Malignancy-associated kidney disease

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ABSTRACT

Malignancy or its treatment affect kidney in several ways. The most common are acute kidney injury and chronic kidney disease. Other form of kidney diseases can also be present such as nephrotic syndrome, tubulointerstitial nephritis, thrombotic microangipathy etc. In addition, electrolyte abnormalities such as hypercalcemia, hyponatremia and hypernatremia, hypokalemia and hyperkalemia, and hypomagnesemia. are observed. Treatment of malignancy associated kidney disease is usually symptomatic. Cessation of the offending agent or other supportive measures if needed i.e. renal replacement therapy are also implemented. .

Key words: malignancy, acute kidney injury, chronic kidney injury, glomerulopathy, thrombotic microangiopathy

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Kidney could be affected by malignancy or its treatment [1]. The most common kidney disease are acute kidney injury and chronic kidney disease as well as electrolyte abnormalities. However, nephrotic syndrome, isolated proteinuria, tubulointerstitial diseases, thrombotic micro-angiopathy and other syndromes can occur.

Acute kidney injury-AKI

Acute kidney injury (AKI) as defined by the RIFLE criteria, is observed in nearly 8 percent of hospitalized patients [2], and in more than 50 percent of patients in the ICU [3]. The two major causes of AKI developing in the hospital are prerenal disease and acute tubular necrosis (ATN). Together, they account for approximately 70 to 75 percent of all causes of AKI. [4,5]. In the PICARD cohort (Program to Improve Care in Acute Renal Disease) [6] the most common causes of AKI were ischemic acute tubular necrosis (including sepsis and hypotension), AKI due to unresolved prerenal factors (hypovolemia, hemorrhage), nephrotoxicity (radiocontrast nephropathy, rhabdomyolysis), AKI with cardiac disease (heart failure, shock), AKI with liver disease (hepatorenal syndrome, cirrhosis), and multifactorial etiologies. Outcomes of AKI ranged from recovery to death and include the development of CKD and progression to ESRD and requirement of renal replacement therapy. AKI is diagnosed in 5% in all hospitalized patients and up to 50% all ICU patients. In the last years a dramatic rise in prevalence of AKI is observed with mortality virtually unchanged within many years reaching up to 50-80% of all dialyzed ICU patients AKI may progress to ESRD, even subclinical episodes of AKI, which are common, may progress to ESRD.

As in any case causes of acute kidney injury in oncology patients are divided into: prerenal; intrarenal; and postrenal. Prerenal AKI may be due to either hypovolemia associated with vomiting and diarrhea associated with chemotherapy (often combined with inadequate fluid intake) [1]. Additionally, in certain malignancies hyperkalcemia is a common finding and may further worsen volume depletion. On the other hand, pharmacotherapy used in cancer patients may also be responsible for prerenal AKI. Commonly used pain killer such as nonsteroidal anti-inflammatory drugs may contribute to acute kidney injury in patients by affecting renal hemodynamics, and reducing effective circulating volume. Similarly, interleukin-2 reduces effective circulating volume due to a capillary leak syndrome. Myeloablative allogeneic hematopoietic cell transplantation could be complicated by hepatorenal syndrome i.e. a form of prerenal AKI [1].

Renal AKI could be divided into glomerular, tubulointerstitial, and vascular diseases in the course of malignancy. Glomerular disease in patients with malignancy, although infrequent [1,7-10], may be caused by viral infections and deposition of tumor antigens within the glomeruli, inducing antibody accumulation and activation of complement [8]. In a case of tumor-induced deposition, appropriate treatment of the disease usually is associated with improvement in kidney injury, while on the other hand, some chemotherapeutic agents such as cyclophosphamide may induce cancer, although typically several years later. Membranous glomerulopathy could be primary (idiopathic) or secondary. The latter one is associated with solid tumours such as BBB (breast, bowel, bronchi), or less often with a hematologic malignancy such as chronic lymphocytic leukemia. Two clinical scenarios are present, either development of membranous glomerulopathy precedes (even for a long time) evident malignancy or cancer has been already diagnosed. Thus diagnosis of membranous nephropathy, with clinically relevant proteinuria or nephrotic syndrome in particular in elderly should prompt to look for and rule out malignancy before any therapy is instituted. The same applies when minimal change disease is diagnosed in particular in elderly, patient should undergo screening for Hodgkin lymphoma or other lymphoproliferative disorders. It appears that abnormal T cells secrete lymphokine toxic to glomeruli. In solid tumors and lymphomas both membranoproliferative and rapidly progressive glomerulonephritis have been described [7,8]. Malignancy appears to be more frequent in patients diagnosed with ANCA vasculitis relative to other forms of vasculitis or general population [11]. Amyloidosis and light chain deposition disease may present as a nephrotic syndrome and/or acute kidney injury or chronic kidney disease. Light chain deposition disease (LCDD) affects both the glomeruli and tubules as a result of plasmatic dyscrasia seen in multiple myeloma or Waldenström's macroglobulinemia. Monoclonal light chains deposits are seen in primary amyloidosis (AL amyloidosis), while less common secondary amyloidosis has been associated with renal cell carcinoma, Hodgkin lymphoma, and chronic lymphocytic leukemia [7,9,12]. As in a case of prerenal AKI, certain drugs may cause renal AKI. High doses of intravenous bisphosphonates, particularly pamidronate, in patients with cancer was associated with focal segmental glomerulosclerosis (FSGS) in a collapsing subtype. It usually present as nephrotic syndrome with AKI. In patients with chronic kidney disease prior treatment, bisphosphonate doses should be appropriately adjusted according to kidney function and the medication should be given slowly. Monitoring of kidney function should be implemented with serial measurements of serum creatinine and urine protein excretion, regardless of the initial renal function.

Tubulointerstitial diseases besides elevation in serum creatinine i.e. AKI may present

also as bland or active urine sediment or leukocyturia. Tubular injury may result from acute tubular necrosis due to sepsis, shock, or nephrotoxic drugs, from drug-induced interstitial nephritis, or from other disorders that occur in patients with and without cancer. In malignancy, there are specific factors which may be responsible for tubular injury such as chemotherapy with cisplatin and ifosfamide, use of high doses of zolendronate, myeloma cast nephropathy, light chain deposition, tumor infiltration or lysozyme released from monocytic or myelomonocytic leukemia cells [13,14]. Cisplatin and ifosfamide, besides severe tubular damage resulting in acute kidney injury, can also cause electrolyte disorders such as hypokalemia and metabolic acidosis. Sometimes polyuria due to nephrogenic diabetes insipidus is observed. Acute tubular necrosis may be caused by high doses of intravenous bisphosphonates, particularly zoledronate [15]. The process underlying the cause of ATN is complex and includes several periods: prerenal (the impairment of perfusion), then onset, deepening and sustain of damage and finally repair of damage. The causes of acute tubular necrosis include: epithelial and endothelial damage due to tubules occlusion, impairment of microvascular flow, immunological and inflammation processes. Main histological changes of ATN are: merging and loss of tubular epithelial cells, focal dilatation of proximal tubules, partial occlusion of tubular lumens by cellular debris and multiple mitoses. The impairment of renal function is usually more marked than histological abnormalities. Moreover, microvascular endothelium is involved in pathogenesis of ATN [16,17]. In the course of multiple myeloma acute kidney injury results from a combination of tubular injury and tubular obstruction (by casts containing light chains). It may be precipitated hypercalcemia, hypovolemia, intravenous contrast, or nonsteroidal anti-inflammatory drugs. In acute leukemia or lymphoma infiltration of the kidney may occur, presenting as with acute kidney injury, a minimal degree of proteinuria and/or hematuria, and palpable enlarged kidneys [18, 19]. Renal outcome depends upon the response to radio- or chemotherapy, the prophylaxis of tumor lysis syndrome is essential to avoid postrenal AKI. In a case of enlarged kidneys and sings of acute kidney injury without known history of malignancy kidney biopsy should be performed to establish the diagnosis and introduced the proper therapy.

The most common vascular cause of AKI in patients with malignancy is thrombotic microangiopathy (TMA) in a form of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. TMNA could be either the effect of malignancy, in particular in the case of adenocarcinoma of the stomach, pancreas, or prostate or more commonly the effect of the therapy with mitomycin C, gemcitabine, Vascular endothelial growth factor (VEGF) inhibitors or radiation plus high-dose of cyclophosphamide for hematopoietic cell transplantation. TMA in this case usually presents as isolated proteinuria and hypertension, rather than kidney impairment. Course of TMA is often variable, because classical laboratory parameters are not always found (anemia, thrombocytopenia, elevated plasma lactate dehydrogenase, low serum haptoglobin, and schistocytosis), Sometimes development of hypertension in previously normotensive patient or worsening of preexisting hypertension may help with the diagnosis of TMA.

Postrenal AKI can be due to either intratubular or extrarenal obstruction. However, malignancy should be considered in any patient with bilateral urinary tract obstruction not due to urolithiasis without history of cancer. Uric acid crystals (in tumor lysis syndrome), light chain casts, or crystallization of certain drugs such as high dose methotrexate may cause intratubular obstruction. In tumor lysis syndrome intrarenal deposition of calcium phosphate is also observed. Tumor lysis syndrome is most common after induction of chemotherapy in high-grade lymphomas or acute lymphoblastic leukemia, however, it may also occur spontaneously with solid cancers with a high proliferative rate or large tumor burden. Severe hyperkalemia and hypocalcemia are the common laboratory findings. Extrarenal obstruction may result from several malignancies including gastrointestinal, urologic, or gynecologic, and usually indicates metastatic disease. Retroperitoneal fibrosis (Ormond's disease) may be either idiopathic or secondary to malignancy. It may not present with severe hydronephrosis and thus invasive diagnostic techniques can help to establish the diagnosis. On the other hand, urinary tract obstruction may unrelated to the malignancy in patients with cancer i.e, benign prostatic hypertrophy in men) [20].

Electrolyte disturbances in malignancy

The most common electrolyte disturbances in cancer are: hypercalcemia, hyponatremia and hypernatremia, hypokalemia and hyperkalemia, and hypomagnesemia. Hyperkalcemia, often found in various malignancies, is mainly due to release of parathyroid hormone related peptide (squamous cell, renal, breast, bladder, ovarian cancer, non-Hodgkin lymphoma, lymphoma, chronic myeloid leukemia, leukemia) or local osteolysis (mediated by cytokines, observed in breast cancer, multiple myeloma, leukemia, lymphoma) [21]. Less often is may be due to ectopic PTH secretion (ovarian, lung, rhabdomyosarcoma, neuroectodermal tumor, thyroid papillary cancer) or ectopic production of 1,25-dihydroxyvitamin D (calcitriol) in patients with lymphoma or ovarian dysgerminomas. Hypercalcemia results in AKI predominantly due to

renal vasoconstriction and hypovolemia. In addition, hypercalcemia in patients with cancer can lead to nephrogenic diabetes insipidus, similarly as in patients with primary or secondary malignancies in the brain (most often lung cancer, leukemia, or lymphoma) localizing in the hypothalamic-pituitary region; as well as neurosurgery for brain tumors is also an important.

Syndrome of inappropriate antidiuretic hormone (SIADH) is diagnosed in patients with small cell lung cancer and brain tumour. However, certain drugs such as high-dose intravenous cyclophosphamide and the vinca alkaloids (vinblastine, vincristine) may also be responsible for SIADH. Hyponatremia in patients with cancer may be associated with volume depletion due to gastrointestinal fluid losses and poor oral fluid intake. Similarly to hyponatremia, hypokalemia in cancer may be due to gastrointestinal fluid losses due to vomiting or diarrhea induced by chemotherapy. Renal potassium losses may be caused by ifosfamide, cisplatin, or lysozymuria in some patients with leukemia, [14,22]. Tumor lysis syndrome may produce hyperkalemia together with hyperphosphatemia, hypocalcemia, and hyperuricemia. Hypernatremia will occur if the patient does not have access to or cannot drink water. Hypomagnesemia found in the cancer patients may be a results of urinary magnesium wasting due to tubular injury in the course of chemotherapy, mainly with cisplatin, persisting even several years after treatment [23,24].

Malignancy or its treatment affect kidney in several ways. Acute kidney injury and chronic kidney disease as well as electrolyte abnormalities such as hypercalcemia, hyponatremia and hypernatremia, hypokalemia and hyperkalemia, and hypomagnesemia. are observed. Treatment of kidney disease in cancer is usually symptomatic. It include also cessation of the offending agent or other supportive measures if needed i.e. renal replacement therapy.

Conflicts of interest

The authors declare that there no conflicts of interest associated with the publication of this paper.

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