Glomerular Diseases Associated With Cancer, Chemotherapy, and Hematopoietic Stem Cell Transplantation

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Many solid and hematological malignancies have been associated with different glomerular diseases. Several case reports and case series of cancer-associated glomerular diseases have shown that treating the cancer may lead to resolution of the glomerular process. Hence, knowledge and approach to cancer-associated glomerular diseases is important for both the caring nephrologists and the cancer specialists. While membranous nephropathy has been classically associated with solid malignancies, minimal change disease has been commonly described with hematologic malignancies, especially non-Hodgkin's lymphoma. Membranoproliferative glomerulonephritis is increasingly being recognized to be associated with chronic hematologic malignancies such as chronic lymphocytic leukemia. In this article, we review various cancer-associated glomerular diseases and their pathogenesis as well as principles of treatment. In addition, we also review glomerular diseases seen after chemotherapy and hematopoietic stem cell transplantation.

Key Words: Cancer, Paraneoplastic glomerulonephritis, Hematopoietic stem cell transplantation, Graft versus host disease, Chemotherapy

Introduction

In 1922, Galloway described the association between Hodgkin's disease and albuminuria.[1] Since then, several solid and hematological malignancies have been associated with various glomerular diseases. Although the exact pathogenesis of this association remains to be determined, it is plausible that this relationship could be a result of abnormal tumor cell products. In addition, several chemotherapeutic agents have now been associated with glomerular diseases. Glomerular lesions have also been described after stem cell transplantation. This can be seen with disease recurrence or in graft versus host disease (GVHD). Treatment for cancer-associated glomerular diseases is primarily directed at treating the underlying malignancy. Remission of the primary cancer is commonly accompanied by improvement in the glomerular manifestations. This article will review glomerular diseases seen with cancer, chemotherapy, and hematopoietic stem cell transplantation (HSCT). Glomerular diseases associated with plasma cell dyscrasias and benign neoplasms will not be reviewed here.

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Membranous Nephropathy

Solid Malignancy-Associated Membranous Nephropathy

Membranous nephropathy (MN) is the most commonly reported glomerular disease in patients with solid malignancies,[2,3] especially with pulmonary and gastric cancers. This association has also been reported in patients with kidney carcinoma, breast cancer, prostate cancer, and various gastrointestinal (colorectal, pancreatic, and esophageal) and hepatic cancers (Fig 1). Thymoma of epithelial origin also has been reported to be associated with MN. Rare associations of MN have been described with malignancies such as sarcoma, testicular seminoma, parotid adenolymphoma, spinal schawnnoma, and carotid body tumor.[2]

The prevalence of malignancy in 240 patients with biopsy-proven MN was approximately 10% in a review conducted by Lefaucher and colleagues.[4] It is interesting to note that only half of these patients had cancer-related symptoms at the time of their biopsy, and most of them were diagnosed with cancer within a year of being diagnosed with MN.[4] The presence of proteinuria in a known case of cancer or development of proteinuria within a few months of diagnosis of cancer should raise strong suspicion of underlying glomerular disease, especially MN. Differentiating primary from solid tumor-associated MN has been a great challenge for nephrologists and pathologists. Several studies have suggested various clinical parameters to help make this differentiation. These parameters include historical clues, serological markers, and histopathological findings on the kidney biopsy. Table 1 summarizes these parameters.

Podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2 R) autoantibodies were first

identified by Beck and colleagues[5] in 2009 in patients with primary MN. These antibodies belonged to the immunoglobulin G (IgG) 4 subclass, suggesting a T helper cell (Th)-2 response.[5] In a study done by Qin and colleagues,[6] 10 patients with solid malignancies and MN were analyzed. It is interesting to note that 3 of these 10 patients had elevated levels of anti-PLA2 R antibodies and moderate glomerular IgG4 deposition on kidney biopsy—findings that are suggestive of an underlying primary MN in these patients with solid malignancies. In addition, all 3 of these patients had persistence or relapse of proteinuria despite tumor resection, suggesting that these were patients likely with primary MN. Hoxha and coworkers[7] have also recently showed enhanced staining of PLA2 R in the glomeruli of patients with primary MN compared with normal staining in patients with tumor-associated MN. As opposed to a predominant IgG4 subclass deposition in primary MN, Ohani and colleauges[8] showed an increased glomerular deposition of IgG1 and IgG2 subtypes in patients with cancer-associated MN (suggesting a different pathogenesis, mainly involving Th-1 mechanisms in cancer-related MN). Hence, on the basis of the above data, the presence of circulating anti-PLA2 R antibodies and/or enhanced glomerular PLA2 R staining with the predominance of IgG4 in the glomeruli of patients with MN are suggestive of primary MN even in the presence of cancer. At the time of this writing, an anti-PLA2 R autoantibody assay was not approved by the U.S. Food and Drug Administration, although it is available in Europe. In addition to the above, the presence of increased inflammatory cells (>8 cells per glomeruli) on kidney biopsies was shown to be more suggestive of cancer-associated MN than primary MN, as reported by Lefachuer and colleagues.[4] However, future studies will need to confirm this finding.

CLINICAL SUMMARY

- Several malignancies have been associated with different glomerular diseases.
- Treatment for malignancy (chemotherapy and hematopoietic stem cell transplantation) has also been associated with glomerular diseases.
- Knowledge and approach to cancer- and chemotherapy-associated glomerular diseases are important for both the caring nephrologists and the cancer specialists.

The possibility for an underlying malignancy should be considered in every case of MN in which cancer is not diagnosed. Age- and sex-appropriate malignancy screening should be performed, which may include fecal occult blood testing, colonoscopy, mammography, and prostate-specific antigen testing. High-risk patients such as smokers could be considered for more detailed testing, such as low-dose chest computed tomography to assess for lung malignancy. As reported by the 2012 Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group, there have not been adequate studies to determine guidelines to assess the cost benefit of these screening procedures in the elderly diagnosed with MN.[9] The risk of finding a malignancy exists for up to 5 years from the time of kidney biopsy, and this could be because of a slowly growing malignancy, the use of cytotoxic therapy for MN, or increased surveillance.[10]

Patients older than 65 years and those with a more than 20 pack-year smoking history are at higher risk for malignancy-associated MN.[4] In their case series, Zech and colleagues reported a cancer prevalence as high as 22% in patients with MN older than 60 years.[5] There is also a possibility of coincidental diagnosis of MN and cancer, especially in an older age group in which both diseases tend to occur.[11]

The possible mechanisms by which solid malignancies may be associated with MN[11] include

(1) In situ immune complex formation, in which antibodies are formed against a tumor antigen that is localized in the subepithelial location or against a podocyte antigen that is identical or similar to the tumor antigen;
(2) Tumor antigens may form circulating immune complexes that are subsequently trapped in glomerular capillaries; and
(3) External factors such as infections with oncogenic viruses or altered immune function that can cause the cancer and MN.[11]

Hematological Malignancy-Associated MN

An association of hematological malignancies such as chronic lymphocytic leukemia (CLL) with MN has been reported.[12] However, CLL has a stronger association with membranoproliferative glomerulonephritis (MPGN), with a ratio of MPGN to MN in a case series of 8 to 1.[12] The finding of fibrillary deposits and monoclonal light-chain deposits on kidney biopsy could suggest an underlying lymphoid malignancy.[12]

HSCT and MN

Kidney injury from underlying glomerular diseases may be seen after HSCT. Other etiologies of kidney disease after HSCT include acute tubular injury, calcineurin inhibitor (CNI) toxicity, and thrombotic microangiopathy (TMA). In HSCT patients with nephrotic-range proteinuria, the kidney biopsy findings may include MN, minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS).[13] However, MN accounts for most cases of HSCT-associated glomerular diseases whereas MCD accounts for most of the remaining cases.[13] Host and donor marrow chimerism in addition to the presence of host lymphocytes surviving conditioning