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Sickle Cell Disease and the Kidney

By Pooja Amarapurkar, Pooja Kalantri, Levard Roberts, and Jose Navarrete

Sickle cell disease and sickle cell trait are associated with several kidney abnormalities. The inner medullary environment of the kidney with low oxygen tension, hyperosmolarity, and acidemia is an ideal setup for hemoglobin polymerization and sickling. Repeated hemolysis, vaso-occlusive episodes, subsequent reperfusion injury, oxidative stress, and inflammation lead to acute and chronic kidney disease (CKD) (1, 2). The various kidney manifestations of sickle cell disease are summarized in Table 1.

Glomerular hyperfiltration and lower mean arterial pressure occur in early years of life. With advancing age, a decline in glomerular filtration rate (GFR) is noted (1–3). Approximately 60% of all patients with sickle cell disease over the age of 45 have some amount of albuminuria. There is a steeper decline in kidney function among adults with albuminuria compared with those without (4).

CKD in sickle cell disease is highly influenced by genetic factors. Coinheritance of alpha-thalassemia is associated with a reduced risk of hemolysis and protection from albuminuria (5). The presence of haplotypes of the APOL1 gene, MYH9 gene, and polymorphism in the bone morphogenic protein receptor 1B promotes albuminuria and CKD in patients with sickle cell disease (6).

The occurrence of nephrotic syndrome due to sickle cell disease is uncommon and is associated with a poor kidney outcome. Human parvovirus B19 infection is an important cause of nephrotic syndrome in this population (7). Sickle cell disease-related end stage kidney disease accounts for 0.1% of the dialysis population in the United States (8). These patients are younger and have high mortality (9). Acute kidney injury (AKI) may occur in approximately 2.3%–13.6% of patients with sickle cell disease who are admitted for vaso-occlusive episodes or acute chest syndrome. Figure 1 describes the pathophysiology of AKI in sickle cell disease (10).

Patients with sickle cell disease should be screened for proteinuria annually starting at age 10. A combination of cystatin C-creatinine-based GFR, a trend rather than an absolute value of creatinine and trend in albuminuria, is preferred to diagnose and follow kidney disease in sickle cell disease. Albuminuria >300 mg/g, decline in kidney function, nephrotic syndrome, persistent hematuria, and hypertension must prompt referral to nephrology (11, 12). Hemodialysis and peritoneal dialysis are well tolerated (13).

Increased incidence of APOL1 risk alleles, higher infection risk, blood group incompatibility, pulmonary hypertension, and inability to tolerate side effects of immunosuppressive drugs are some reasons for lower rates of transplantation in sickle cell disease. Even with these limitations, patients have significantly better outcomes after kidney transplant compared with dialysis (14).

There is no specific treatment for sickle cell disease-related kidney disease. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers remain the mainstay therapy. With patients living longer, the burden of CKD is increasing in this population. Thus, a multidisciplinary approach with hematologists and nephrologists is needed to manage these patients. At our institution, Emory University School of Medicine, we have successfully implemented a CKD clinic for sickle cell disease patients. This clinic has improved access and timeliness to nephrology care. It serves as a great platform for epidemiological, clinical, and basic science research and helps deliver comprehensive care to patients with sickle cell disease. We hope to collaborate with other centers to improve care for this vulnerable population. ■

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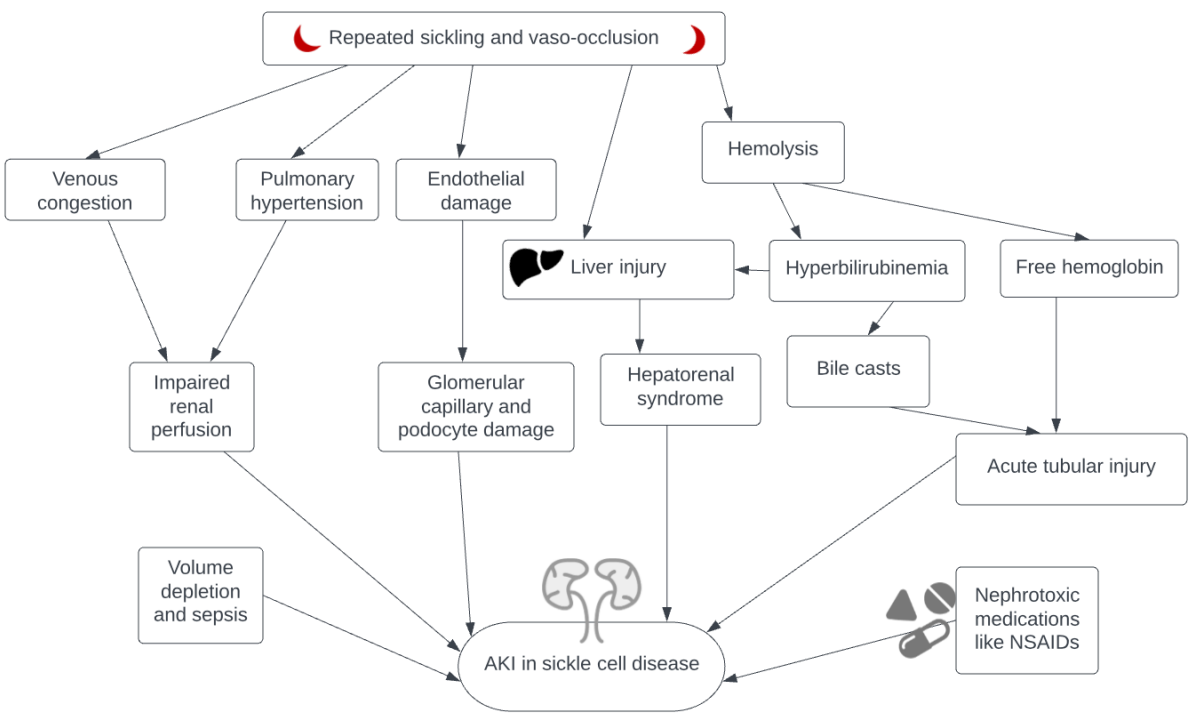
Table 1. Kidney manifestations of sickle cell disease

Glomerular hyperfiltration: Early childhood and young adults
Albuminuria
Glomerular pathology: • Focal segmental glomerulonephritis • Membranoproliferative glomerulonephritis • Thrombotic microangiopathy
Proximal tubular hyperfunction: • Increased phosphate secretion • Increased creatinine secretion
Tubular iron deposits
Hyposthenuria (decreased urinary concentration ability)
Impaired distal tubular hydrogen ion and potassium handling (hyperkalemia and metabolic acidosis)
Hematuria
Renal papillary necrosis
Renal medullary carcinoma

Figure 1. Pathophysiology of acute kidney injury in sickle cell disease



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Overview of Onconephrology in Europe: An Essential Subspecialty with Increasing Importance

By Sheila Bermejo

Cancer is a worldwide epidemic that has increased its prevalence exponentially over the last decades. In 2020, 19.3 million new cases of cancer were diagnosed, and there were 10 million deaths from cancer worldwide (1). Cancer patients are susceptible to chemotherapy and immunotherapy treatments that can cause renal complications, such as acute kidney injury (secondary to glomerular disease, acute interstitial nephritis, or acute tubular necrosis), electrolyte disorder, proteinuria, and others (2). Additionally, a higher prevalence of cancer has been demonstrated in patients with chronic kidney disease from various types, those with a kidney transplant, and patients on kidney replacement therapy (Figure 1). Because of a lack of randomized clinical trials that test oncologic treatments in the population with renal diseases, patients with a lower glomerular filtration rate have less opportunity to receive some oncologic treatments. Thus, it is important to optimize their renal function with nephrologist intervention.

For these reasons, multidisciplinary care is important for cancer patients with diminished kidney function. Based on this idea, onconephrology was born. Onconephrology was originally considered a subspecialty that has increased in importance over the last decade, with the purpose to address accurate care of cancer patients and to diagnose and prevent complications. This increase in interest and importance of onconephrology has been evident in multiple ways (3). For example, the number of oral presentations dedicated to onconephrology topics at ASN Kidney Week has increased in the last several years. Likewise, this is also seen in Europe. During the last two European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congresses (2020 and 2021), there has been an increase in onconephrology topics. In 2020, ERA-EDTA offered a symposium, "New immune therapies and onconephrology." In addition, a pre-congress course was dedicated to onconephrology (4). During the most recent congress in 2021 (58th ERA-EDTA Congress), there was a symposium dedicated to onconephrology with three lectures and a second symposium, entitled "AKI in special situations," in which one of the lectures was "AKI in oncology patients" (5).

The recent formation of the American Society of Onconephrology (ASON) in the United States demonstrates the advances of this subspecialty, but this type

Figure 1. The spectrum of renal diseases in cancer patients

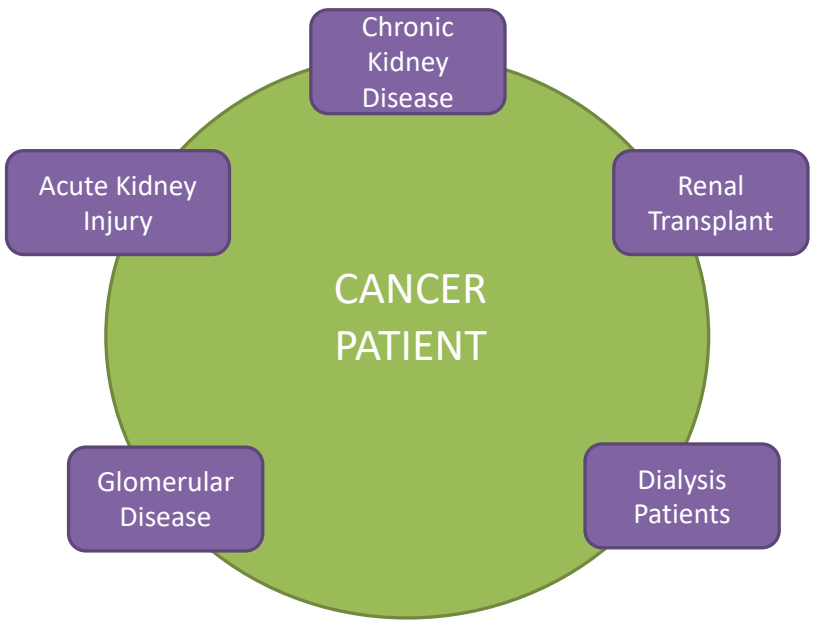

Figure 2. Distribution of onconephrology articles published in recent years in two European journals