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Original Article

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Causes and Results of Nephrology Consultation in Oncological Diseases: A Single-Center Experience

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198

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ABSTRACT

Objective: Cancer and kidney diseases are closely related since the incidence of cancer is increased in patients with chronic kidney disease and various manifestations of kidney injury occur in cancer patients. We aimed to examine the diagnoses, reasons for consultation, and recovery status of oncologic patients who were consulted on an outpatient basis to the nephrology clinic.

Methods: One hundred thirty-three patients were retrospectively included. Analysis was performed by recording the etiology of kidney disease, and laboratory results at the first and last visit.

Results: The mean age of the patients was 62.7 (37-86) years and 52.6% of patients were female. The mean follow-up time was 15.6 ± 11.9 months. The most frequently consulted malignancy group was gastrointestinal (n = 39) and urogenital system tumors (n = 36). Ranking of the reasons for consultation according to frequency: acute kidney injury (n = 60), chronic kidney disease (n = 35), proteinuria (n = 20), electrolyte imbalance (n = 14), and others (n = 4). When patients who were consulted for chronic kidney disease were excluded, the 3 most common etiological diagnoses of the consultation reasons were chemotherapy-related toxicity (n = 26), dehydration (n = 16), and chemotherapy-associated proteinuria (n = 16). While progression was observed in 21.6% of the patients consulted with acute kidney injury, progression was observed in 8.6% of the patients consulted with chronic kidney disease. Proteinuria regressed in 75% of the patients consulted for proteinuria.

Conclusion: In this study, it was determined that those diagnosed with gastrointestinal and urogenital system cancer were consulted to nephrology more frequently and clinical improvement was observed in the vast majority of patients. The concept of onco-nephrology should be further expanded.

Keywords: Consultation, nephrology, oncology

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INTRODUCTION

Cancer is a leading cause of death worldwide, with approximately 10 million deaths in 2020.[1] Cancer and its treatment can cause several serious complications, and in many cases fatal, a burden on patients. Cancer-associated thrombosis, cardiovascular/mental/neurologic complications are some of the most known examples.[2] Cancer and kidney diseases are closely related to each other. Some cancers themselves and some conditions that develop during the disease process also affect the kidneys and cause complications. The presence of kidney impairment in a cancer patient may worsen the prognosis of that patient and increase mortality.[3] Cancer may affect the kidney through the toxic effects of the medication or radiation or the so-called paraneoplastic nephropathies, mainly as glomerular lesions, or even after reduction of kidney mass post nephrectomy due to kidney cancer.[4] In addition, patients on dialysis and particularly transplants are at high risk for the onset of cancer due to the status of immunosuppression.[4] Thus, there is a rapidly growing field between kidney disease and cancer, which has been dubbed Onco-Nephrology.

This area of sub-specialization combines the unique knowledge and efforts of several specialty groups, including nephrologists, oncologists, urologists, pharmacologists, intensive care specialists, and palliative care specialists.[5] Multidisciplinary team working and by taking action to improve integrated care by applying already-known methods of addressing cancer-related complications and comorbidities. Onco-Nephrology is already an important area with a large number of inter-consultations and covers all areas of kidney involvement in cancer patients. In this study, we aimed to examine the diagnoses, reasons for consultation, and recovery status of oncologic patients who were consulted on an outpatient basis to the nephrology clinic.

METHODS

The investigation conforms to the principles outlined in the Declaration of Helsinki. The local ethics committee approved the study (Protocol code: 09.2020.1009). All over age 18-years cases who were consulted to the nephrology outpatient clinic from the oncology clinic between 10/9/2015 and 10/9/2018 were included. Diagnostic evaluation of gender, age, comorbidities (diabetes mellitus, hypertension), cancer diagnosis, and reason for consultation were recorded. Analysis was performed by recording the etiology of kidney disease, laboratory results related to the indication for consultation (creatinine, estimated glomerular filtration rate (eGFR), proteinuria, electrolyte levels), and laboratory results at the last visit of follow-up times. All eGFR values were calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. Acute kidney injury was defined as a sudden increase (over several days to weeks) in the serum creatinine level of ≥0.3 mg/dL (≥26.4 µmol/L) or ≥ 50% from baseline and/or a reduction in urine output of <0.5 mL/kg/h for more than 6 hours. Proteinuria was evaluated as spot urinary protein creatinine ratio or 24-hour urine protein.

MAIN POINTS

- Cancer and kidney diseases are closely related to each other. The kidneys may be directly or indirectly injured by cancer. On the other hand, the presence of kidney impairment in a cancer patient may worsen prognosis and increase mortality.
- Important areas in onco-nephrology include acute kidney injury (AKI)/chronic kidney disease (CKD) in cancer patients, nephrotoxic effects of anticancer therapy, paraneoplastic kidney manifestations, pain management, contrast-induced nephropathy, electrolyte imbalance, and proteinuria.
- In the present study, we showed that gastrointestinal and urogenital system cancers were consulted to nephrology more frequently and ranking of the reasons for consultation according to frequency was AKI, CKD, proteinuria, electrolyte imbalance and the 3 most common etiological diagnosis of the consultation reasons were chemotherapy-related toxicity, dehydration, and chemotherapy-associated proteinuria.
- Plans include the development of training courses in epidemiology, patient monitoring, guidelines for the management of kidney patients with cancer, and cancer patients with impaired kidney function.

Statistical Analysis

All statistical tests were performed with a commercially available Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA). Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean (min-max) or mean ±SD.

RESULTS

One hundred thirty-three patients were retrospectively included in the study. The mean age of the patients was 62.7± (37-86 years old) and 52.6% of patients were female. The mean follow-up time was 15.6 ±1.9 months. Clinical and demographic data of the patients are shown in Table 1.

The most frequently consulted malignancy group was gastrointestinal (n = 39) and urogenital system tumors (n = 36). The first 5 cancer diagnoses most frequently consulted were colon + rectum (n = 28), lung (n = 17), breast (n = 15), kidney cell carcinoma (n = 15), and ovary (n = 10), respectively (Figure 1).

Ranking of the reasons for consultation according to frequency is as follows: acute kidney injury (AKI) (n = 60), chronic kidney disease (CKD) (n = 35), proteinuria (n = 20), electrolyte imbalance (n = 14), and others (n = 4) (Figure 2). Acute kidney injury causes were chemotherapy-related toxicity (n = 26), dehydration (n = 16), post-kidney (n = 10), nephrectomy (n = 5), sepsis (n = 1), contrast-induced (n = 1), and biopsy-proven acute tubular necrosis (n = 1). When patients who were consulted for

Table 1. Clinical and Demographic Data of the Patients

	Patients (n = 133)
Mean (min-max) age years	62.7 (37-86)
Sex, female, n (%)	70 (52.6)
Mean Follow-up time, months	15.6 ± 11.9
Diabetes mellitus, n (%)	32 (24.1)
Hypertension, n (%)	69 (51.9)
Malignancy type, n (%)	
Gastrointestinal	39 (29.3)
Urogenital	36 (27.1)
Lung	17 (12.8)
Breast	15 (11.3)
Others	26 (19.5)
Reasons for consultation, n (%)	
Acute kidney injury	60 (45.1)
Chronic kidney disease	35 (26.3)
Proteinuria	20 (15.0)
Electrolyte imbalance	14 (10.5)
Others	4 (3.0)

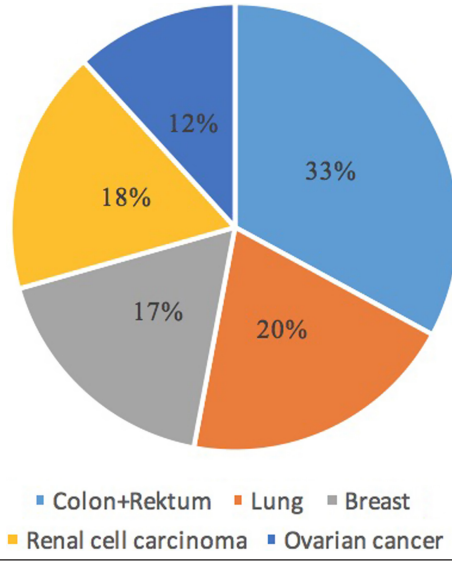

Figure 1. Most frequently consulted cancers (%).

CKD were excluded, the 3 most common etiological diagnoses were: chemotherapy-related toxicity (n = 26), dehydration (n = 16), and chemotherapy-associated proteinuria (n = 16). While improvement was observed in 73.3% (n = 44) of the patients consulted with AKI, progression was observed in 21.6% (n = 13) (last laboratory results of 3 patients could not be reached). Only 3 (8.6%) of the patients sent for chronic kidney disease (CKD) follow-up had enough progression to progress, while the remaining 32 (91.4%) had a stable clinical course. Proteinuria causes were bevacizumab (n = 11), sunitinib (n = 4), everolimus (n = 1), ibandronic acid (n = 1), diabetic nephropathy (n = 1), focal segmental glomerulosclerosis (n = 1), and paraneoplastic (n = 1). Proteinuria regressed in 75% (n = 15) of the patients consulted for proteinuria, and an increase was found in 15% (n = 3) (laboratory results of 2 patients were not available). Electrolyte imbalance was observed in 14 (10.5%) of the patients, and the most common cause was hyponatremia (n = 6, 42.9%). Other reasons for consultation were urinary tract infection, kidney vein thrombosis, hydronephrosis, and hematuria.

DISCUSSION

Important areas in onco-nephrology include AKI/CKD in cancer patients, nephrotoxic effects of anticancer therapy, paraneoplastic kidney manifestations, pain management, contrast-induced nephropathy, electrolyte imbalance, and proteinuria.[4]

In the present study, we showed that gastrointestinal and urogenital system cancers were consulted to nephrology more frequently and ranking of the reasons for consultation according to frequency was AKI, CKD, proteinuria, electrolyte imbalance and the 3 most common etiological diagnosis of the consultation reasons were chemotherapy-related toxicity, dehydration, and chemotherapy-associated proteinuria. Acute kidney injury is a common kidney complication in cancer patients. As a result of 2 studies, it was reported that AKI is the most frequent kidney complication occurring in 12%-49% of terminal cancer patients, and the presence of AKI has a negative impact on patient survival.[6,7] Similarly, the most common reason for consultation was AKI (45.1%) in our study. In a recent study, it was shown that approximately 10% of 163 071 cancer patients who were followed up over 7 years developed severe AKI requiring dialysis.[8] In the same study, it was also revealed that the annual incidence of AKI increased approximately 5 times during the study. This can be explained by the cumulative increase in drug-related kidney toxicity over the years. Conventional chemotherapeutic agents like platinum compounds, ifosfamide, methotrexate, and gemcitabine can injure all nephron segments and kidney vasculature by activation of apoptosis, inflammation, tubular obstruction, or ischemia and this kidney injury is often dose and duration related.[9] Targeted cancer treatments, cancer immunotherapies, and other drugs (as bisphosphonates, sirolimus, etc.) can also cause AKI in several different ways.[9] In a

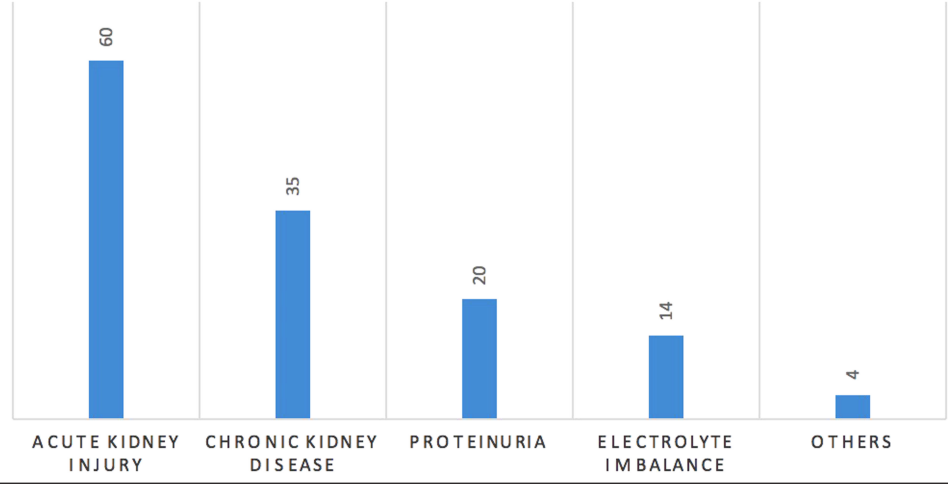

Figure 2. Causes of nephrology consultation (n).

study conducted on cancer patients treated in the ICU in France; sepsis, hypovolemia, urinary tract obstruction, tumor lysis syndrome (TLS), and hypercalcemia were reported as the most common etiologies other than drugs.[10]

In our study, the most common cause of AKI was chemotherapy-related toxicity and other diagnoses were dehydration, obstructive nephropathy (post-kidney), nephrectomy, sepsis, contrast-induced nephropathy, and biopsy-proven acute tubular necrosis. Since hematological cancers and inpatient consultations were not included in our study, we did not detect any cases of TLS in the etiology of AKI and could only diagnose sepsis in 1 patient. However, considering that AKI increases mortality in cancer patients, early recognition and treatment of AKI seem to be very important, and clinical improvement was observed in 73.3% of the patients consulted with AKI in our cohort.

Chronic kidney disease may be pre-existing in a significant portion of cancer patients. This is because comorbidities such as diabetes and hypertension are common in cancer patients, as well as especially cancers of the urinary system may contribute to the development of CKD. Chronic kidney disease is negatively related to mortality in cancer patients and also itself is a well-known risk factor for malignancy.[11-13] Launay-Vacher and colleagues reported that only 50% of cancer patients had an eGFR above 90 mL/min/1.73 m^2.[14] In another study, it was revealed that 30% of cancer patients had an eGFR of less than 60 mL/min/1.73 m^2.[15] However, it is known that the incidence of cancer increases over the age of 65 years. Physiologically, loss of eGFR due to aging may lead to a frequent diagnosis of CKD in cancer patients, even though they do not have intrinsic kidney disease. This situation is still being discussed in the field of nephrology and a new approach that includes age-related physiological eGFR loss that would be more accurate to classify CKD. Nevertheless, a portion of the cancer population who had clinically significant CKD that would require care as drug dose adjustment and worsening of pre-existing CKD is an important problem in this population. In our study, CKD prevalence was 26.3% and 91.4% of CKD patients remained stable during the follow-up period in the study population. This is because of close monitoring, early recognition, and timely management of the conditions that may complicate CKD. Therefore, cancer patients with CKD must clinically be followed by a multidisciplinary team including nephrologists.

Glomerular damage mechanisms range from podocytopathy to thrombotic microangiopathy and may present with proteinuria. Conventional drugs (gemcitabine, mitomycin-c), targeted cancer treatments (anti vascular endothelial growth factor (anti-VEGF), tyrosine kinase inhibitors, cancer immunotherapies (interferons, CTLA-4 inhibitors, PD1 inhibitors, and other drugs such as sirolimus) may cause proteinuria.[9] In our study, the most common cause of proteinuria was bevacizumab treatment. Bevacizumab (anti-VEGF) which has anti-angiogenic and immunomodulatory properties is a new targeted therapy agent against several solid cancers. Proteinuria due to VEGF inhibition has more than 1 mechanism. VEGF is produced from podocytes and activates the VEGF 2 receptor located on the glomerular capillary. Inhibition of this stimulus results in loss of endothelial fenestration and podocyte damage.[16] In addition, it may contribute to proteinuria due to VEGF inhibition, sub-acute thrombotic microangiopathy, and hypertension due to bevacizumab use.[17] The second most common etiology was sunitinib treatment. It has been reported that sunitinib, like bevacizumab, causes proteinuria due to its anti-VEGF effects.[18] In our study, although rare, well-known etiologies of proteinuria such as diabetic nephropathy and focal segmental glomeruloseclerosis (FSGS) were also found. In patients receiving bevacizumab, it is recommended to follow up proteinuria with dipstick, to measure urinary protein quantitatively, and if it is +2 interrupting the treatment recommended in the presence of proteinuria over 2 g/day. If nephrotic level proteinuria is detected, treatment can be terminated. We apply this management method and angiotensin converting enzyme/ angiotensin receptor bloker (ACE/ ARB) treatment to patients treated with bevacizumab with proteinuria in our clinic. Eventually, proteinuria regressed in 75% of the consulted patients in our cohort, however, since these drugs provide significant benefits to patient survival, the profit and loss balance needs to be taken into account.

Electrolyte disturbance, which is also an important complication, is encountered in cancer patients. They can worsen the outcome of cancer patients by causing significant morbidity, yet a rapid correction of abnormality seems to have a positive effect on cancer patients. Various causes may contribute to electrolyte disturbances in cancer patients, which are as follows: paraneoplastic syndrome of inappropriate antidiuresis and TLS, anticancer treatments, and other concomitant clinical conditions or treatments. However, the source of electrolyte disturbance is often multifactorial and requires careful consideration. These electrolyte disturbances usually involve sodium, potassium, calcium, and magnesium serum levels. Particularly hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion is common in cancer patients.[19] Similarly, the most common electrolyte disturbance was hyponatremia in our study. Hyponatremia is associated with increased mortality, a shorter time to treatment failure, and difficulty in controlling the disease.[20] Even hyponatremia may be a marker of occult neoplasms in patients who have not been diagnosed with cancer before.[21] Other electrolyte disorders may be seen in cancer patients, for example, dehydration can cause hypernatremia. Hypercalcemia of malignancy is a paraneoplastic syndrome and a common metabolic emergency.[22] Regular monitoring, timely treatment, and correction of the underlying cause of electrolyte imbalance is important to reduce morbidity and mortality in cancer patients.[23]

The major limitation of our study was the small sample size and its retrospective nature. We also did not include hematological malignancies and hospitalized patients. Because of increasing global cancer rates, we believe our study will help to

understand the importance of onco-nephrology despite these limitations.

CONCLUSION

As a result of the study, it was determined that those diagnosed with gastrointestinal and urogenital system cancer were consulted to nephrology more frequently. The fact that both chemotherapy-related toxicity/proteinuria and dehydration are more common in these cancers may explain this situation. As a result, clinical improvement was observed in the vast majority of patients and nephrologists should be involved in the management of cancer patients. Plans should include the development of training courses in epidemiology, patient monitoring, guidelines for the management of kidney patients with cancer and cancer patients with impaired kidney function.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Marmara University Ethics Committee (Protocol No. 09.2020.1009).

Informed Consent: Verbal informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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