

Nephrotic Syndrome Can Be a Marker for Prostatic Carcinoma

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Abstract

Paraneoplastic syndromes (PS) represent a large spectrum of symptoms, associated with malignant diseases. PS can be diagnosed in asymptomatic patients with occult carcinoma, clinically active cancer, and during clinical remission, suggesting a recurrence of the neoplasm. The underlying mechanisms of PS are not completely understood but several authors have suggested that the increased production of biologically active immune factors and cytokines from the neoplastic cells may underlie the etiology of PS. Although rare, the renal involvement of patients with prostatic carcinoma has been reported. The most common paraneoplastic-associated glomerulopathy in prostatic cancer is the membranoproliferative glomerulonephritis with nephrotic syndrome (NS). In this review, we aimed to discuss the incidence of nephrotic syndrome secondary to prostatic carcinoma, its challenging diagnosis, clinical manifestation, and treatment.

Keywords

Paraneoplastic Syndromes, Prostatic Carcinoma, Malignancy-Associated Glomerulonephritis, Nephrotic Syndrome, (Bio)Marker

1. Introduction

Paraneoplastic syndromes (PS) are associated with the presence of occult or active underlying malignancy. According to literature data, PS affect up to 8% of patients with cancer [1]. The development of PS is mediated by an intricate interaction between tumor antigens, hormones and cytokines, secreted by the neoplastic cells [2]. Since PS mirror an occult or clinically inactive malignancy, its prompt recognition will ultimately lead to early diagnosis of a cancer in its curable stage [3]. The term paraneoplastic syndrome was proposed in the 1940s

and currently is used to define specific “disorders caused by cancer, but not a direct result of cancer invasion of the affected organ or tissue” [1] [4]. Usually, the diagnosis of PS is made in the middle-aged and older patients [2]. Importantly, persons with family history for cancer, presenting with nonspecific symptoms and syndromes, must undergo cancer specific screening. Nonspecific syndromes may precede the clinical manifestations of the tumor, which representing poor prognostic factor [3]. Most frequent neoplasms, which are associated with PS are the pulmonary small cell carcinoma, breast, ovaries and lymphomas. PS encompass wide range of various symptoms and syndromes, also including damage in kidney functions [5]. Interestingly, although prostatic carcinoma is the most common malignancy in men, kidney are rarely involved in malignant process and to the best of our knowledge, only five cases have been reported thus far as one of the first disease manifestation [6]. However, the precise discrimination of secondary from the idiopathic nephrotic syndrome is crucial due to underlying malignancy. Although the underlying mechanisms of PS are not completely understood, it is thought that they are immunologically driven. The intricate interplay of tumor antigens and antitumor antibodies, expression of fetal antigens, host-antibody response, and the circulating tumor-antigen-antibody complex, underlie the development of PS [3] [5]. Furthermore, in the secondary nephrotic syndrome the immune complexes lead to alteration of the glomerular basal membrane, leading to proteinuria [5] [7]. Of note is that there no relationship between the severity of PS and tumor stage and PS may appear at any stage of tumor development [2]. The most frequent paraneoplastic syndromes, reported in the literature are: i) endocrine paraneoplastic syndromes; ii) SIADH (Syndrome of Inappropriate Antidiuretic Secretion); iii) Hypercalcemia; iiiii) Cushing syndrome; iiiiii) Hypoglycemia [8].

The aim of this review is to describe the incidence of nephrotic syndrome in prostate cancer. We have performed detailed analysis of the world literature for a period of 30 years back and we identified only five reports thus far. The literature search for this review was conducted using PubMed, Research gate and ScienceDirect databases, using the keywords Paraneoplastic syndromes, prostatic carcinoma, and nephrotic syndrome. To the existing list of reported cases of prostate cancer with nephrotic syndrome, we have added a new case (*based on personal observations and communications*). The publication of this case will be performed in a later stage in collaboration with the principal investigator (Y.F.).

2. Material and Methods

Literature search of MEDLINE database using PubMed, Research gate, and Web of Science was used to identify the potential articles, discussing the topic. The following key words were used to search the published literature: paraneoplastic syndromes, prostatic carcinoma, malignancy-associated glomerulonephritis, and nephrotic syndrome. The inclusion criteria in this review were: 1) study published as an original paper; 2) reports written in English; and 3) papers providing new data and novel findings, relevant to the topic area. Data extracted from

these articles included the name of the first and/or corresponding author, year of publication, study design, sample size, geographic region, study outcomes and results.

2.1. Nephrotic Syndrome as a Part of Paraneoplastic Syndromes

Paraneoplastic syndromes are associated with the distant effect of humoral factors, produced by the tumor [8]. In between different PS, including the paraneoplastic endocrine, neurological, dermatological, and hematological syndromes, the glomerular diseases with nephrotic syndrome, secondary to malignancies are also important integral part in the malignant phenomenon in humans. Nephrotic syndrome (NS) can represent a primary kidney-specific disease or malignancy-associated glomerulonephritis [3]. However, irrespective the underlying cause, their common feature is the glomerular injury with proteinuria [2] [3]. In contrast, kidney diseases, affecting renal tubules and/or interstitium do not cause nephrotic syndrome (e.g. interstitial nephritis). *Galloway and al.* in 1922 first hypothesized the possible relationship between nephrotic syndrome and cancer [9]. In 1939, *Corning and al.* reported the association of NS with Hodgkin disease [2]. Renal involvement in prostate cancer is very rare and the first case report, describing such association was published by *Stuart and al* in 1986 [10]. *Lee and al* [11] have published the first large study of secondary nephrotic syndrome in 1966. Secondary NS includes specific changes in renal function, where the alterations of glomerular filtration barrier are driving factors of this pathological process. This is due to the accumulation of abnormal bio-products, produced by the tumor cells, which trigger the cascade of cell-to-cell interactions and deleterious immunological alterations, leading to disruptions of glomerular basement membrane. [2] [12] There are several clinical criteria proposed for the diagnosis of the secondary NS: (a) clinical and histological remission occurs after complete surgical removal of tumor or chemotherapy induced remission of the disease; (b) renal relapse is associated with the neoplasia recurrence; (c) causal relationship exists if proteinuria develops 6 months before or after the initial diagnosis of cancer [3].

2.2. Nephrotic Syndrome as a Manifestation of Underlying Prostate Cancer

Renal involvement in patients with prostatic carcinoma is a very rare event, most commonly demonstrated by the membranoproliferative glomerulonephritis with nephrotic syndrome (MN with NS), minimal change disease, crescentic glomerulonephritis (CGN), focal segmental glomerular sclerosis, IgA nephropathy, and mesangioproliferative glomerulonephritis [2] [13]. Morphological feature of MN is the thickening of glomerular basement membrane, proliferation of mesangial cells, and influx of mononuclear inflammatory cells. Renal biopsy reveals visceral epithelial cell swelling, collapsed glomerular capillary tuft, and severe tubule-interstitial inflammation and microcytic dilatation of renal tubules [13]. Cytoplasm in the engorged epithelial cells sometimes sloughs into the lumen as

little chunks of cytoplasm containing droplets of lipoproteins and proteins. The light and polarized microscopy shows the appearance of these lipid accumulations in the urine, called oval fat bodies. The hallmark of NS reflects the mechanism of glomerular damage, *i.e.* the subepithelial deposition of immune complex in glomeruli, detected by serial electron microscopy scans. Oval fat bodies are seen on polarized microscopy, suggested as non-specific markers for kidney damage [2] [3]. Although the precise mechanism of the renal injury is not fully understood, recently the common belief is that the neoplastic lesion (e.g. prostatic carcinoma) triggers the onset of severe cellular and immune dysregulations, leading to a complex cell-to-cell interactions [3] [14]. Therefore, the pathogenesis of malignancy-associated nephrotic syndrome may be mainly immunological. Three possible mechanisms of glomerular damage have been suggested: a) in situ immune complex formation; b) formation of circulating immune complexes from the tumor antigens; c) impact from oncogenic viruses or altered immune function, resulting in immune complex deposition in glomeruli. In addition, *Lefacheur and al.* reported that the paraneoplastic membranous nephropathy is frequently associated with increased IgG1 and IgG2 levels, as well as with the increased number of inflammatory cells in glomeruli—a finding that is a diagnostic feature of the paraneoplastic glomerulonephritis [7] [14] [15].

Risk Factors

Several risk factors have been pointed out to contribute to the development of membranous nephropathy with NS: age > 65 years, male gender and long history of smoking, and racial factors [2] [5] [14].

2.3. Clinical Manifestation

The hallmark of paraneoplastic renal injuries is the nephrotic syndrome: nephrotic—range proteinuria higher than 3 g/24h, associated with hypoalbuminemia, generalized edema, hyperlipidemia, and elevated creatinine [12]. It was estimated that 10 to 20% of nephritic patients over the age of 60 years might have a concurrent malignancy—more often a solid tumor, including prostate cancer [3]. Although prostatic carcinoma is the most common malignancy in men, to the present only few cases of prostatic carcinoma, associated with nephrotic syndrome are reported (**Table 1**). Of note that the most challenging and important part in the diagnostics and management of these glomerulopathies is the prompt recognition of PN syndrome and treating of the underlying malignancy [5] [6] [7]. In addition, the critical point in the evaluation of such patients must be the prompt discrimination of primary and malignancy-associated MNs. Timely recognition of both occult or clinically active cancers in these patients is life-saving and therefore, requires high index of suspicion in patients at risk, adequate treatment and regular extended diagnostic work-up.

2.4. Diagnostics

In addition to patient's history and physical examination, one must take into

Table 1. Cases of prostatic carcinoma associated with paraneoplastic glomerulopathies and nephrotic syndrome. Abbreviations: MN—membranous glomerulonephritis; MPGN—membranoproliferative glomerulonephritis; CGN—crescentic glomerulonephritis; Tx—therapy; PCa—prostatic carcinoma; NS—nephrotic syndrome; CS—corticosteroids; CFS—cyclophosphamide; CPA—cyproterone acetate; DES—diethylstilbestrol; RP—radical prostatectomy; RT—radiotherapy.

Authors	Age y/o	Type of renal alteration	Serum creatinine	Proteinuria	PSA	Therapy for prostatic cancer	Therapy of nephrotic syndrome	Outcome
Stuart K, 1986	n/a	MN	n/a	n/a	n/a	n/a	CS	Remission
Haskell L.P and al. 1990	81	CGN	n/a	n/a	n/a	Orchiectomy; DES + RT	CS	Died
Pai P and al. 1996	n/a	MPGN	133 (μmol/l)	7.4 g/day	n/a	DES	CS	Remission
Matsuura H, 2000	74	MN	n/a	12.9 g/day	290 ng/ml	DES	CS	Remission
Ahmed MS, 2007	75	MPGN	85 (μmol/l)	5.5 g/day	n/a	CPA	CS	Remission
Fradet Y, 2010 (unpublished data, personal communication)	71	MN	72 (μmol/l)	16.7 g/day	93 ng/ml	RP + RT	CS + CSF	Remission

account also the risk factors, contributing to NS and malignancy, such as age, gender and bad habits (*i.e.* smoking history). PSA testing with digital rectal examination are an integral part in screening and standard of practice, particularly in elderly subjects. Along with the routine laboratory tests, the initial sonographic evaluation may demonstrate enlarged, oedematous kidneys. Furthermore, radiological tests like CT scan and/or MRI will help to identify the origin of NS and possibly, the underlying neoplasm. Specific immunological tests like antinuclear antibodies, rheumatoid factor, HCV test, complement profile with cryoglobulins, and monoclonal immunoglobulins will contribute to identify the origin of the nephrotic syndrome. Finally, to confirm the the diagnosis of nephrotic syndrome complicating prostate cancer, both renal and prostate biopsy must be performed, which reveals specific histopathological changes of membranous nephropathy and the presence of prostate cancer (**Figures 1(a)-(d)**). Immunofluorescence demonstrates beaded granular deposits of IgG(c), and the electron microscopy confirms thickening of the glomerular basement membrane (d).

2.5. Treatment

Typically, the clinical remission of NS occurs after definitive treatment (*i.e.* surgical removal and/or chemotherapy, radiotherapy). This also will confirm the relationship between neoplasm and NS. In majority of patients, the renal function improve dramatically in response to corticosteroids treatment [2] [5]. Despite the initiated management, the time rate of complete remission of NS varies and can be different, with a mean time about 38.6 months for proteinuria to disappear [10]. Critical point in NS/proteinuria management is the infusion therapy, combined with corticosteroid, immunosuppressive and cytostatic therapy, followed by surgical and/or chemotherapy of the primary disease (*i.e.* prostate cancer) [7]. The authors have reported that the clinical course of patients with secondary NS also depends on tumor behavior [2]-[11]. Importantly, in case

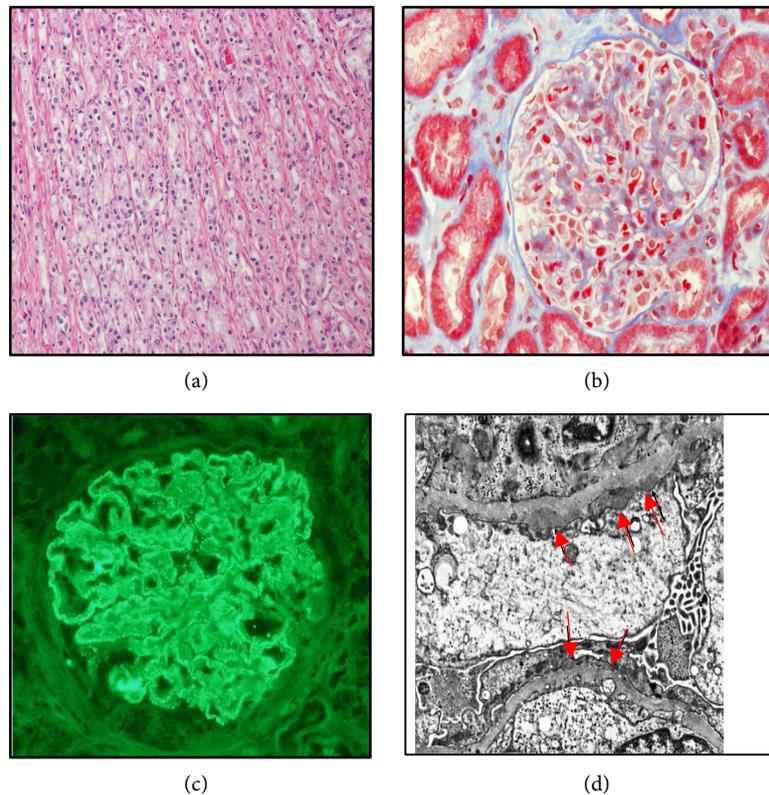


Figure 1. (a) Light microscopy of prostatic specimen with the appearance of prostatic adenocarcinoma (Gleason score 9). H&E, 100 \times ; (b) Renal biopsy specimen. Light microscopic appearance of a glomerulus with membranous nephropathy. Masson Trichrome, 400 \times ; (c) Immunofluorescence microscopy shows granular capillary wall stain for IgG; (d) Electron microscopy confirms subepithelial immune-type electron-dense deposits, 4000 \times .

of recurrence of proteinuria and nephrotic syndrome, a prompt work up for cancer screening (relapse or detection of a new malignancy) is required [12]. In patients with secondary NS simultaneously with the symptomatic management of NS, the main goal is to perform a cancer-specific targeted therapy for the primary carcinoma [15]. Therefore, the prompt recognition of this syndrome followed by an appropriate treatment of the underlying malignancy is lifesaving. Finally, we would like also to highlight the important role of multidisciplinary approach, used for the management of such patients. The team should involve ICU specialists, nephrologists, urologists, radiologists, pathologists and oncologists. After clinical remission, the follow-up must include regular physical examination, urinalysis, PSA testing, and renal function tests with protein/creatinine ratio detection. This is of extreme importance, because the eventual relapse of NS may be due to the cancer recurrence or to a presence of new malignancy. In addition, the assessment of renal function is mandatory.

3. Prognosis

When early detected, prostate cancer is curable. Therefore, the prognosis of pa-

tients with malignancy-associated nephrotic syndrome is highly dependent on timely recognition of the underlying malignancy. The clinical ability to discriminate the idiopathic from secondary nephrotic syndrome is crucial and the aggressive treatment that targets both nephrotic syndrome and cancer, will affect the patient's outcome. The literature reports have shown that a prompt and adequate treatment of cancer leads to resolution of glomerular disease [5].

4. Conclusion

Membranous nephropathy with nephrotic syndrome, secondary to prostatic carcinoma is a very rare event and only few cases up to now were reported in the world literature. However, its prompt recognition, followed by an adequate treatment of both kidney damage and cancer can be lifesaving. Digital rectal examination and PSA screening in men at risk for prostate cancer are integral part in the initial diagnostics of these patients and must be performed by all clinicians. Furthermore, the specific immunological and radiological tests, combined with multidisciplinary approach are essential for the diagnostics and management of such patients. Taken together, the reported evidence thus far suggests that malignancy-associated nephrotic syndrome may be considered as a (bio) marker for the presence of different malignancies, including prostatic carcinoma.

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