Paraneoplastic glomerular diseases and malignancies

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Contents

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Abstract

Paraneoplastic glomerulopathies are rare manifestations of neoplastic disease to be distinguished from iatrogenic renal damage. Solid tumors are preferentially associated with membranous nephropathy, whereas Hodgkin's lymphomas are associated with minimal change disease. The most common neoplasia associated with paraneoplastic glomerular disease are carcinomas of the lung and of the gastrointestinal tract. Nephrotic syndrome is the most frequent presentation of paraneoplastic glomerulopathy and the most critical glomerular disease regarding prognosis and patient care.

Renal biopsy is recommended in patients with glomerular proteinuria or nephrotic syndrome and cancer, depending on life expectancy and therapeutic options. The primary treatment must be directed at the cancer in all cases. Symptomatic treatment of the nephrotic syndrome with diuretics and ACE inhibitors is justified. Prevention of nephrotic syndrome complications, i.e. thromboses and infections, should also be addressed and systematic regular renal follow-up is warranted. All treatments should be regularly reviewed to avoid toxicity, associated renal function loss or low albumin levels for patients receiving albumin-binding drugs.

Epidemiologic studies have low evidence-based value. There is no widely accepted experimental model of the association of glomerulopathy and cancer. Thus, epidemiologic and mechanistic studies are needed to determine the true prevalence of paraneoplastic glomerulopathies and investigate new pathophysiologic approaches.

1. Introduction

Paraneoplastic syndromes are manifestations of neoplastic disease. The term 'paraneoplastic syndrome' refers to clinical manifestations not directly related to tumor burden, invasion or metastasis, but caused by the secretion of tumor cell products (such as hormones, cytokines, growth factors and tumor antigens) [1]. Among paraneoplastic syndromes, the concept of paraneoplastic glomerulopathy was first suggested by Galloway in 1922, with the description of a nephrotic syndrome associated with Hodgkin's disease [2]. After Galloway, many authors have also reported cases of patients with both cancer and glomerular disease, but the causal link remains unclear.

'Glomerulopathy' is a general term for glomerular damage. A nephrotic syndrome is a massive urinary protein loss resulting in hypoalbuminemia and edema. It is one of the most common clinical presentations of glomerulopathy. Since the most frequent glomerular disease associated with solid tumors is membranous nephropathy, and since it is usually manifested by a nephrotic syndrome, we will particularly focus on these two issues [1,3–5].

The diagnosis of paraneoplastic syndrome may be suspected in the presence of the following criteria: (i) no obvious alternative etiology for the associated syndrome; (ii) existence of a time relationship between the diagnosis of the syndrome and cancer; (iii) clinical (and histological) remission after complete surgical removal of the tumor or full remission achieved by chemotherapy; (iv) recurrence of the tumor associated with an increase of associated symptoms [1,6].

Different glomerular diseases are associated with different neoplasms: whereas the nephrotic syndrome is generally due to membranous nephropathy (MN) in patients with solid tumors, cases of minimal change disease (MCD), IgA nephropathy (IgA-N), focal and segmental glomerulosclerosis (FSGS), mesangiocapillary glomerulonephritis, crescentic glomerulonephritis, amyloidosis and thrombotic microangiopathies have also been reported. The most common neoplasias associated with paraneoplastic glomerular disease are carcinomas of the lung and of the gastrointestinal tract [5]; MCD is strongly associated with Hodgkin's lymphoma [7].

The purpose of this review is to analyze the characteristics and occurrence of both the glomerular disease and cancer, and to identify their major interactions. The following description is the result of a systematic search of the Pubmed database using the following items: 'cancer AND glomerulopathy', 'cancer AND glomerular disease', 'cancer AND

membranous nephropathy', 'cancer AND minimal change disease', 'cancer AND IgA nephropathy', 'cancer AND focal segmental glomerulosclerosis', 'cancer AND mesangiocapillary glomerulonephritis', 'cancer AND crescentic glomerulonephritis', 'cancer AND amyloidosis', 'cancer AND thrombotic microangiopathy', 'cancer AND glomerular disease AND children' and 'cancer AND glomerular disease AND treatment'.

The value of the different studies was classified according to the French Evidence-Based Medicine Scores defined by the ANAES (National Agency for Habilitation and Evaluation In Public Health) in 2000 [8]: level 1 studies correspond to systematic reviews and randomized controlled trials; level 2 studies correspond to low-power randomized controlled trials, non-randomized controlled trials and cohort studies; level 3 studies correspond to case/control studies; and level 4 studies correspond to retrospective studies, case series, and descriptive epidemiological studies.

2. Interactions between cancer and glomerular disease

2.1. Cancer in the presence of glomerular disease

In 1966, a first study found that 11% of nephrotic syndromes in adults were associated with malignant tumors [9]. This prevalence depends on the age of the patients and the type of glomerular lesion: 69% of the patients who had both nephrotic syndrome and cancer had membranous nephropathy [4]. Three recent contributions to the epidemiology of cancer in the presence of glomerular disease can be highlighted. A French study of 240 patients with membranous nephropathy undergoing renal biopsy reported 10% of neoplasias [3]. The highest prevalence was observed in patients older than 60 years [10–12]. In a series of 155 patients suffering from membranous nephropathy, the prevalence of cancer was related to age: 10% of the patients over 60 had a malignancy, versus 1% in the group under 60 [11]. Moreover, the prevalence of malignancy is five times higher in patients with MN than in a reference population [13]; other studies have reported similar data [3,14].

Data of the Danish Kidney Biopsy Registry, which includes all kidney biopsies performed in Denmark since 1985, show an excessive incidence of cancer after the diagnosis of renal disease in patients with a biopsy-proven glomerulopathy compared to the general population [14]. Patients presenting malignancies before renal biopsy were excluded from the study. A total of 102 *de novo* cancers was found in 1958 patients, representing a two- to three-fold excess over the expected number at 1 year and 1–4 years after the biopsy. However, this result was not confirmed at 5 years and thereafter. Cancers were found in the colon in women, in the lung and skin in men and in lymphoid tissues in both genders. Malignancies were associated with extracapillary glomerulonephritis, membranous nephropathy and

mesangiocapillary glomerulonephritis in men, and with minimal change disease in women. Three hypotheses have been suggested to explain these data: (i) an undiagnosed cancer associated with antigen deposit may have caused glomerular disease; (ii) immunosuppressive therapies used in glomerular disease may have triggered tumor cells; (iii) viral infection may have induced both glomerulopathy and cancer by three potential mechanisms: intrinsic viral oncogenic activity, disrupted renal clearance of biological mediators associated with oncogenesis, or both [14].

In the Tromso study, Jorgensen et al. described an association between albuminuria and cancer in a prospective cohort of 5425 participants without history of diabetes, cancer or macroalbuminuria: after adjustment, participants with albumin-to-creatinine ratio (ACR) in the highest quintile were 8.3- and 2.4-fold more likely to develop bladder and lung cancers, respectively, than those with ACR in the lowest quintile [15].

The evidence-based value of these studies is generally low (level 4) except for the Danish Kidney Biopsy registry and the Tromso study (level 2).

2.2. Glomerular disease in the presence of cancer

The true incidence of glomerular disease associated with malignancy is not known; although many patients with malignant disease have urinary abnormalities, they are seldom referred for invasive nephrological investigation aimed at identifying the underlying renal lesion [5]. Furthermore, renal damage in a context of cancer can be explained by many etiologies other than paraneoplastic glomerulopathies [1]. We will review data from clinical and autopsy studies, then focus on smaller studies of patients with different types of cancers and on the temporal relationship between neoplasia and glomerular disease.

Two clinical studies have investigated the prevalence of proteinuria in cancer patients. The prevalence of proteinuria and hematuria in 600 patients with lung cancer was 10 and 7%, respectively [16]. This relatively high prevalence can be accounted for by the low threshold used for proteinuria (0.1 g/L). Another study comparing 504 patients with cancer (seven different sites) and 529 healthy controls [15], all presenting with normal serum creatinine values, found significantly more frequent proteinuria in patients with malignancy than in controls (58 versus 22%, $p < 0.001$). Patients with myeloma and urinary tract neoplasia had been excluded. Several control individuals were at high risk of proteinuria (stroke, heart attack, etc.), thus explaining the high prevalence of proteinuria in the control group. Again, the chosen threshold of proteinuria was low (0.1 g/L), possibly leading to an overestimation of the true incidence of nephropathy in cancer patients. The actuarial analysis showed a median survival of 4.5 months in patients with proteinuria compared to 10 months in those without proteinuria ($p < 0.001$) [17].

Data on glomerular damage at autopsy in patients dying from solid neoplasia are conflicting. There are technical lim-

Table 1
Immune glomerular deposits according to the site of neoplasia (autopsy study)

Site of carcinoma	Number of patients	Glomerular deposits/total (%)
Bronchogenic	31	9.7
Digestive	48	27
Urological/gynecological	25	12
Oral/pharyngeal	25	12
Total	129	17

its to *post-mortem* kidney study, with increased background fluorescence when kidneys are examined between 2 and 38 h following death [18]. A review of data on glomerular damage in patients with cancer showed that 17–30% of the patients who died from cancer had glomerular immune deposits at autopsy [5]. These results are controversial: an autopsy study of 129 patients who died from solid tumors and 55 controls was performed in 1985 [19]. Glomerular deposits were observed in 17% of cancer patients and in 5.4% of controls ($p < 0.05$). The presence of glomerular deposits according to the site of cancer is summarized in Table 1 [19]. Other studies have found a low prevalence of glomerular deposits in patients with solid tumors and a study conducted in a series of patients with bronchogenic carcinomas has shown that no glomerular deposit could be detected by immunofluorescence [20].

Classically, MCD is associated with Hodgkin's disease whereas MN is generally linked to solid tumors [9]. The malignancies most frequently associated with glomerular disease are lung and gastrointestinal tract adenocarcinomas [21]. Other tumors have been reported as single cases or small series. Paraneoplastic glomerular diseases are rarely linked to breast cancer, though it is one of the most frequent solid tumors in women [22], or to prostate carcinoma and ovarian and uterine tumors [21]. However, recent data have described the association of MN and prostate carcinoma [3]. Low-grade tumors, such as spinal cord tumors, pheochromocytoma, benign ovarian teratoma or carotid body tumors are also known to cause glomerular disease [23,24].

There is no association between the site, the type or size of the malignancy and the associated glomerulopathy [5].

A temporal relationship between glomerulopathy and cancer is suspected when glomerular proteinuria develops in the 6 months before or after the diagnosis of malignancy [1,21]. The nephrotic syndrome usually precedes tumor development by several months: in the study by Burstein et al., proteinuria was antedated or occurred at the same time as cancer in 80% of patients [25]. Nevertheless, an exception to this rule was reported in 2005 with a series of 21 cases of nephrotic syndrome associated with malignant thymoma [26]. Of these 21 cases, 47% had occurred 8–180 months after curative treatment of thymoma. Pathological examination revealed 14 MCD and only 4 MN. MCD responded to treatment with corticosteroids or other immunosuppressive drugs (cyclophosphamide, cyclosporine). Cell-mediated

immunity might be involved here, as demonstrated by the specific association of thymic cell proliferation and immunity dysregulation reported by Hoffacker et al. [27]. Dysregulation of immunity is commonly observed in patients with Hodgkin lymphoma, for whom minimal change disease is a common paraneoplastic syndrome [7,26].

In patients in complete clinical remission of both cancer and glomerulopathy, histologic remission is generally not proved. Complete double remissions are rarely reported in the literature, probably because carcinomas associated with nephropathy are often incurable at the moment of diagnosis [4,22,28,29]. Moreover, a renal biopsy is rarely performed in this context. When a remission is reported, a rapid improvement is generally observed [24]. Yet, not all the patients have renal improvement after treatment or remission of the tumor [30]. Renal relapse is often associated with recurrence of neoplasia [25], but the two conditions can evolve independently: tumor recurrence can occur in the absence of proteinuria [31] or secondary glomerulopathy may develop by itself [30,32]. In this case, the paraneoplastic nature of the glomerulopathy must be discussed, even if no other etiology for the nephrotic syndrome has been found.

In conclusion, none of these series attained a level of evidence 2 or 3; epidemiological studies were those with the lowest evidence-based value. Two studies of high evidence level (level 2) nevertheless suggested that the relative risk of finding a cancer is increased by at least twofold in case of nephrotic syndrome or albuminuria. Conversely, no studies could determine the real incidence of glomerular impairment in cancer, but they indicated a link between several particular glomerulopathies and specific cancers. The following paragraphs will describe different case reports that may help define the association between such diseases. However, it must be emphasized that these studies only have low evidence value (level 4).

3. Different types of glomerular diseases associated with cancer

All cases reported below cannot be considered as true paraneoplastic glomerulopathies since some determining criteria are sometimes missing.

3.1. Membranous nephropathy (MN)

3.1.1. Epidemiology, pathology and etiology

Membranous nephropathy is the most frequent form of nephrotic syndrome in adults [33] and the most frequent paraneoplastic glomerulopathy associated with solid tumors [1,5]. This chronic glomerular disease leading to chronic renal failure in 16% of patients [34] is characterized by a uniform thickening of the glomerular capillary wall due to diffuse subepithelial immune deposits in the absence of inflammatory or proliferative changes (Fig. 1). Males represent up to 70% of patients with MN [35]. There is a
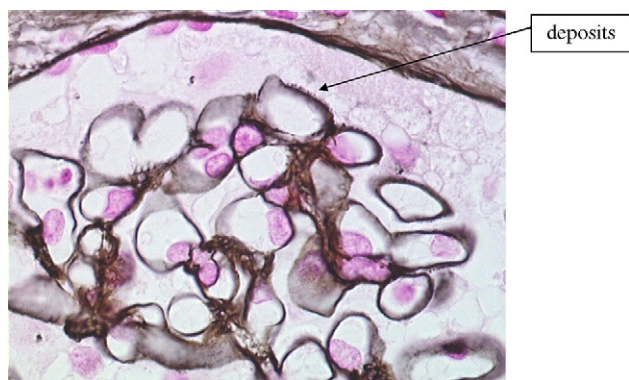
Fig. 1. Membranous nephropathy (reticulin). There are diffuse subepithelial deposits leading to a uniform thickening of the glomerular capillary wall.

peak age of onset in the fourth and fifth decades of life [36].

Two-thirds of cases are idiopathic. The most frequent etiologies of secondary MN are infections, autoimmune diseases and drug toxicity [3]. The frequency of these different etiologies varies with age and geographic location [37].

3.1.2. Membranous nephropathy and cancer

The prevalence of neoplasia in MN patients is summarized in Table 2 [3,10,12,25,32,36,38,39]. Three characteristics are associated with a higher risk of cancer in these patients: two clinical factors (age and smoking) and one pathologic feature (presence of more than eight inflammatory cells per glomerule) [3]. Evidence of renal failure at initial presentation seems to be more frequent in malignancy-associated MN [25]. Renal evolution (in conjunction with neoplastic evolution) has only been reported in seven patients with MN and cancer: two were in complete remission after treatment of the tumor, four had proteinuria in association with tumor recurrence or metastasis, and one evolved to end-stage renal disease [25].

Many solid tumors have been described to cause MN; general data are summarized in Table 3 [3,10,12,22,23,25,26,28–30,32,34,36,38–93]. Gastric and bronchus carcinoma are the most frequent neoplasia associated with membranous nephropathy; however, renal cell carcinoma, prostatic carcinoma and thymoma are a little more frequent than other tumors. To date, MN association

Table 2
Prevalence of secondary membranous glomerulonephritis and prevalence of neoplasia in membranous nephropathy

Author	Year	Number of patients	Neoplasia/total (%)
Row et al.	1975	66	11
Chavaz et al.	1977	92	8
Noel et al.	1979	140	1
Zech et al.	1982	30	22
Kingswood et al.	1984	24	12
Cahen et al.	1989	82	5
Burstein et al.	1993	107	8
LeFaucheur et al.	2006	240	10

Table 3
Membranous nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal carcinoma	10
Justaglomerular cell tumor	1
Gastro − intestinalcancers	
Esophagus carcinoma	2
Gastric carcinoma	15
Pancreatic or Vater ampulla carcinoma	3
Colorectal carcinoma	5
Liver cell adenoma	1
Hepatocellular carcinoma	1
Uro-genital cancer	
Breast cancer	5
Small cell carcinoma of the endometrium	1
Squamous cell carcinoma of the cervix uteri	1
Choriocarcinoma	1
Bladder carcinoma	2
Prostatic carcinoma	9
Melanoma	1
Brain tumor	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Bronchial carcinoid tumor	2
Small cell carcinoma	6
Lung and bronchus carcinoma	13
Mesothelioma	2
Laryngeal cancer	2
Thymoma	7
Other tumors	
Solid tumors without details	57
Squamous cell carcinoma of the mandible	1
Sarcoma	3
Carotid body tumor	1
Chordoma of sacro-coccygeal region	1
Spinal schwannoma	1
Testicular seminoma	1
Adenolymphoma of the parotid	1
Adrenal ganglioneuroma	1

with hematological malignancies has been described in only 23 cases [94].

3.1.3. Pathophysiology

The pathophysiology of idiopathic MN currently remains uncertain: the identification of human antigens has been unsuccessful to date. The model usually studied is rat Heymann nephritis: the nephritogenic target antigen, gp 330 or megalin, is a resident glycoprotein of coated pits in the glomerular and proximal tubule epithelium of rats. Intravenous injection of anti-gp 330 antibodies gives rise to immune deposits in glomeruli, inducing passive nephritis. However, in humans, megalin is only expressed on the proximal tubule and not on the podocyte [95].

The existence of a biological link as described between glomerular disease and lymphoplasmocytic disorders, such as monoclonal immunoglobulin deposit, remains unclear in solid tumors [1].

Several reports have demonstrated the presence of tumor antigens and/or specific antibodies in the glomeruli of patients with paraneoplastic glomerulopathies. Tumor antigens described were carcinoembryonic antigen [28,96–98], prostate specific antigen [99], melanoma antigens [100], and non-identified tumor antigens [30]. Several authors have reported a cross-reaction between eluates from glomeruli and tumor antigens [28,30], providing evidence for a role of the immune complex in paraneoplastic glomerulopathy.

Carcinomas generate different types of antigens responsible for the production of specific antibodies: tumor-associated antigens, re-expressed fetal antigens, viral antigens or non-tumor autologous antigens [21].

Three mechanisms can explain the presence of glomerular immune deposits in membranous nephropathy [37]: the antigen/antibody complex can be formed in blood with a secondary glomerular deposition or directly in glomerular tissue. In these cases, antigens are not glomerular components; however, antibodies can also be directed against native glomerular antigens.

An increased glomerular permeability to proteins, resulting in passive deposit of specific tumor antigens and corresponding antibodies, can also be hypothesized.

Indeed, immune glomerular deposits without proteinuria are frequent in patients with solid neoplasia [19]. Therefore, it is difficult to identify the primary factor of glomerular injury in the absence of animal models. Abnormal immune responses are also reported in patients with cancer, with exacerbation of allo and auto-immunity [101]. These patients may thus be predisposed to develop immune complex, and therefore glomerular injury.

3.2. Minimal change disease (MCD)

3.2.1. Epidemiology and pathology

In this type of glomerulopathy, heavy selective proteinuria contrasts with an absence of lesions on light microscopy (Fig. 2). However, MCD is associated with ultrastructural alterations of glomerular epithelial cells, such as epithelial cell foot process effacement confirmed by electron microscopy.

Patients usually present with nephrotic syndrome. MCD represents 10% of all idiopathic nephrotic syndromes in adults, with a male preponderance. Different etiologies have been described: idiopathic origin, infectious diseases, drugs, allergies and malignancies (especially Hodgkin's disease) [102].

3.2.2. Minimal change disease and cancer

Although usually associated with Hodgkin's lymphoma [7], MCD has also been described in patients with solid tumors, as summarized in Table 4 [9,26,70,103–140]. The cancers most frequently reported in association with MCD are renal cell carcinoma and thymoma. To date, at least 94 MCD have been described in association with hematological malignancies [94].
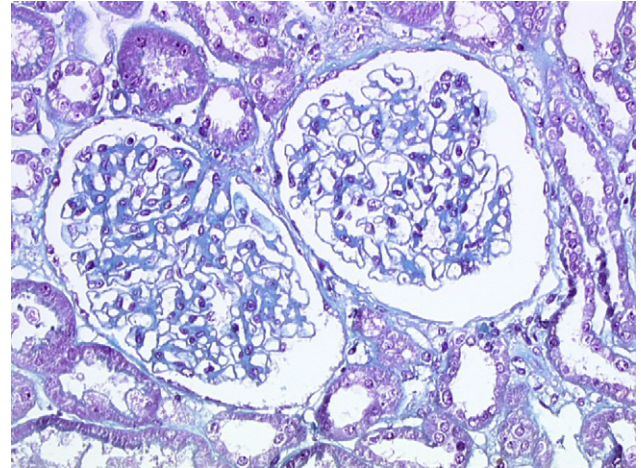
Fig. 2. Minimal change disease (Masson Trichrome): glomerules are normal on pathological examination.

3.2.3. Pathophysiology

Minimal change nephropathy may be induced by cytokines secreted by infiltrated lymphocytes and macrophages, which would increase glomerular permeability. The role of lymphoid tissues in the systemic and glomerular reaction induced by a solid tumor can thus be hypothesized. The general inflammation caused by the tumor evolves into granulomas, with cytokine production.

Moreover, immunologic disorders, involving macrophages and TH2 lymphocytes, are present in MCD [141].

Table 4
Minimal change disease and cancer

Type of cancer	Number of cases
Renal cancer	
Renal oncocytoma	1
Renal cell carcinoma	6
Gastro-intestinal cancers	
Esophagus carcinoma	1
Pancreatic carcinoma	2
Colorectal carcinoma	6
Uro-genital cancer	
Ovarian carcinoma	1
Breast cancer	2
Urothelial carcinoma	2
Bladder carcinoma	1
Melanoma	1
Respiratory tract cancer	
Anaplastic bronchus carcinoma	1
Small cell lung cancer	1
Lung and bronchus carcinoma	7
Mesothelioma	1
Thymoma	26
Other rare tumors	
Angiomyolipoma	1
Retroperitoneal sarcoma	1
Mediastinal Neurilemmoma	1
Vaginale testis mesothelioma	1
Undifferenciate carcinoma	1

The Buffalo/Mna rat (spontaneous thymoma, myasthenia and glomerulopathy, due to a dominant genetic abnormality) is known to have MCD-like glomerular damage and FSGS [26]. This animal model is characterized by an early onset of selective proteinuria and nephrotic syndrome, leading to MCD and secondary FSGS. The recurrence of proteinuria after transplantation in Buffalo/Mna rats and the remission of glomerular lesions in Buffalo/Mna kidneys transplanted into normal hosts suggest that these rats express circulating proteinuric factors [142]. Moreover, they present immune abnormalities (renal macrophage activation and TH2 polarization) in parallel with the initiation and the progression of the nephropathy [141]. However, two observations are in favor of an independency of nephrotic syndrome and thymoma in these rats: first, two autosomic dominant genes have been found to determine susceptibility to glomerular sclerotic lesions in the involved chromosome region; second, some studies suggest that thymectomy does not modify the incidence of nephropathy [141]. Therefore the link between thymoma, myasthenia and nephropathy has yet to be clarified.

Mechanisms of proteinuria in MCD still remain incompletely understood: an electrochemical disorder of the glomerular basal membrane (loss of glomerular negative charges) has historically been the first hypothesis to explain the contrast between normal glomeruli on light microscopy and massive proteinuria [143,144]. Recent data have shown the essential role of the slit diaphragm and its proteins in human glomerular diseases [145]. Both cellular and humoral immune responses are altered in idiopathic MCD [146,147]. Cytokines (e.g., Il2, Il4, and Il13) and growth factors (especially VEGF, Vascular Endothelial Growth Factor) also seem to play an important role by increasing the permeability of the glomerular basal membrane to proteins [102,134]. In 2004, Taniguchi et al. described a patient with rectal adenocarcinoma associated with MCD and elevation of VEGF [134]. After tumor resection and no other treatment for nephrotic syndrome than albumin infusions, proteinuria disappeared and VEGF decreased to normal levels. Immunohistochemistry revealed a strong expression of VEGF in the tumor cells. In 2001, high levels of circulating VEGF in association with proteinuria were reported in children with both steroid-responsive and steroid-resistant primary nephrotic syndromes [148]. From these data, Taniguchi et al. hypothesized that the glomerular disease was a consequence of the overexpression of VEGF induced by the cancer. Moreover, they proposed to measure VEFG levels in case of cancer associated with glomerulopathy and to administrate vascular growth factor antagonists to patients with unresectable tumors and high VEGF levels [134]. However, recent data have highlighted the complex biology of VEGF and very cautious conclusions should be drawn: podocyte-specific overexpression of VEGF results in podocyte proliferation and collapsing glomerulopathy whereas intermediate VEGF levels (50% of normal) lead to proteinuria [149], as emphasized by the observation of a proteinuria in 64% of cancer patients treated with high-dose VEGF-antibody [150]. More-
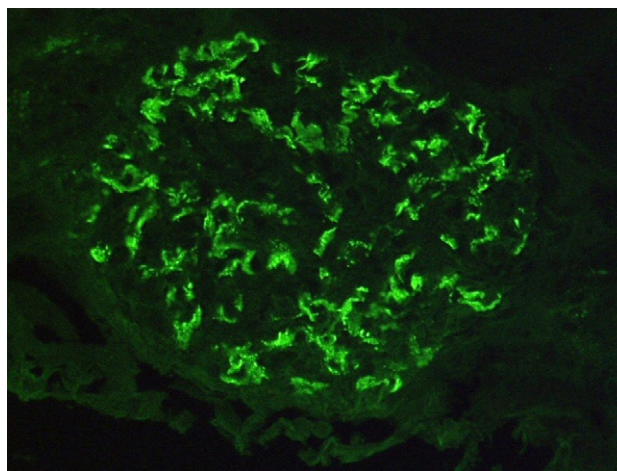

Fig. 3. IgA nephropathy (immunofluorescence): diffuse mesangial IgA deposits.

over, functional VEGF polymorphisms are known to be associated with the development of end-stage renal disease in males [151].

3.3. Ig A nephropathy (IgA-N)

3.3.1. Pathology and etiologies

This glomerular disease is characterized by the presence of diffuse IgA deposits in the mesangium. Light microscopy also reveals increased extracellular matrix and hypercellularity in the mesangium (Fig. 3).

The primitive and most frequent form of the disease ('Berger's disease') is limited to the kidney. It is characterized by recurrent gross hematuria during upper respiratory tract infections, isolated persistent microscopic hematuria and/or proteinuria [152]. IgA-N can rarely be revealed by a nephrotic syndrome, an acute renal failure and/or arterial hypertension. Primary IgA-N is usually considered as a slowly progressive glomerulopathy: up to 80% of patients have normal renal function after 2–5 years of follow-up [153]. Chronic kidney disease is present in 50–70% of patients after 20 years of follow-up, whereas end-stage renal disease is present in 20–50% [154]. However, global outcome varies with the severity of histological lesions. Some variables are known to be associated with poor prognosis: male gender, Afro-American race, hypertension, older age at presentation, elevated baseline serum creatinine, presence of crescents or sclerosis on biopsy and heavy proteinuria [155–157].

IgA-N is also associated with a particular type of vasculitis (Henoch Schönlein purpura) and can also be secondary to other diseases affecting the liver (cirrhosis, especially alcohol-induced), the mucosa (inflammatory bowel disease, celiac disease, cystic fibrosis), the immune system (e.g., rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, etc.), as well as infectious diseases, iatrogenic etiologies (mitomycin), and malignancies [154,158].

Table 5
IgA nephropathy and cancer

Type of cancer	Number of cases
Renal cancer	
Renal oncocytoma	1
Renal cell carcinoma	15
Gastro-intestinal cancers	
Esophagus carcinoma	1
Respiratory tract cancer	
Small cell lung cancer	1
Lung and bronchus carcinoma	1
Solid neoplasias, without details	6

3.3.2. IgA-nephropathy and cancer

In 1984, Mustonen et al. studied the frequency of neoplasia among 184 patients with IgA-N; 23% of the patients over 60 years had cancer versus none of the 158 patients under the age of 60 [159]. This incidence seems to be higher than in the general population where it is estimated to be about 1% [152]. Mainly associations with cancer of the respiratory tract, the buccal cavity and the nasopharynx are described. Mesangial IgA deposits have been found at autopsy in patients dead of a gastro-intestinal neoplasia without prior clinical evidence of nephropathy [19]. Moreover, it has been hypothesized that invasion of the intestinal mucosa by malignancy leads to increased circulating IgA level and therefore to formation of mesangial deposits [159]. IgA-N may also be caused by alcohol consumption, which is frequent in these patients: IgA produced by intestinal plasma cells interact with food antigens that cross the intestinal mucosa damaged by alcohol, leading to the formation of immune complexes [160,161]. Circulating immune complexes (IgA1 and IgA2) have actually been detected in the blood of cirrhotic patients [162].

Data about IgA nephropathy and cancer are summarized in Table 5 [159,163–171].

A strong association between renal cell carcinoma and IgA-N has been reported. A study of 60 kidneys after surgery for renal cell carcinoma revealed 18% of IgA-N, which is unexpectedly high for this type of glomerulopathy (Table 6) [170] and unlikely to be fortuitous. When excluding secondary and aspecific etiologies of glomerulopathies (diabetes, nephrosclerosis, focal and segmental glomerulosclerosis), IgA-N remains the only primary glomerular disease associated with renal cell carcinoma. Usual etiologies of IgA-N were not found in this group. Postoperative

Table 6
Renal cell carcinoma and underlying glomerulopathies [167]

Type of glomerulopathy	Number of cases (%)	Percentage
No nephropathy	21	35
Tubulo-interstitial nephritis	16	27
IgA nephropathy	11	18
Focal-segmental glomerulosclerosis	5	8
Nephrosclerosis	4	7
Diabetic nephropathy	3	5
Total	60	100

regression of proteinuria and hematuria was observed in 6 of the 11 patients with IgA-N, within 2–3 months after surgery [170]. No MCD was reported, which seems to be in contradiction with the strong association between MCD and renal cell carcinoma presented in Table 4. However, the term 'no nephropathy' may well include minimal change disease since only light microscopy observations were performed in this study.

3.3.3. Pathophysiology

The pathophysiology of IgA-N remains unclear. There is a strong association between IgA-N and HLA-DR4 [157]. At least four abnormalities in the immune regulation of IgA have been described in patients with primary IgA nephropathy: (i) increased serum IgA level in more than 50% of patients, (ii) increased level of activated T helper cells and IgA-bearing B lymphocytes, (iii) overexpression of TGFß and Il4 in CD4 cells, and (iv) IgA deposits in the mesangium. Moreover, IgA1 glycoproteins involved in IgA-N have structural alterations: they are polymeric, undergalactosylated and undersialylated. Renal deposition of circulating IgA immune complexes may play an essential role in the pathophysiology of the disease and recurrence is frequent after renal transplantation [152,172].

3.3.4. Paraneoplastic Henock Schölein purpura

The association of IgA-N and necrotic skin lesions and/or arthritis is indicative of a paraneoplastic Henoch Schönlein purpura (HSP). To date, at least 20 cases of HSP in association with malignancies have been reported [173,174]. Risk factors for cancer in HSP patients seem to be male gender, older age and clinical presentation (joint involvement without prior infection) [173]. A recent retrospective comparison of 129 patients with HSP and age-matched healthy controls has demonstrated a significantly increased relative risk (5.25) of malignancy in the HSP group [175]. A case of iatrogenic HSP after intravesical administration of bacillus Calmette Guerin has been described [176].

3.4. Focal segmental glomerulosclerosis (FSGS)

3.4.1. Pathology, pathophysiology and etiologies

FSGS is characterized by focal (only some glomeruli are affected) and segmental (only a segment of the glomerulus is affected) lesions of the glomeruli in the deeper cortex, with areas of glomerular sclerosis and tuft collapse. Tubular atrophy and interstitial fibrosis are common [177]. MCD and FSGS have long been considered as two forms of the same disease. Transition forms between the two entities have been described. However, recent data seem to demonstrate that they represent different entities [178]. FSGS is secondary to podocyte dysregulation, leading to podocyte lesions and usually irreversible secondary fibrosis [179].

This glomerulopathy represents 20% of all nephrotic syndromes in adults. Clinical hallmarks include proteinuria, nephrotic syndrome, arterial hypertension and progressive

Table 7
Focal-segmental glomerulosclerosis and cancer

Type of cancer	Number of cases
Renal cancer	
Renal oncocytoma	1
Renal cell carcinoma	5
Gastro-intestinal cancers	
Esophagus carcinoma	1
Cystic duct carcinoma	1
Uro-genital cancer	
Breast cancer	1
Melanoma	1
Respiratory tract cancer	
Lung and bronchus carcinoma	1
Mesothelioma	1
Thymoma	4
Rare tumors	
Pheochromocytoma	1
Hydaditiform mole	1
Sarcoma	1

Table 8
Mesangiocapillary glomerulonephritis and cancer

Type of cancer	Number of cases
Renal cancer	
Wilms tumor	1
Renal cell carcinoma	3
Gastro-intestinal cancers	
Gastric carcinoma	2
Uro-genital cancer	
Ovarian germinal tumor	1
Breast cancer	2
Prostatic carcinoma	1
Bladder carcinoma	1
Melanoma	3
Respiratory tract cancer	
Small cell lung cancer	1
Lung and bronchus carcinoma	4
Pulmonary carcinoid tumor	2
Thymoma	1
Other tumors	
Hydaditiform mole	1
Carcinomas without details	4
Benign tumor	1
Abdominal desmoplastic round cell tumor	1

loss of renal function [177]. FSGS represents an important cause of end-stage renal disease, accounting for up to 20% of dialysis needs [177]. Again, a male preponderance has been described. The amount of daily proteinuria is the best predictor of outcome, with high levels being associated with rapid evolution to end-stage renal disease [102]. The estimated rate of recurrence of FSGS after renal transplantation is about 30–40% [177]. This glomerular disease represents the common final pathway for a wide variety of kidney diseases [177]. Many etiologies can be found, such as idiopathic lesions, congenital nephropathies and vesicoureteral reflux, infectious diseases (especially HIV infection), diabetes and obesity, sickle-cell disease, drugs and malignancies [177].

3.4.2. Focal and segmental glomerulosclerosis and cancer

Data about cancer and FSGS are summarized in Table 7 [126,180–188]. To date, at least 15 cases of FSGS in association with hematological malignancies have been described [94]. Glomerular toxicity of pamidronate in patients with cancer has also been described, mainly FSGS [189].

3.5. Mesangiocapillary glomerulonephritis (MCG)

3.5.1. Pathology and pathophysiology

Also called membrano-proliferative glomerulonephritis, this progressive chronic glomerulonephritis is characterized by mesangial proliferation and thickening of the capillary wall partly due to subendothelial extension of the mesangium. Cellular increase is caused by mesangial cells and also infiltrating leucocytes. Three sub-types have been described: types I and III are variants of immune complex-mediated disease whereas type II has no known association with the immune complex but is likely associated with a dysregulation of complement pathways [190].

3.5.2. Mesangiocapillary glomerulonephritis and cancer

This glomerulopathy is more typical of lymphoproliferative disorders [191], but a few cases of solid neoplasia and membranoproliferative glomerulonephritis have been described. Data about MCG and cancer are summarized in Table 8 [4,9,40,92,98,100,192–206]. To date, 34 cases of MCG associated with hematological malignancies have been described [94]. Interestingly, one of these cases reported the association of both membrano-proliferative glomerulonephritis and intra-glomerular metastasis in a 88-year-old man with lung cancer and nephrotic syndrome [195].

3.6. Crescentic (or rapidly progressive) glomerulonephritis

3.6.1. Pathology and pathophysiology

Rapidly progressive is the term used to describe the clinical course of several forms of glomerulonephritis; their common characteristic is the presence of crescents [207]. The stimulus for crescent formation is the accumulation of fibrin in Bowman space, as a result of necrosis or disruption of the glomerular capillary wall with or without immune deposits. Three types of crescentic glomerulonephritis have been described: glomerulonephritis associated with glomerular basement membrane antibodies (type I), glomerulonephritis and granular immunoglobulin deposits (type II), and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis without deposits (type III) [207].

3.6.2. Crescentic glomerulonephritis and cancer

Whitworth et al. [208] and Biava et al. [209] have reported respectively four and six cases of malignancies in two series

Table 9
Crescentic glomerulonephritis and cancer

Type of cancer	Number of cases
Renal cell carcinoma	10
Gastro-intestinal cancers	
Esophagus carcinoma	1
Gastric cancer	5
Liver carcinoma	1
Colorectal carcinoma	1
Uro-genital cancer	
Ovarian/Fallopian tube carcinoma	1
Breast cancer	3
Prostatic carcinoma	3
Bladder carcinoma	1
Skin squamous cell carcinoma	1
Respiratory tract cancer	
Larynx and pharynx carcinoma	2
Small cell lung cancer	1
Lung and bronchus carcinoma	3
Thymoma	3
Thyroid neoplasia	1
Kaposi sarcoma	1
Solid tumors, without details	10

15 ANCA positive. 1 anti-GBM positive.

of 60 and 80 patients diagnosed with crescentic glomerulonephritis. All the neoplasias occurred in patients older than 40 years, with a prevalence of malignancy of 20% in this group [209]. Data about crescentic glomerulonephritis and cancer are summarized in Table 9 [26,99,175,196,208–232].

ANCA-mediated glomerulonephritis, which is usually associated with primitive vasculitis, has also been described in at least 11 solid tumors [215,217,220,224, 225,228,233,234]. A recent retrospective review of 200 patients with ANCA-associated vasculitis has demonstrated a significantly increased relative risk (6.02) of malignancy when compared to age-matched controls [175]. Interestingly, a retrospective comparison of 477 patients with Wegener's granulomatosis and 479 patients with rheumatoïd arthritis has shown a similar incidence of associated cancer in the two groups. However, seven renal cell carcinomas were reported in the granulomatosis group versus only one in the other group, leading to an odd-ratio for developing renal cell carcinoma of 8.73 (95% confidence interval: 1.04–73.69). The link between high renal cancer incidence and ANCA-producing Wegener's granulomatosis remains unclear [235].

3.7. Amyloidosis

Amyloidosis has been essentially described in patients with Hodgkin's lymphoma and myeloma. A strong association between renal cell carcinoma and amyloidosis is suspected [236]. A review has concluded that 24–33% of all tumor-associated amyloidoses were associated with renal cell carcinomas [5,237]. The tumor may secrete either a precursor of amyloid proteins (that could therefore precipitate in glomeruli) or an enzyme involved in the pathophysiology of amyloidosis [21].

3.8. Cancer-associated thrombotic microangiopathy (TMA)

This is a multisystemic disorder leading to thrombocytopenia, hemolytic anemia and ischemic manifestations (due to platelet agglutination), with possible damage to the central nervous system and the kidney. The pathophysiology of the disease shows an increased representation of ultra-large von Willebrand factor (vWF) forms. TMA can be secondary to a deficit (either congenital or acquired) in vWF metalloprotease (also called ADAMTS 13), or a dysregulation of complement pathways [238]. TMA syndromes in cancer can be due to the status of the tumor itself or to iatrogenic etiology (mitomycin C, gemcitabin) [239]. In cancer, the pathophysiology of TMA remains unclear: both damaged endothelium and the presence of a protease-inhibitor could contribute to the disease [240]. Most cancer-associated TMA have been reported in patients with mucin-producing carcinomas (particularly gastric, lung and breast cancers) [239,240]. Cases seem to be more frequent when the malignancy is widely disseminated [241] or, on the contrary, when there is an isolated invasion of the bone marrow [242].

3.9. The physiopathological hypothesis in paraneoplastic glomerulopathies

Physiopathological mechanisms of glomerulopathies have been described but few are applicable to paraneoplastic glomerulopathies. Only one animal model (Buffalo/Mna rat) is currently available, but the existence of a real link between nephropathy and thymoma in this spontaneous animal model is also debatable.

Various pathways could explain the occurrence of paraneoplastic glomerulopathies: the immunological pathway (and especially a dysregulation of T cell immunology), the vascular pathway (including vascular proliferation and impaired glomerular permeability due to VEGF and VEGF-receptor dysregulation, possibly also involving other cytokines), the antibody pathway (with the presence of antibodies directed against specific glomerular antigens), and the deposits pathway (with the presence of deposits of cancer-related antigens in the glomeruli). In the absence of experimental models, it seems unlikely that the pathophysiology of paraneoplastic glomerulopathies can be clearly demonstrated.

4. Paraneoplastic glomerulopathies in children

Association of malignancy with nephrotic syndrome is rare in children. Of 66 children with nephrotic syndrome studied in 1975, seven had a neoplasia [32]. As far as we know, only six cases of membranous nephropathy associated with a solid malignant tumor have been reported in the literature. These data are summarized in Table 10 [6,24,32,243,244]. A membranoproliferative glomerulonephritis has been described in association with

Table 10
Membranous nephropathy and cancer in children

Author	Date	Age (years)	Gender	Localisation
Row	1975	3	Girl	Wilms
Zheng	1979	4	Boy	Neuroblastoma
Papper	1984	4	Boy	Neuroblastoma
Beauvais	1989	7	Girl	Benign ovarian tumor
Lopez	1989	4	Boy	Wilms
Tourneur	2000	7	Girl	Orbital rhabdomyosarcoma

a desmoplatic round cell tumor in a 11-year-old girl [205].

In children, an original association of glomerulopathy (congenital nephrotic syndrome revealing diffuse mesangial sclerosis), pseudohermaphroditism and nephroblastoma, termed the Denys-Drash syndrome, has been described [245]. This syndrome is due to a mutation in the WT1 gene. This gene is also implicated in nephroblastoma and in Frasier syndrome (FSGS, progressive glomerulopathy, male pseudohermaphroditism and gonadoblastoma) [246]. These syndromes do not represent paraneoplastic syndromes but it is noteworthy that both Wilms' tumor and glomerulopathy are induced by the same genetic abnormality.

5. Paraneoplastic glomerulopathies and oncology practice

5.1. Definitions

Paraneoplastic renal lesions are mainly glomerular. Other renal lesions consist in tubulo-interstitial damage and/or vascular lesions. Predominant glomerular lesions may be suspected in the presence of proteinuria (especially over 1 g/day) or nephrotic syndrome, microscopic or painless gross hematuria without blood clots, arterial hypertension, and/or decreased glomerular filtration rate and progressive renal disease [247].

A nephrotic syndrome is defined by biological criteria: proteinuria greater than 3 g/day, hypoprotidemia (less than 60 g/l) and hypoalbuminemia (less than 25 g/l), leading to edema [247]. Nephrotic syndrome can be associated with other abnormalities such as hypogammaglobulinemia, thrombocytosis, hypovolemia, modifications of coagulation factors (increase of pro-thrombotic factors and decrease of anti-thrombotic factors) and hyperlipidemia, and with complications such as acute renal failure, denutrition, infections and thromboembolism [247].

There are multiple etiologies for glomerular diseases, depending on the type of glomerulopathy. In developed countries, the most frequent etiologies are diabetes mellitus and macro- and micro-vascular diseases. However, systemic lupus erythematosus, primitive IgA nephropathy, hemolytic and uremic syndrome, infectious diseases, iatrogenic etiologies, cryoglobulinemia, or systemic vasculitis may also be evoked, in addition to paraneoplastic etiology.

5.2. Histological diagnosis of glomerulopathies

Although clinical and biological data may provide some orientations, histological diagnosis, performed by percutaneous renal biopsy, is mandatory to formally establish the diagnosis of the glomerulopathy. Furthermore, it can determine the prognosis of the patient (for example, the presence of crescents is a sign of poor prognosis) and help the therapeutic decision. However, the interest of systematic renal biopsy in this context may be discussed since the underlying glomerulopathy is MN in 60–80% of patients [248].

5.3. Treatment of a glomerulopathy

Treatment depends on the etiology: corticosteroids are the standard first-line treatment in this setting. However, non-steroid immunosuppressive therapies (e.g., cyclophosphamide, azathioprin, cyclosporine or rituximab) and/or plasmapheresis can be used in case of corticosteroid treatment failure or in certain etiologies.

Non-specific supportive treatments, such as dietary support and prevention of cardio-vascular risks, are widely used for nephroprotection. Reduction of blood pressure in case of arterial hypertension and decrease of proteinuria are the two main objectives of this global management approach. Proteinuria can be reduced by different treatments acting principally on two levels: preglomerular vasoconstriction (with protein restriction, non-steroidal anti-inflammatory drugs and cyclosporine A) and postglomerular vasodilatation (with ACE inhibitors and AT1 receptor antagonists) [247].

Symptomatic treatments can also be used in nephrotic syndromes, as described below.

5.3.1. Edema
When edema is extensive, sodium and water restriction may be necessary, depending on the tolerance and the clinical response. Diuretics like furosemide are often used. They must be used with caution, especially in patients with functional hypovolemia. Intravenous albumin administration should be restricted to patients with severe clinical hypovolemia or functional renal failure [247].

5.3.2. Infections
Infections are classical complications of nephrotic syndromes. The main microorganisms involved are *Streptococcus pneumoniae, Haemophilus* and Gram-negative bacteria [247]. In developing countries, other causes can also be involved, especially tuberculosis [249]. Inducing the remission of massive proteinuria remains the first prophylaxis of infections. In adults, prophylactic antibiotherapy is not used. However, when a clinical infection occurs, parenteral and rapid antibiotherapy should always be performed [247].

5.3.3. Thromboembolism

Thromboembolism, in both the arterial and venous circulations, is the second classical complication of nephrotic syndromes [250]. It occurs in about 10% of adult patients, with subclinical incidence in 50% of cases [247]. Malignancy is another etiology of thrombophilia [251]. Membranous glomerulopathy is particularly associated with renal vein thrombosis, which must be evoked in a patient with nephrotic syndrome, lumbar pain, gross hematuria, renal enlargement and renal failure. Treatment of symptomatic thrombosis uses warfarin, with a goal of achieving an international normalized ratio between 2 and 4 [250]. In the general population with venous thrombosis, the treatment should last a minimum of 3 months, but in patients with nephrotic syndrome, it is probably reasonable to continue warfarin until serum albumin is greater than 25 g/l [247]. The interest of prophylactic anticoagulation in patients with nephrotic syndrome remains unclear; randomized trials are warranted. No consensus exists on the prophylactic treatment to be used: either warfarin, subcutaneous low molecular weight heparin or low-dose aspirin [250]. Patients should of course be mobilized; sepsis and dehydration should also be avoided [247].

5.3.4. Other complications of nephrotic syndrome

The other possible complications are lipid abnormalities (that occur in 90% of patients with proteinuria greater than 3 g/day), protein wasting, alteration in carbohydrate metabolism and urinary losses of transport proteins. The treatment of hyperlipidemia associates dietary measures and statins [247]. Protein restriction is usually advised [252] but must be used with care in patients with malignancies for whom denutrition is an important complication.

In conclusion, diuretics, corticosteroids and ACE inhibitors are frequently used for the first-line treatment of nephrotic syndromes.

5.4. Treatment of both cancer and paraneoplastic glomerulopathy

In a patient with glomerular proteinuria or nephrotic syndrome and cancer, a renal biopsy can be considered, depending on life expectancy. The therapeutic schedule should vary with the etiology of the renal disease. The management of patients with cancer and paraneoplastic nephrotic syndrome should focus on the following elements [5]:

- the extension of neoplasia should be rapidly assessed to determine whether complete tumor removal is feasible. The primary treatment should be directed at the cancer in all cases [248].
- Symptomatic treatment of the nephrotic syndrome by diuretics is justified. In the majority of patients the use of furosemide with sodium and water restriction is sufficient. To our knowledge, no studies of corticosteroid therapy in paraneoplastic glomerulopathies have been reported in the literature, even if this schedule is often used for the treatment of nephrotic syndrome. Immunosuppression should be avoided in MN because it may exacerbate the malignancy [248].
- Prevention of nephrotic syndrome complications should also be performed.
- Systematic renal follow-up and urinary testing are mandatory (serum creatinine, albuminemia, 24 h-proteinuria).
- All treatments should be regularly reviewed to avoid toxicity in the case of associated renal function loss. Drugs binding to albumin may be used with care.

5.5. Prognosis of paraneoplastic glomerulopathy

In patients with malignancies, proteinuria seems to be a factor of poor prognosis, as described above [17]. A 75% mortality 12 months after the diagnosis of MN and 3 months after the diagnosis of cancer has been reported [4]. This poor prognosis justifies the adoption of a multidisciplinary approach with nephrologists and oncologists. A reasonable therapeutic schedule tailored to the patient's prognosis may be proposed.

6. Other renal complications of cancer

Paraneoplastic glomerulopathy is a rare type of renal complication of neoplasia. Other renal complications of cancer have been described: either mechanical complications (ureteral compression, vascular compression or invasion, obstructive uropathy by retroperitoneal fibrosis, infiltration of renal parenchyma), or iatrogenic complications (electrolyte disorders, acute renal failure, tumor lysis syndrome, radiation nephropathy, chemotherapy complications with drug-induced tubulointerstitial disease, thrombotic microangiopathy, lithiasis and FSGS secondary to bisphophonate exposure) and renal vein thrombosis [1,239]. Metastases of a solid tumor to the kidney associated with renal failure and proteinuria remain uncommon, despite high renal blood flow. When metastases are present, they are usually bilateral and multiple [21].

7. Conclusion

The link between malignancies and nephrotic glomerulopathies is difficult to prove; however, it is suggested by clinical features such as close temporal relationship and parallel evolution (improvement, resolution, relapse) [5].

Table 11 summarizes all the results of different types of glomerulopathies and different main neoplasia. As described by other authors, gastro-intestinal and respiratory tract neoplasia are frequent etiologies of paraneoplastic glomerulopathies; however thymoma and renal cell carcinoma are two specific tumors often described in association with glomerular disease.

Two medical approaches are possible for the treatment of paraneoplastic glomerulopathies: the nephrologic one and

Table 11
Summary

	Membranous nephropathy	Minimal change disease	IgA nephropathy	Focal and segmental glomerulosclerosis	Mesangiocapillary glomerulonephritis	Crescentic glomerulonephritis	Total
Thymoma	7	26		4	1	3	41
Gastrointestinal neoplasia							47
Stomach and esophagus	17	1	1	1	2	6	28
Pancreas, cystic duct and Vater ampulla	3	2		1			6
Colorectal	5	6				1	11
Liver	1					1	2
Urogenital cancer							
Renal cell carcinoma	10	6	15	5	3	10	49
Prostate	9				1	3	13
Bladder, urothelium	2	3			1	1	7
Breast	5	2		1	2	3	13
Ovarian and fallope		1			1	1	3
Respiratory tract cancer							45
Pharynx-larynx	2					2	4
Small cell carcinoma	6	1	1		1	1	10
Lung and bronchus carcinoma	14	8	1	1	4	3	31
Mesothelioma	2	2		1			5
Melanoma	1	1		1	3		6
Sarcoma	3	1		1		1	6
Brain tumor	1						1

the oncologic one. In nephrology, the main problem will be to determine how thorough the search for neoplasia should be in a patient with unexplained nephrotic syndrome, depending on the general context and on the patient's own risk factors. Patients should be followed-up carefully after the diagnosis of an 'idiopathic' nephrotic syndrome [248]. In oncology, the main goal is to provide the patient with the best global treatment, with adapted cancer-specific therapies and supportive care. It is recommended to screen for proteinuria at diagnosis and during the course of the disease.

Nevertheless, it is very difficult to determine the real incidence and prevalence of paraneoplastic glomerulopathies. To our knowledge, no specific animal model, except the Buffalo/Mna rat, can be used to investigate new pathophysiological mechanisms of paraneoplastic and possibly idiopathic glomerulopathies. This absence of animal models also represents a strong limitation to demonstrating the mechanistic link between neoplasia and glomerulonephritis.

Reviewers

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Conflicts of interests

None.

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