Cancer-associated glomerulopathy; an updated review on current knowledge

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ABSTRACT

Cancer-associated glomerulopathy (CAG) is a rare type of glomerular disease and a complication of malignancy. It is not absolutely related to the tumor burden, invasion, or metastasis however is supposed to be caused by tumor cell products. The recognition of cancer-related glomerulopathy is clinically crucial because it can be the first sign of an underlying malignancy. The most common glomerular diseases which are caused by malignancy are paraneoplastic glomerulopathy. Membranous nephropathy is the most common glomerular pathology associated with solid tumors. 

Keywords: Cancer-associated glomerulopathy, Glomerulonephritis, Vasculitis, Glomerular filtration rate, Renal biopsy, Cancer-related glomerulopathy

Introduction

Cancer-associated glomerulopathy (CAG) is a rare, secondary type of glomerular disease and a complication of malignancy (1). It is not straightforwardly related to the tumor burden, invasion, or metastasis however is thought to be caused by tumor cell products, like tumor antigens, growth factors, cytokines, and hormones (1,2). The identification of CAG is clinically fundamental because it can be the first sign of an underlying malignancy (3). The most common glomerular lesions that are caused by cancers is paraneoplastic glomerulopathy (4). Membranous nephropathy is the most common glomerular pathology associated with solid tumors (5). Various solid tumors, comprising lung cancers or renal cell carcinomas have been connected with vasculitis or rapidly progressive glomerulonephritis (3-8). This review paper provides an overview of the current understanding of CAG, including its pathogenesis, clinical presentation, diagnostic criteria, and management strategies.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including; cancer-associated glomerulopathy, glomerulonephritis, vasculitis, cancer-related glomerulopathy, glomerular filtration rate and renal biopsy.

An overview on CAG

The distorted immune reaction accompanying by malignancies may predispose the extension of CAG (1). Moreover, tumor cells can produce hormones, growth factors, cytokines, and tumor antigens that can disrupt the normal immune response and lead to immune dysregulation. This can result in the deposition of immune complexes in the glomeruli, leading to inflammation and damage (9,10). Correspondingly, the in-situ formation of immune complexes, with antibodies targeting a tumor

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antigen localized in the glomeruli, may contribute to the development of CAG (11,12). Likewise, exposure to chemotherapy is a risk factor for developing glomerular diseases. Chemotherapy can cause direct damage to the glomeruli or trigger an immune response that leads to glomerular injury (13,14). Moreover, glucocorticoids, immunosuppressive agents, or biologic medications which are administered to treat chronic glomerulonephritis can interfere with the immune response and favor the extension of cancer or may themselves be oncogenic (3,15).

**Mechanistic impact of CAG**

Cancer-related glomerulopathy is a rare form of glomerular lesion and a complication of cancer. It is not directly related to the tumor burden, invasion, or metastasis however it is assumed to be caused by tumor cell products, like tumor antigens, hormones, growth factors, and cytokines (1,2). Tumor cell products can disrupt the normal immune response and lead to immune dysregulation. This can result in the deposition of immune complexes in the glomeruli, leading to inflammation and damage (10,16). Additionally, the deposition of immune complexes in the glomeruli can trigger an inflammatory response, leading to glomerular injury. This situation manifests as various glomerular diseases, including membranous nephropathy, rapidly progressive glomerulonephritis, and vasculitis (17,18). Consequently, the glomerular injury caused by CAG can result in impaired kidney function. This condition can lead to symptoms such as proteinuria, hematuria, decreased urine output, and decreased glomerular filtration rate (19). Otherwise, glucocorticoids, immunosuppressive agents, or biologic medications that are conducted to treat chronic glomerulonephritis can interfere with the immune response and favor the development of malignancy or may themselves be oncogenic (3,15).

**CAG versus idiopathic glomerulopathy**

Cancer-related glomerulopathy can be differentiated from idiopathic glomerulopathy by considering several factors. For example, CAG is more common in older adults, while idiopathic glomerulopathy can occur at any age (3,5,20). Moreover, the presence of an underlying malignancy is a risk factor for developing CAG. In contrast, idiopathic glomerulopathy is not associated with an underlying malignancy (3,21). Likewise, patients with CAG may present with symptoms related to the underlying malignancy, such as weight loss, fatigue, and night sweats. In contrast, patients with idiopathic glomerulopathy may present with symptoms related to kidney dysfunction, such as proteinuria, hematuria, and decreased urine output (22,23). Furthermore, the histopathological findings on renal biopsy can help differentiate CAG from idiopathic glomerulopathy. Notably, CAG may show glomerular changes that are consistent with a paraneoplastic process, such as immune complex deposition, mesangial proliferation, and crescent formation (24,25), while idiopathic glomerulopathy may show different histopathological findings, such as minimal change disease, focal segmental glomerulosclerosis, or membranous nephropathy (26,27). Meanwhile, individuals with CAG should be screened for underlying malignancy, while patients with idiopathic glomerulopathy do not require routine cancer screening (24,28).

**Histological features that differentiate cancer-associated glomerulopathy from idiopathic glomerulopathy**

Differentiating CAG from idiopathic glomerulopathy can involve examining the histological features observed in renal biopsies. Here are some histological features that can help differentiate CAG from idiopathic glomerulopathy (21,29). Cancer-related glomerulopathy may show the deposition of immune complexes in the glomeruli, which can be visualized using immunofluorescence or immunohistochemistry (30-32). This condition may also exhibit mesangial proliferation, characterized by an increase in mesangial cells and matrix within the glomeruli (33,34). Besides, crescent can be observed in CAG (35). Cancer-related glomerulopathy may show alterations in the glomerular basement membrane, such as thickening or spikes (36,37). Moreover, inflammatory cells, such as lymphocytes and macrophages, may be present in the glomeruli in this disease.

**Immunofluorescence findings in cancer-associated glomerulopathy**

The immunofluorescence findings in CAG can vary depending on the specific glomerulopathy associated with the underlying malignancy (5). Immunofluorescence staining may reveal the presence of immune complexes in the glomeruli. These immune complexes can consist of various components, such as immunoglobulins (IgG, IgM, IgA), or complement proteins (C3, C1q) (1,38). Meanwhile, the immune complexes may exhibit a granular or linear staining pattern within the glomeruli (39). Accordingly, the immune complexes may be deposited in the subepithelial or mesangial regions of the glomeruli (40,41). Immunofluorescence staining can also help determine the subclasses of IgG involved in the immune complex deposition. Different subclasses of IgG, such as IgG1, IgG2, IgG3, and IgG4, may be observed (42).

**Prevalence of cancer-associated glomerulopathy**

The prevalence of CAG varies depending on the population studied and the specific glomerulopathy...
Chemotherapeutic agents can cause various types of glomerular diseases in cancer patients. Chemotherapeutic agents, such as interferon, have been associated with the development of minimal change disease (60). In addition, bisphosphonates, have been associated with the development of focal segmental glomerulosclerosis (63). Likewise, chemotherapeutic agents, such as interferon, anti-vascular endothelial growth factor (VEGF) agents, tyrosine kinase inhibitors, and bisphosphonates, have been associated with the development of membranous nephropathy (64,65). Notably, chemotherapeutic agents, such as interferon, have been associated with the development of thrombotic microangiopathy (66). Furthermore, chemotherapeutic agents, such as gemcitabine, have been associated with the development of crescentic glomerulonephritis (60).

**Clinical presentation**

Patients with CAG may present with nephrotic syndrome, acute kidney injury, or asymptomatic proteinuria. The clinical presentation can vary depending on the underlying malignancy and the specific histological subtype of glomerular injury (67).

**Diagnostic challenge**

Cancer-related glomerulopathy can present a diagnostic challenge because it can mimic other glomerular diseases. It is important for clinicians to consider the possibility of an underlying malignancy when evaluating patients with glomerulopathy (68).

**Prognostic implications**

The presence of CAG can have prognostic implications for both the kidney disease and the underlying malignancy. It is important to identify and treat CAG early to prevent further kidney damage and to initiate appropriate cancer treatment (69,70).

**Treatment of cancer-associated glomerulopathy**

The treatment of CAG depends on the underlying cancer and the severity of kidney damage. Immunosuppressive therapy, such as steroids and cyclophosphamide, can be used to treat primary CAG. In secondary cancer-related glomerulopathy, treatment is focused on controlling the underlying cancer and managing the associated nephrotic syndrome (13).

**Conclusion**

Cancer-related glomerulopathy is a rare kidney disorder that occurs in patients with cancer. The pathogenesis of CAG is believed to be associated with the production of tumor-associated factors that affect the glomerular basement membrane and podocytes. The diagnosis of CAG requires a kidney biopsy, and treatment depends on...
the underlying cancer and the severity of kidney damage.

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