.2</td>
<td>2.9</td>
</tr>
<tr>
<td>FBS/PPBS/glycated Hb</td>
<td>110/121/6.3</td>
<td>86/134/5.5</td>
</tr>
<tr>
<td>Total cholesterol/triglycerides</td>
<td>241/292</td>
<td>279/320</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Urine routine</td>
<td>Protein 3+ 2–3 WBC</td>
<td>Protein 3+ 10–12 pus cell/HPF</td>
</tr>
<tr>
<td></td>
<td>No red blood cell (RBC)</td>
<td>Casts absent</td>
</tr>
<tr>
<td>Urine protein creatinine ratio</td>
<td>7.7 (0.28 after 6 cycles of chemotherapy)</td>
<td>4.2 (reduced to 0.12 after 2 months of chemotherapy)</td>
</tr>
<tr>
<td>C3 compliment</td>
<td>101.0–180</td>
<td>109.0–180</td>
</tr>
<tr>
<td>C4 complement</td>
<td>20.10–40</td>
<td>26.10–40</td>
</tr>
<tr>
<td>ANA/antids-DNA</td>
<td>Negative/positive</td>
<td>Negative/Positive</td>
</tr>
<tr>
<td>Antineutrophilic cytoplasmic antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antiphospholipase A2 receptor antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cancer antigen 125</td>
<td>79 (0–35 IU/mL)</td>
<td>–</td>
</tr>
</tbody>
</table>

FBS, Fasting blood sugar; HPF, High power field; PPBS, Post prandial blood sugar

Cytokines like cardiotrophins like cytokine-1, and tumor antigens, which ultimately affect the kidney. Theoretically, the diagnosis of paraneoplastic glomerulopathy should rely on three strong criteria. First, clinical and histologic remission occurs after complete surgical removal of the tumor or chemotherapy-induced complete remission of the disease, which was also seen in our cases. Second, a renal relapse accompanies the recurrence of the neoplasia. Third, a pathophysiologic link is established between the two diseases, including the detection of tumor antigens and antitumor antibodies within subepithelial immune deposits. This was difficult in our cases as electron microscopy could not be done in our patients for logistical reasons. A glomerulopathy can antedate diagnosis of a primary neoplasm by several months to years (as seen in our cases) and, in some cases, postdate it. Treatment of primary neoplasm, whether surgical or chemotherapy, has been found to be curative for paraneoplastic glomerular disease in most of the cases reported in the literature.

Neoplastic diseases may also cause a positive antinuclear antibody (ANA) test. ANA has been reportedly found in the sera from lung, breast, and head and neck cancer patients. ANAs are autoantibodies to nuclear cell components that are formed when the cell’s nuclear content is exposed to the extracellular milieu as the cell dies by apoptosis or necrosis. In this context, its presence could be simply epiphenomena, or it could also represent an immune response to restrain tumour spreading. ANA can be found in 35–50% of malignant breast tumors. We also found an association of ANA with breast cancer in our second case.

Although it is generally agreed that a search for malignancy is warranted in all patients presenting with apparently idiopathic MN, particularly those over the age of 50, it should also be the case for MCD and FSGS. It is suggested that in addition to a thorough history of personal and hereditary cancer risk factors, physical examination, and standard biologic tests, one should undertake basic routine cancer screening procedures, including a chest radiograph. More importantly, these patients should be closely followed, as the malignancy could be occult and not detectable on initial routine screening.

Conclusion

Nephrotic syndrome is common in adults. However, it could be a rare paraneoplastic presentation of malignancy. Age-appropriate cancer screening should ideally be done in any patient above 50 years of age with nephrotic syndrome to avoid catastrophic consequences of using immunosuppressive therapy and flaring up the primary malignancy. ANA could be associated with several other conditions apart from Lupus, like breast cancer and rheumatoid arthritis. It is a useful immune biomarker in autoimmune states and could also help in raising suspicion of cancer in appropriate clinical situations.

References