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Renal Diseases Associated with Malignancies

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ABSTRACT

The kidney may be involved in patients with malignancy for a variety of reasons: the kidney is the site of a primary tumor or a secondary tumor; malignancies may have an indirect effect on kidney through electrolyte disorders; oncological therapy may have an adverse effect on renal function. Malignancies may be associated with a variety of renal complications. These include: acute kidney injury, chronic tubulointerstitial and vascular pathologies as well as paraneoplastic glomerulonephritis. The importance of the understanding this particular concern for the nephrologist, is not only because it can lead to delayed diagnosis of cancer but also because incorrect diagnosis may lead to harmful treatment. Lastly, an already existing occult cancer that is recognized too late may be wrongly attributed to the immunosuppressive therapy used to treat the original, presenting renal disease. Glomerular diseases associated with malignancy are often substantially improved by the cure of the proliferative disorder, which points to the importance of etiological investigations in patients with a glomerulopathy of unknown origin.

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Introduction

The kidney may be the site for a primary or less commonly a secondary tumor. Primary or secondary tumors may exert an effect by *pressure* at the hilum compressing the renal artery / vein or to the renal outflow tract by compression of the ureter. Lymphomatous or leukaemic infiltrates may affect kidney s psychological mechanisms.

There are described many indirect effects of malignancies on the kidney and these may be summarised into:

1. Hypokalaemia and /or hyponatraemia from prolonged vomiting;
2. Hypercalcaemia from marrow infiltration, prolonged immobilization, or the secretion of PTH substances;
3. Hyponatraemia from inappropriate ADH secretion [1].
4. Therapy may also have an adverse effect on renal function by drug nephrotoxicity or/and adverse effects of radiation.

A number of glomerular, tubulo-interstitial and vascular renal diseases can be associated with solid or hematopoietic malignancy and may often represent the first clinical manifestation of an underlying cancer [2].

The term paraneoplastic syndrome refers to clinical manifestations that are not directly related to tumor burden, invasion, or metastasis but are caused by the secretion of tumor cell products, such as hormones, growth factors, cytokines, and tumor antigens. The concept of paraneoplastic glomerulopathy was introduced by Galloway in 1922. The relationship between malignancy and glomerular disease is better understood, allowing a more precise diagnostic approach and the description of new entities.

Authors	No. patients	Cancer (%)	GN	Type of cancer	Time of diagnosis
Birkeland	1958	102 (5.2)	MN, MCD, MPGN, diffuse endocapillary GN	Colon, lung, skin, lymphatic and hematopoietic tissue	<1 year from biopsy: 27. 1–4 years from biopsy: 53, >4 years from biopsy: 22
Zeng	390	12 (3.1)	MN	LCDD, thyroid, GI, mediastinal	ND
Lefaucher	240	24 (10.0)	MN	Lung, stomach, prostate	At the time of biopsy: 21, during follow-up (max 1 year): 3

Ehrenreich	167	3 (1.8)	MN	ND	ND
Bjorneklett	161	33 (20.5)	MN	Lung, colon-rectum, prostate	Nine cases before diagnosis of MN three cases <6 months after biopsy
Abe	137	2 (1.5)	MN	ND	ND
Rihova	129	8 (6.2)	MN	Lung, colon, prostate	Five at the time of biopsy
Pai	120	17 (14.1)	MN, MPGN, crescentic GN, FSGS	Bronchogenic, GI, breast	Six at the time of biopsy, four within 1 year
Cahen	82	4 (3.2)	MN	ND	ND

Table 1: Evidence of cancer-related glomerulopathies (MN membranous nephropathy, MCD minimal change disease, MPGN membrano-proliferative glomerulonephritis, LCDD light chain deposition disease, FSGS focal segmental glomerulosclerosis, GI gastrointestinal, ND not detected).

Malignancy -Associated Nephropathy

The prevalence of renal involvement in patients with cancer has been analyzed in autopsy and clinical series. The most common presentation of the malignancy-associated nephropathy is a nephrotic syndrome and in approximatively 40% of patients the nephrotic syndrome presents prior to the diagnosis of malignancy. The true incidence of glomerulopathy in malignancy is not known as many patients with malignant disease have minor urinary abnormalities [4]. Data from autopsy series are conflicting because of technical limits to postmortem study. Clinical studies have revealed haematuria and /or proteinuria in a significant number of patients with tumors and autopsy studies have revealed glomerular immune deposits in 17-30% of patients with malignancy although usually the glomerular histological changes are minor [4,5].

The prevalence of cancer in patients with glomerulopathy is in present controversial. The first study, published by Lee et al., found that 11% of patients with the nephrotic syndrome had carcinoma [6]. Analysis of the Danish Kidney Biopsy Registry, which included all biopsies performed in Denmark since 1985, showed that the risk for cancer at 1 year and 1–4 years after the diagnosis of glomerulopathy was increased by 2.4- and 3.5-fold, respectively, compared with risk in the general population [7]. It is difficult to establish a causal relationship between the malignancy and the glomerular changes and frequently a causal link can only be inferred. In some patients it is possible to detect tumor antigens with glomerular deposits.

A causal relationship, however, is suggested if nephrotic range proteinuria develops either 6 months before or after the diagnosis of a malignancy. The relationship between glomerular disease and cancer can at times be misleading because of potential detection bias (e.g., in the case of membranous nephropathy, in which patients are likely to be more aggressively screened for cancer); the demographic
characteristics of the population (e.g., membranous nephropathy and cancer tend to occur more often in the elderly); and the use of alkylating agents to treat glomerular disease, which can itself lead to subsequent malignancies.

An association between cancer and glomerular disease is possible and it is probably related to altered immune responses in the presence of a malignancy [8]. Studies on murine models documented that T-helper 2 polarization has an important role in the development of thymomaassociated glomerular lesions in MCD and FSGS and an overexpression of interleukin (IL)-13, a T-helper 2 cytokine, induces MCD in rats [9,10]. Furthermore, it is known that tumoral antigens can induce anti-tumour antibodies and consequently immune complex deposition in the glomeruli (sub-epithelial deposition in MN) [11,12]. However, the diagnosis of paraneoplastic glomerulopathy is problematic due to the possible biases listed above and to the difficulty in identifying the tumor when GN is diagnosed (delayed diagnosis of malignancy). The sequence of events in the patient's clinical history can help in differentiating a paraneoplastic glomerulopathy from malignancy caused by treatment of the GN. After cancer is diagnosed, a careful retrospective investigation of the radiological findings can also help in detecting small lesions that could have been misinterpreted. It is important to establish whether GN occurred in the presence of malignancy since ablation of cancer may result in remission of glomerular lesions.

Types of Malignancy

A wide variety of benign and malign tumors have been associated with nephropathy [3,13] [Table 1]. Adenocarcinomas of the lung and gastrointestinal tract (stomach, colon, rectum) are the most common tumors associated with nephropathy. There are two interesting remarks: the nephropathy associated with carcinoma of breast is rarely despite the high incidence of this tumor, and although there are only rare reports of benign tumors associated with a nephropathy, angiomyolipoma occurs in patients with tuberous sclerosis and there is frequently renal involvement.

Glomerular Pathology

The most common nephropathy identified is that of membranous glomerulonephritis. This occurs in approximately 70% of patients reported to have malignancy associated nephrotic syndrome. Although membranous nephropathy is the most frequent glomerulonephritis associated with solid tumours, and minimal change disease is the most frequent glomerular disease associated with Hodgkin lymphoma, many exceptions exist [14]. In fact, other forms of glomerular diseases, including focal segmental glomerulosclerosis, membrano-proliferative glomerulonephritis, IgA nephropathy and rapidly progressive glomerulonephritis may also be associated with solid tumours. On the other hand, not only minimal change disease, but also membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and Ig nephropathy may be associated with hematologic malignancies [8]. Thus, specific tumours are not necessarily associated with a specific type of GN. There is no association between the nature, site, and size of malignancy, and any particular glomerular appearance. It would appear that the glomerular response relates more to the immunological events than to the nature of the provoking tumour. But for how long should a

patient with glomerulopathy be screened for cancer? Even in the case of a paraneoplastic glomerulopathy, cancer may be clinically discovered years after the diagnosis of renal disease. Indeed, many tumours require years or even decades before exhibiting clinical symptoms. In the meantime, these hidden tumours may release antigens that trigger the production of antibodies leading to the formation of circulating immune complexes or renal deposits of antigens that react with antibodies resulting in local formation of immune complexes.Whatever the mechanism, the deposition of immune complexes may cause inflammation, release of reactive oxygen species and complement activation, possibly leading to glomerular damage. However, besides the few cases of late recognition of cancer in a paraneoplastic glomerulopathy, one should take into account that glucocorticoids, immunosuppressive agents, or biologic medications that are used to treat chronic GN strongly interfere with the immune response and can favour the development of malignancy or may themselves be carcinogenic [7]. In the absence of guidelines, we recommend that patients who have undergone or undergo long-term immunosuppression should receive complete screening for cancer every 5 years if aged <50–60 years, or every 3 years if they are older.

Conclusion

The association of malignant disease and nephrotic syndrome is well recognized and is immunologically mediated. Although the most common histological appearance is membranous nephropathy a wide variety of glomerular appearances are recognized. There is no association between the site, size, or type of malignancy and the associated glomerular disease.

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