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The Challenging Management of Cancer: An Immunonephrologist's Perspective

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Keywords
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Abstract
Introduction: Onconephrology is an emerging medical subspecialization that focuses on the numberless interrelations between cancer and kidney diseases. Tumor cells evade immune surveillance through activation of immune checkpoint pathways that suppress antitumor immune responses. By blocking checkpoints, new anticancer agents disrupt immune homeostasis but potentially induce immune-mediated diseases. Nephrologists and nephroimmunologists should be able to treat the nephrotoxic sequelae of cancer therapy and ensure continuation of the life-saving treatment. ***Methods:*** Thirty-seven renal biopsies have been carried out over 42 months in oncologic patients, that is, 5.2% of the total native renal biopsies were carried out in the same period. The commonest diagnoses (>6 cases) were interstitial tubular nephritis, membranous glomerulopathy, IgA nephropathy, vasculitis, and focal and segmental glomerulosclerosis. ***Case Presentation:*** Three example cases, including focusing on key questions which could involve the nephrologists are reported in detail. They include a cancer-related Goodpasture Syndrome, the peculiar toxic effects of pemetrexed on tubular cells, and the intriguing relationship between bevacizumab and cryoglobulinemic glomerulonephritis. ***Conclusion:*** As shown by these 3 example cases, nephrologists need to be open-minded with regard to kidney biopsy in order to get a timely diagnosis. Nephrologists also need to improve their knowledge of cancer biology and therapy in order to prevent kidney problems, manage therapy-related immune-mediated disorders, and improve patient life expectancy.

Introduction

Onconephrology is an emerging medical subspecialization focused on the numerous interrelations between cancer and kidney diseases [1]. A number of glomerulopathies, tubulopathies, and vascular renal diseases can herald the presence of an underlying cancer. On the other hand, patients with malignancy often experience renal complications including acute kidney injury (AKI), fluid and electrolyte disorders, and CKD, sometimes as a sequela of cancer treatment [2, 3]. Several aspects of cancer-

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Table 1. Overview of bevacizumab and ICIs (commercially available or in [phase III trials])

Target	Drug name	Agent name	FDA approved indications
VEGF	Avastin	Bevacizumab	Colon, lung, kidney, and, brain cancers
CTLA-4	Yervoy	Ipilimumab	Metastatic melanoma
	MEDI-1123	Tremelimumab	Phase III
PD-1	Opdivo	Nivolumab	Metastatic melanoma
	Keytruda	Pembrolizumab	Metastatic melanoma, PD-L1-positive non-small cell lung cancer, head and neck cancer
	Libtayo	Cemiplimab	Metastatic CSCC or locally advanced CSCC
PD-L1	Tecentriq	Atezolizumab	Urothelial cell carcinoma, non-small cell lung cancer
	Bavencio	Avelumab	Metastatic Merkel cell carcinoma
	Imfinzi	Durvalumab	Unresectable stage III NSCLC
IDO	INCB-24360	Epacadostat	Phase III

ICI, immune checkpoint inhibitor; CSCC, cutaneous squamous cell carcinoma; NSCLC, non-small cell lung cancer.

related nephropathies are unique and are becoming more and more difficult to manage because of the patients' comorbidities and the increasingly extensive use of different types of chemotherapy regimens.

Most nephrologists are aware of the common side effects of conventional chemotherapy regimens that include cisplatin, methotrexate, melphalan, and cyclophosphamide. Among others, acute tubular necrosis and thrombotic microangiopathy (TMA) are major injuries [4–6]. Treatment of cancer is rapidly evolving, and targeted therapy, which has been widely used in recent years, is one of the main developments (Table 1) [7]. Furthermore, the toxicity profile is completely different from conventional chemotherapy [8]. Due to accelerated approval (and limited experience), knowledge of the toxicity profile of these agents is often lacking, and clinicians have to face novel and often under-recognized adverse effects [9]. Targeted therapies and immunotherapies are associated with a wide range of adverse events (AEs) resulting from common signaling pathways involved in malignant behavior and normal homeostatic functions of various organs [10].

Cancer immunotherapy, such as anti-cytotoxic T-lymphocyte-associated protein 4 and anti-programmed death 1, has revolutionized the treatment of malignancies by engaging the patient's own immune system against the tumor rather than targeting the cancer directly [11]. Tumor cells evade immunosurveillance and progress through several mechanisms, including activation of immune checkpoint pathways that suppress antitumor immune responses. Immune checkpoint inhibitors (ICIs) reinvigorate antitumor immune responses by interrupting co-inhibitory signaling pathways and promote immune-mediated elimination of tumor cells [12]. As a consequence, these novel compounds can trigger immune-related AEs that affect 1 or more organs. These inflammatory events can be serious and occasionally life-threatening [13]. How do these autoimmune events occur? The toxicities of cancer immunotherapy are largely determined by the immunosuppressive tumor microenvironment that cooperates to contrast antitumor immunity by complex mechanisms involving Treg cells, MDSCs, γδT cells, TAMs, and other inhibitory immune checkpoints, all of which may play a role in inhibiting antitumor immune responses and limiting autoimmunity at the same time. By blocking these checkpoints, ICIs disrupt this immune homeostasis and therefore induce immune-mediated diseases, such as vasculitis and glomerulonephritis, that closely resemble the idiopathic forms [14].

While initial studies reported a small incidence of checkpoint inhibitor-related renal toxicity, recent data suggest a higher incidence rate, that is, closer to 13–29% [15, 16]. Patient survival benefits from different lines of anticancer treatment in advanced states and requires preservation of renal function. Several studies on cancer management showed renal impairment to be a major cause of therapy discontinuation [17, 18]. The potential

reversibility of the renal side effects affects the therapeutic strategy, since there are a number of agents that cannot be prescribed in case of kidney failure. Preventive measures and extensive workups aimed at anticipating the causes of upcoming glomerular filtration rate (GFR) decline are needed to avoid stage 4 or 5 renal failure, which could compromise any future cancer therapy [19].

Anticancer drugs may lead to numerous forms of renal toxicity, including glomerulonephritis. On the contrary, the presence of cancer may be heralded by a glomerular disease [20, 21]. In these cases, only renal biopsy can really shed light on the underlying mechanisms. Cancer also constitutes one of the main causes of kidney transplant-associated morbidity and mortality. The cumulative incidence of solid organ cancers after kidney transplantation increases from 4 to 5% after 5 years to 10% after 10 years and to >25% after 20 years [22]. Posttransplant malignancies can arise by any one of 3 mechanisms: de novo, donor-related, and recurrent cancers. Prolonged immunosuppression as well as environmental and host factors each play a prominent role in transplant recipient carcinogenesis. Chronic immunosuppressive therapy impairs immunosurveillance of cancer cells, resulting in greater risk of malignancy in organ recipients. In addition, the direct carcinogenic effects of select immunosuppressive drugs coupled with a higher incidence of oncoviral infections contribute to the pathogenesis of malignancies after solid organ transplantation [23]. Moreover, several causative factors are associated with increased risk of posttransplant cancer: exposure to carcinogenic agents (sunlight, smoking, diet, and alcohol consumption) [24], advanced age of the recipient and genetic predisposition to cancer or history of malignancy in the donor or recipient [25], and extended time on dialysis before transplantation [26]. The management of cancer after kidney transplantation continues to be complex given the need to balance the risk of graft rejection and the reduction/variation of immunosuppressive therapy, the nephrotoxic effects of some chemotherapeutic agents and the drug-to-drug interactions. For example, T-cell response as a result of using ICIs may increase the risk of acute rejection [27]. The few case reports on the use of these agents in kidney transplant recipients gave conflicting results [28, 29]. M-TOR inhibitors have been suggested to be protective owing to their simultaneous immunosuppressive and anti-cancer effects [30].

To emphasize the role of the nephrologist in the management of cancer patients, we report 3 example cases focusing on key questions which involve the nephrologist before and during cancer treatment. The role of renal biopsy in driving the diagnostic process and management of cancer-/drug-related renal toxicity is specifically highlighted.

Methods

In 2017, a multidisciplinary medical clinic devoted to cancer patients having nephrologic or immunological complications had been launched in our Department of Medicine. From its beginning, this activity involved a nephrologist with specific expertise in rheumatologic issues. The main problems which had to be faced included both dose adaptation of oncologic agents to renal impairment, but also timely management of AKI of any cause and urinary abnormalities, and aggressive approach to any immune-mediated and cancer-related AE potentially limiting full treatment of patients. Thirty-seven renal biopsies have been carried out over 42 months in oncologic patients (i.e., 5.2% of the total native renal biopsies carried out in the same period). The commonest diagnoses (>6 cases) were interstitial tubular nephritis, membranous glomerulopathy, IgA nephropathy, vasculitis, and focal and segmental glomerulosclerosis. Three representative cases of the multifaceted interactions between cancer, novel oncologic agents, and immune disorders will be described and discussed.

A Putative Link between Lung Cancer and Goodpasture Syndrome

A 66-year-old man was admitted to our unit in February 2019 due to rapidly progressive kidney failure. His past medical history included chronic obstructive lung disease. Stage IIA localized lung squamous carcinoma had been diagnosed in June 2018, and he underwent pulmonary resection. No adjuvant chemotherapy was started due to persistent systemic symptoms and recurrent fever. In December 2018, chest computerized tomography (CT) had ruled out cancer recurrence, and at that time he had normal renal function. Serum Cr (sCR) was 0.8 mg/dL corresponding to an estimated GFR (eGFR) of 94 mL/min/1.73 m^2 using the simplified Modification of Diet in Renal Disease (MDRD) equation. After 2 months, the patient experienced worsening of systemic symptoms (asthenia, hyporexia, nausea, and vomiting) and the appearance of macrohematuria with rapidly progressive renal failure. On admission, his blood pressure was 150/95 mm Hg, and physical examination was normal. Laboratory tests indicated elevated sCR levels (5.9 mg/dL). Microscopic examination of urine sediment showed >100 RBCs/HPF with granular casts. Dialysis was started, and a kidney biopsy was performed. The histological findings, which are shown in Figure 1, revealed crescentic glomerulonephritis. Thirty-two out of 33 glomeruli showed widespread segmental necrosis and partial or circumferential cellular crescents with hemorrhagic dissociation. Immunofluorescence showed intense linear staining of the GBM with IgG. CT showed recurrence of lung adenocarcinoma in the right hilar region (shown in Fig. 2). During hospitalization, double serum positivity of anti-GBM antibodies (>310 UI/mL) and antimyeloperoxidase antibodies were reported. A clinical diagnosis of Goodpasture disease was made. After discussion of the clinical picture with oncologists, apheresis treatment and immunomodulatory therapy with rituximab (lymphoma protocol)

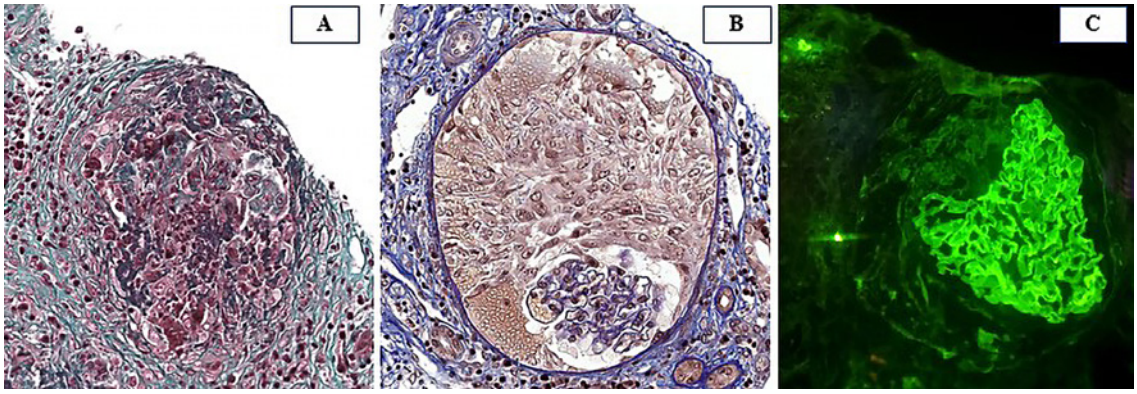

Fig. 1. Widespread segmental necrosis and partial or circumferential extracapillary cellular crescents (trichrome stain) (**A**); Epithelial circumferential crescents with hemorrhagic dissociation (AFOG stain) (**B**); Intense linear staining of the GBM with IgG (+++) (**C**).

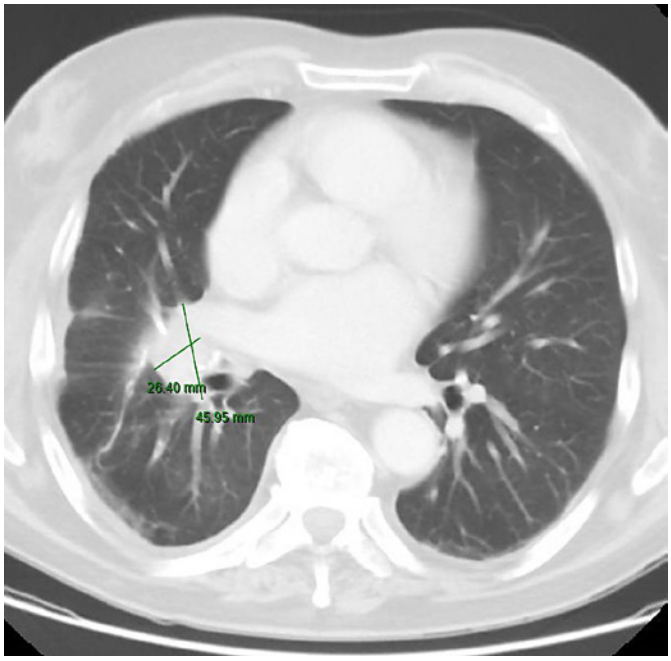

Fig. 2. CT showing a recurrence of lung adenocarcinoma in the right hilar region. CT, computed tomography.

and corticosteroids were started [31]. A significant reduction in the anti-GBM antibody titer (45 UI/mL) was observed after 7 apheresis sessions (14th day). However, 7 days later, his anti-GBM antibody levels rose again. A cycle of radiotherapy was also started, and despite resumption of diuresis, recovery of renal function was not sufficient to allow discontinuation of dialysis.

The combination of Goodpasture disease and antineutrophil cytoplasmic antibody-associated vasculitis is not exceptional. However, to the best of our knowledge, their association with recurrent pulmonary adenocarcinoma has never previously been reported. The diagnosis of double-seropositive vasculitis was based on serological findings (anti-GBM and anti-MPO were positive) and on histopathological findings that revealed crescentic glomerulonephritis with linear staining of IgG in the glomeruli by immunofluorescence analysis of the kidney biopsy sample. Autoimmune disorders are very common and well-studied in hematological diseases which are associated with an immune imbalance. They are less common in solid tumors and are classified as paraneoplastic syndromes of unclear pathogenesis. Those most often associated with paraneoplastic autoimmune phenomena are ovarian and prostate carcinomas [32]. Co-presentation with both double-seropositive vasculitis and lung cancer is very rare. In a review that was published in 2013, Rollins and Lindley [33] studied the association between malignancy and antineutrophil cytoplasmic antibody-associated vasculitis and found that in the majority of cases, cancers are secondary to the pro-carcinogenic effects of the therapies that are administered.

In this case, the physiopathological mechanisms of co-presentation with both double-seropositive vasculitis and pulmonary cancer remain unclear. A hypothesis that cannot be ruled out is the role of cancer antigens as a trigger of vasculitis.

Delayed and Peculiar Toxic Effects of Pemetrexed on Tubular Cells

A 66-year-old man was admitted to our unit in January 2019 because of rapidly progressing kidney failure. He was a former tobacco smoker (20–25 cigarettes/day). Stage IV lung adenocarcinoma with nodal metastases had been diagnosed in February 2018. Treatment began in March 2018 and consisted of 5 sessions with carboplatin and pemetrexed (PEM) (500 mg/m^2). On account of the good response that was observed in June 2018, the chemotherapy protocol was changed and PEM alone was continued. His past medical history included hypertension, smoking-related chronic obstructive lung disease, ischemic heart disease (2016 and 2017, respectively), and cerebral ischemia (2014).

Before beginning chemotherapy, his SCr level was 0.8 mg/dL, corresponding to an eGFR of 114 mL/min/1.73 m^2 using the MDRD equation. In December 2018, his plasma Cr levels rose to 2.1 mg/dL, corresponding to an eGFR of 38 mL/min/1.73 m^2, and

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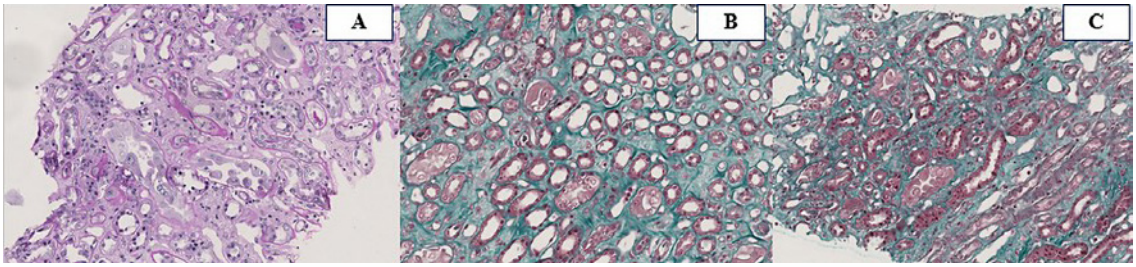

Fig. 3. Nuclear irregularities (PAS stain) (**A**); Nucleomegaly (trichrome stain) (**B**, **C**).

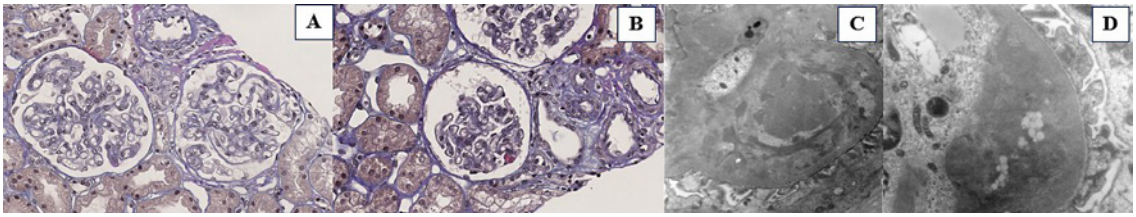

Fig. 4. Basement membrane reduplication (AFOG stain) (**A**); Hyalin thrombus (AFOG stain) (**B**); Electron microscopy: structured deposits (**C**, **D**).

PEM treatment was discontinued. After discontinuation, his Cr plasma levels continued to rise, reaching sCr 2.8 mg/dL. On admission, his blood pressure was 140/80 mm Hg and physical examination was normal. Sporadic consumption of non-steroidal anti-inflammatory drugs was reported. His 24-h proteinuria was estimated at 0.5 g/day. Microscopic hematuria appeared without leukocyturia. Blood tests showed anemia (10.2 g/dL), with no laboratory signs of hemolysis or schistocytes. Immunological parameters were negative. No gamma-globulin abnormalities were seen in plasma protein electrophoresis. Kidney ultrasound showed 2 well-differentiated, normal-sized and normal-shaped kidneys with a regular outline and no impediments. A kidney biopsy was performed. The histological findings, which are shown in Figure 3, revealed acute tubular necrosis associated with marked nucleomegaly. The glomeruli, interstitial compartment, and vessels were normal. There were no thrombotic microangiopathic lesions, glomerular or tubular basement membrane deposits, or arteriolar hyalinosis. Immunofluorescence did not show any immune complex deposits. Viral infections were ruled out. A genetic test excluded the presence of polymorphisms associated with PEM toxicity, and the NGS TruSight One Expanded (630 genes) was negative. In the following weeks, renal function recovered and immunotherapy with anti-PDL1 antibodies was started. At his last visit, lung CT scan and renal function were stable. PEM is a new-generation multitarget antifolate agent with proven broad-spectrum activity in several types of human cancers, including non-small cell lung cancer and mesothelioma [34]. Maintenance therapy with PEM has emerged as a novel therapy for patients with non-progressive advanced non-squamous cell lung cancer after induction. PEM maintenance therapy holds tremendous potential in improving the survival of patients with advanced pulmonary adenocarcinoma [35]. Major side effects include myelosuppression and cutaneous reactions. An increasing number of cases documenting acute kidney injury with PEM have been published [36, 37]. Recently, several cases of PEM-induced tubular injury were reported in the international literature including interstitial nephritis and fibrosis as well as diabetes insipidus [36]. However, only few of these patients underwent renal biopsy [37]. In every case, the authors describe an acute decline of kidney function occurring 1 or 2 weeks after treatment initiation, with further worsening occurring after therapy discontinuation [38]. In a recent study, 50% of the patients receiving maintenance treatment combining PEM and bevacizumab had to stop due to AKI [39]. However, renal impairment in our patient occurred later, after 10 maintenance cycles, and the pathological features were very peculiar.

The Intriguing Relationship between Bevacizumab and Cryoglobulinemic Glomerulonephritis

A 57-year-old woman was admitted to our unit in April 2019 for nephrotic syndrome. Stage IIIC ovarian cancer had been diagnosed in October 2016. She underwent 5 sessions with carboplatin, paclitaxel, and bevacizumab. On account of good response, she underwent total hysterectomy with bilateral salpingo-oophorectomy in January 2017, and adjuvant chemotherapy with bevacizumab was resumed 1 month later. Her past medical history included hypertension. Before beginning maintenance chemotherapy, her plasma Cr level was 0.7 mg/dL, corresponding to an eGFR of 107 mL/min/1.73 m^2 using the MDRD equation, urinalysis was negative, and urine proteinuria (uPt) was 0.2 g/day. In March, the urine test revealed the presence of proteins (uPt: 3.5 g/day), and treatment was discontinued. After discontinuation, uPt continued to rise and reached 6.5 g/day (1 month later). On admission, her blood pressure was 120/70 mm Hg, and physical examination revealed edema in the legs. Blood tests showed severe

hypoalbuminemia (1.7 g/dL) and hypoproteinemia (4.2 g/dL), hypofibrinogenemia (106 ng/mL), hypo IgG (522 mg/dL), and hypo-C4 (6 mg/dL). Her immunological profile revealed the presence of SSA (Ro52) and anti-centromere B antibodies as well as the presence of hypocryoglobulins. Kidney ultrasound showed 2 well-differentiated, normal-sized and normal-shaped kidneys with a regular outline and no impediments. A kidney biopsy was performed. The histological findings (shown in Fig. 4) revealed the presence of basement membrane reduplication, hyaline thrombus, subendothelial deposits, and glomerular mesangial expansion. Immunofluorescence was positive for IgM and C3 in the glomerular basal membrane and in mesangial areas. Electron microscopy confirmed the presence of structured subendothelial deposits.

Corticosteroid therapy with prednisone (0.8 mg/kg) was started. In the following weeks, proteinuria rapidly decreased and therapy with Bevacizumab was resumed with a maintenance dose of prednisone of 5 mg/day. At her last visit, proteinuria was 0.5 mg/day, and C4 levels were within the normal range.

The molecularly target drug bevacizumab, an inhibitor of vascular endothelial growth factor, inhibits tumor angiogenesis and is effective against various malignant tumors. Bevacizumab increases the risk of high-grade proteinuria and hypertension. Histologically, most patients show TMA. However, several patterns have been described (minimal change disease, focal segmental glomerulosclerosis, and IgA vasculitis) [40–42]. Recently, Person et al. [41] described a distinctive histopathological pseudothrombotic pattern unlike the previously reported TMA. This pattern includes some features similar to cryoglobulinemic membranoproliferative glomerulonephritis. The authors reported the absence of cryoglobulins and complement activation [41]. Our patient's renal biopsy showed a typical pattern of cryo-membranoproliferative glomerulonephritis. Histological findings were in accordance with the serological finding of hypocomplementemia C4 and the presence of hypocryoglobulins. The absence of specific blood tests prior to bevacizumab administration does not allow ruling out the presence of cryoglobulins before starting therapy. On the contrary, the progressive reduction of C4 would suggest a direct pathogenetic role of bevacizumab. Bevacizumab may have triggered antibody production leading to cryoglobulin-mediated glomerulonephritis.

Discussion

A number of cancer patients suffer from various disease-/therapy-related disorders that need the cooperative approach of different specialists to face the entire spectrum of problems and establish clinical priorities. The goal remains patient survival combined with an adequate quality of life. Nephrologists and (for the last few years) nephroimmunologists are called upon to balance the nephrotoxic effects and the consequences of discontinuation of cancer therapy. The challenge, especially in the era of target therapies, is to allow the patient to continue life-saving treatments. Nephrologists and nephroimmunologists should be able to cure the nephrotoxic sequelae of cancer therapy and ensure the continuation of the life-saving treatment. Our experience highlights the importance of including a nephrologic consultation and assessment within the multidisciplinary care in order to provide the patients with an integrated team approach to health care in which medical and allied health-care professionals consider all relevant treatment options and collaboratively develop a tailored treatment plan for each patient.

As demonstrated by the 3 example cases, nephrologists 1st need to be open-minded (and experienced) with regard to kidney biopsy, otherwise they would be better off not dealing with these cases at all because they would lose the challenge and endanger the lives of their patients. Second, cancer therapy may cause both acute and chronic kidney injuries. The progressive introduction of novel target therapies has increased the chances of detecting several combinations of cancer and apparently distal CKD. Nephrologists need to improve their knowledge of cancer biology and therapy in order to prevent kidney problems, resolve them, and improve patient outcomes.

Statement of Ethics

Subjects gave their written informed consent to publish their case (including publication of images from renal biopsy). Data collection has been conducted according to the Italian regulation on rare diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: R. Fenoglio and D. Roccatello. Resources: Savino Sciascia. Data curation: Emanuele De Simone and Giulio Del Vecchio. Writing original draft preparation: R. Fenoglio and D. Roccatello; Supervision: G. Quattrocchio and M. Ferro. All authors have read and agreed to the published version of the manuscript.

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