The role of Contrast-Enhanced Ultrasound for evaluating renal perfusion dynamics in partially reversible acute cortical kidney ischemia in a patient with sepsis

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Introduction

Sepsis represents a life-threatening organ dysfunction determined by a maladaptive systemic inflammatory host response to infection. One of the most common organ dysfunctions is acute kidney injury (AKI), responsible for the high rate of mortality in sepsis [1,2].

The physiopathology of sepsis-induced AKI is still not completely understood. Nevertheless, the implication of multiple mechanisms, including activation of blood coagulation, inflammation and glomerular endothelial cells damage, are generally accepted [2]. Sustained activation of coagulation pathways may lead to disseminated intravascular coagulation (DIC), while endothelial cell damage induces platelets aggregation and thrombotic microangiopathy (TMA), both responsible for widespread microvascular thrombosis in different organs, including kidneys [3,4].

In these circumstances, diagnostic imaging of AKI is challenging and always limited. Imaging techniques are used to describe the morphology, function and perfusion status of the kidneys. Contrast-enhanced computed tomography (CT) is considered the “gold standard” in many kidney pathologies but in the case of AKI, administration of iodinated contrast agents increases the risk of further kidney function impairment [5]. Currently, contrast-enhanced ultrasound (CEUS) is regarded as the modality of choice for evaluating patients with AKI, considering its lack of nephrotoxicity and excellent sensitiv-
Laboratory findings revealed increase in serum creatinine within 48 hours (from 1.74 mg/dl to 6.02 mg/dl), which, along with persistent anuria, suggested the acute onset of AKI. Elevated inflammatory markers and leukocytosis were present, which, in context of the organ dysfunction (SOFA score ≥2), unraveled sepsis. Impaired coagulation was observed, including prolonged prothrombin time, as well as a highly increased D-dimer level, decreased fibrinogen and thrombocytopenia, revealing the presence of overt DIC. In addition, evidence of marked anisocytosis and schistocytes (10%) in the peripheral blood smear, together with rapid development of hemolytic anemia, suggested TMA overlap. The Coombs test was negative. Regarding the etiology of sepsis, successive blood and urine cultures were collected along with assessment of multiple viral and autoimmune seric markers. All tested negative.

A B-mode ultrasound of the kidneys revealed loss of corticomedullary differentiation, while color Doppler ultrasound indentified bilateral hypovascularity of the renal parenchyma (fig 1). Accordingly, CEUS was performed, using 1.6 ml of SonoVue injected intravenously (SonoVue, Bracco Imaging S.p.A, Milan, Italy). Absence of contrast agent enhancement in the bilateral renal cortex, with homogeneous enhancement of the medulla, demonstrated acute onset of renal cortical ischemia (fig 2a). The circulatory pattern of the kidneys was finer depicted by the parametric perfusion map, demonstrating increased hilar perfusion in contrast with loss of perfusion in the renal cortex (fig 2b).

Consequently, emergency restoration of fluid and electrolyte balance was initiated, together with empirical antibiotics. In spite of intense hydration and stimulation of diuresis, the patient presented persistent anuria. She was, therefore, referred to the Nephrology Department in order to start dialysis. Erythrocyte mass transfusion was indicated for correcting the rapidly evolving hemolytic anemia, while fresh frozen plasma was administrated for the coagulation disorders. Persistence of severe infection required administration of broad-spectrum antibiotics. In response to therapy, the clinical and biological findings improved, as evidenced by the normalization of coagulation parameters and amelioration of hemolysis. Severe infection was successfully controlled.

Nevertheless, after four weeks of repeated hemodialysis, increased creatinine level persisted (5.8 mg/dl), along with a gradual increase in urine output. Color Doppler ultrasound revealed presence of vascular signal in the renal parenchyma, indicating resumption of the vascular flow (fig 3a). Additionally, CEUS emphasized homogeneous enhancement of the whole renal cortex during the arterial phase, suggesting “desobstruction” of the kidney microcirculatory system (fig 3b). The situation was interpreted as a partially reversible renal cortical ischemia in the context of persistent impaired kidney function.

**Discussion**

Sepsis represents the most frequent cause of AKI in critically ill patients. It associates a dysregulated inflammatory host response to infection, which leads to over
expression of inflammatory mediators, subsequent coagulation pathway activation and onset of DIC [2,3]. Moreover, sepsis induces damage of the endothelial glycocalyx layer and exposure of endothelial adhesion molecules, determining increased platelets aggregation and local microthrombi formation, with development of TMA [8].

Commonly, the differential diagnosis between DIC and TMA is difficult, the two pathologies often being associated [9]. Abnormal values of the coagulation tests, including D-dimers, prothrombin time and fibrinogen, are suggestive of DIC, TMA generally presenting normal values [4]. Microangiopathic hemolytic anemia, demonstrated by the presence of fragmented red blood cells (schistocytes) in the peripheral blood smear, is a frequent association in DIC patients, yet invariably associates with TMA, <1% schistocytes being in favor of isolated DIC, while ≥1% suggesting TMA associated with DIC [10].

In acute cortical kidney ischemia, color Doppler ultrasound is the first imaging technique used to evaluate focal perfusion defects. It is characterized, however, by decreased diagnostic sensitivity in cases of slow blood flows, with limitations such as angle dependency and attenuation of ultrasounds [11,12]. According to the latest EFSUMB Guidelines, CEUS is considered an excellent diagnostic technique for detecting acute parenchymal ischemia of the kidney, similar to CT imaging, being able to overcome the limitations of conventional Doppler ultrasound [11].

Ultrasound contrast agents have the particularity of being eliminated by exhalation through the lungs, avoiding the kidneys and are, therefore, suitable in cases of impaired kidney function [5,11]. However, intravenous administration of SonoVue is not being licensed in pregnancy, while breastfeeding represents a contraindication in some countries [7]. Both macro- and microvasculature of the kidneys are visualized in real time by CEUS. The contrast agent is initially visible in the renal artery and its main branches, followed by rapidly enhancement of the renal cortex. Complete cortical enhancement is acquired at the end of the cortical phase, 15-30 s after contrast administration. The parenchymal phase starts with enhancement of outer medulla, followed by progressive fill in of renal pyramids, 25 s–4 min after contrast injection [11]. In acute cortical ischemia, CEUS excellently depicts an unenhanced peripheral cortical continuous rim viewed in all phases, in an otherwise enhanced kidney, allowing a fast and reliable diagnosis [12].

In conclusion, in patients who developed AKI in the context of unspecified etiology sepsis, CEUS can represented an excellent imaging technique to diagnose acute renal cortical ischemia in an emergency. Moreover, the value of CEUS in depicting the partial remission of cortical thrombotic process over time must be highlighted.

References
1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-810.
2. Majumdar A. Sepsis-induced acute kidney injury. Indian J Crit Care Med 2010;14:14-21.
3. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis-Associated Disseminated Intravascular Coagulation and Thromboembolic Disease. Medit J Hemat Infect Dis 2010;2:e2010024.
4. Sakamaki Y, Konishi K, Hayashi K, et al. Renal thrombotic microangiopathy in a patient with septic disseminated intravascular coagulation. BMC Nephrol 2013;14:260.
5. Chang EH, Chong WK, Kasoji SK, et al. Diagnostic accuracy of contrast-enhanced ultrasound for characterization of kidney lesions in patients with and without chronic kidney disease. BMC Nephrol 2017;18:266.
6. Girometti R, Stocca T, Serena E, Granata A, Bertolotto M. Impact of contrast-enhanced ultrasound in patients with renal function impairment. World J Radiol 2017;9:10-16.
7. Piscaglia F, Nolsøe C, Dietrich CF, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): Update 2011 on non-hepatic applications. Ultraschall Med 2012;33:33-59.

Fig 3. a) Color Doppler ultrasound indentified normal vascular signal in the renal parenchyma, indicating resumption of the vascular flow; b) CEUS demonstrated homogeneous enhancement of the entire renal cortex during the arterial phase, suggesting „desobstruction” of the kidney microcirculatory system
8. Gómez H, Kellum JA. Sepsis-induced acute kidney injury. Curr Opin Crit Care 2016;22:546-553.
9. Wada H, Matsumoto T, Suzuki K, et al. Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy. Thromb J 2018;16:14.
10. Lesesve J, Martin M, Banasiak C, et al. Schistocytes in disseminated intravascular coagulation. Int J Lab Hematol 2014;36:439-443.
11. Sidhu PS, Cantisani V, Dietrich CF, et al. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Short Version). Ultraschall Med 2018;39:154-180.
12. Siracusano S, Bertolotto M, Ciciliato S, Valentino M, Liguori G, Visalli F. The current role of contrast-enhanced ultrasound (CEUS) imaging in the evaluation of renal pathology. World J Urol 2011;29:633-638.