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Original Investigation

Acute Kidney Injury in Adults With Hemophagocytic Lymphohistiocytosis

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Background: Acute kidney injury (AKI) in the setting of hemophagocytic lymphohistiocytosis (HLH) is poorly characterized. This study aims to describe the incidence, clinical and biological features, and outcome associated with AKI in this population.

Study Design: Case series.

Setting & Participants: Patients with secondary HLH admitted to a single center from February 2007 through January 2013. 95 patients were included in the study.

Predictor: AKI.

Outcomes: Recovery of kidney function, 6-month mortality, and complete remission of the underlying disease.

Measurements: AKI was defined according to the KDIGO 2012 guideline. Recovery of kidney function was defined as improvement in serum creatinine level, with return to baseline serum creatinine level ±26.5 μmol/L.

Results: HLH was related to hematologic malignancy in 73 (77%), infectious disease in 21 (22%), and autoimmune disease in 9 (10%) patients and was multifactorial in 10 (11%) patients. The cause was undetermined in 2 (2%) patients. The incidence of AKI during HLH is high (62%), and 59% of the AKI population required renal replacement therapy. Main causes of AKI were acute tubular necrosis (49%), hypoperfusion (46%), tumor lysis syndrome (29%), or HLH-associated glomerulopathies (17%). At 6 months, 32% of the patients with AKI had chronic kidney disease. Two factors were associated independently with 6-month mortality by multivariable analysis: AKI stage ≥ 2 (OR, 2.61; 95% CI, 1.08-6.29; $P = 0.03$) and an underlying hematologic malignancy (OR, 3.1; 95% CI, 1.05-9.14; $P = 0.04$). In patients with hematologic malignancy, AKI was associated with lower 6-month complete remission (non-AKI, 25%; AKI patients, 5%; $P = 0.05$).

Limitations: Retrospective study, lack of histologic data.

Conclusions: AKI in patients with HLH is frequent and adversely affects remission and survival. Early intensive management, including administration of etoposide, nephrotoxic drug withdrawal, prevention of tumor lysis syndrome, or aggressive supportive care, might improve kidney function and survival.

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INDEX WORDS: Hemophagocytosis; hemophagocytic lymphohistiocytosis (HLH); acute kidney injury (AKI); AKI etiology; renal failure; renal replacement therapy (RRT); kidney disease outcome; prognosis; mortality; remission; hematological malignancy.

The pathophysiology of hemophagocytic lymphohistiocytosis (HLH) involves natural killer cell and cytotoxic T-cell dysregulation with uncontrolled lymphocyte and histiocyte activation and proliferation, which results in cytokine overproduction and hemophagocytosis.[1-6] HLH is either primary, as seen in several genetic diseases affecting the cytotoxic pathway preferentially in children,[7] or secondary to an underlying disorder, primarily malignancy, severe infection, or autoimmune disease in adults.[8-12] Clinical symptoms usually include fever, lymphadenopathy, hepatosplenomegaly, jaundice and sometimes skin rash, neurologic symptoms, hemodynamic failure and acute kidney injury (AKI).[11,13-17] Biological symptoms include pancytopenia, hypofibrinogenemia sometimes leading to disseminated intravascular coagulation, hyperferritinemia, hypertriglyceridemia, liver test result abnormalities, and hyponatremia.[1,3,14,18,19] Diagnosis of HLH, first defined by the FHL (Familial HLH) Study Group of the Histiocyte Society,[20] associates clinical and biological criteria, including histologic evidence of hemophagocytosis.[20] Because HLH may lead to multiple-organ failure[21] with high mortality rates (up to 50%),[11,12,22]

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patients often require intensive care unit (ICU) admission.

Data concerning AKI during HLH are scarce. Glomerulopathies and tubulointerstitial lesions associated with HLH, including acute tubular necrosis, have been reported previously.[17,23] At least 30% of patients with HLH seem to be affected by AKI, but definitions used in previous studies were restrictive.[11,24] Therefore, incidence, characteristics, and outcome of AKI in patients with secondary HLH remain unknown. To this end, we conducted a retrospective study in 95 patients with secondary HLH admitted to our ICU. We determined the incidence, clinical and biological features, and outcome associated with AKI in this population.

METHODS

This retrospective cohort was performed in the medical ICU of the Saint-Louis University Hospital, Paris, France, a 650-bed public hospital with 330 beds for patients with hematologic malignancies and solid cancers. The ICU is a 12-bed medical unit that admits 750 to 850 patients per year, of whom about one-third have hematologic malignancies.

Patients

We included all adults with secondary HLH admitted to our ICU from February 2007 through January 2013. We defined HLH according to the HLH-2004 criteria,[25] meaning 5 of these 8 criteria: fever, splenomegaly, cytopenia affecting at least 2 lineages (hemoglobin < 9 g/dL, platelets $< 100 \times 10^9$/L, and neutrophils $< 1.0 \times 10^9$/L), hypertriglyceridemia with triglyceride level ≥ 3 mmol/L and/or hypofibrinogenemia with fibrinogen level ≤ 1.5 g/L, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer cell activity, ferritin level ≥ 500 mg/L, and soluble CD25 level $\geq 2{,}400$ U/mL. Our hospital policy is to admit to the ICU all patients with HLH with a diagnosis of at least 1 organ failure before being transferred in the department of clinical immunology. In consequence, during the study period, 93% of patients fulfilling diagnostic criteria of HLH were admitted to the ICU. In patients with multiple HLH episodes, only the first episode was recorded. All patients were managed by the ICU team together with the hematology-immunology team. The diagnosis of HLH was confirmed by at least 1 senior hematologist (L.G. and D.B.) and 1 senior intensivist (E.A., L.Z., and E.C.). No data allowing patient identification were collected.

In order to evaluate the true incidence of AKI induced by HLH, we compared the incidence of AKI in this cohort with a cohort of 202 patients admitted to the ICU with newly diagnosed high-grade malignancy and without HLH. This cohort includes 169 patients admitted between 2007 and 2010 who have been reported previously[26] and has been completed with 33 patients admitted between 2011 and 2013.

Definitions

As mentioned, HLH was defined according to the HLH-2004 definition.[25]

Definition and staging of AKI were defined according to the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) guideline.[27] Decisions regarding the initiation, discontinuation, and modalities of renal replacement therapy (RRT) were made by senior nephrologists (F.A., L.Z., M.-N.P., and E.C.), based on the guidelines from Bellomo and Ronco.[28] The creatinine value used for baseline was the value obtained 3 months before ICU admission. The serum creatinine assay was traceable to an isotope-dilution mass spectrometry reference measurement procedure.

Proteinuria was defined as protein-creatinine ratio > 30 mg/mmol or protein excretion > 0.3 g/d. Nephrotic-range proteinuria was defined as protein-creatinine ratio > 300 mg/mmol or protein excretion > 3.0 g/d.

Tumor lysis syndrome was defined according to the Cairo-Bishop criteria.[29]

Thrombotic microangiopathy was defined as thrombocytopenia and microangiopathic nonimmune hemolytic anemia.

The diagnosis of acute tubular necrosis was based on the following: the history and course of events that resulted in decreased tissue perfusion and subsequent postischemic acute tubular necrosis; no evidence of another cause of AKI, such as glomerulonephritis, acute interstitial nephritis, thrombotic microangiopathy, or urinary tract obstruction; to discriminate prerenal disease (hypoperfusion) from acute tubular necrosis, we looked at urinalysis findings (eg, urine sodium/potassium concentration, fractional excretion of sodium, and fractional excretion of urea) and the response to fluid repletion (if sufficient fluid was given to reverse any signs of volume depletion [eg, hypotension, low fractional excretion of sodium, and urine-sodium concentration]), and return of serum creatinine level to baseline within 24 to 72 hours was considered to represent correction of prerenal disease, whereas persistent AKI was considered to represent acute tubular necrosis; and duration of kidney failure (typically 7-21 days).

The diagnosis of glomerulopathy was based on urine sediment and degree of proteinuria. Patients with a persistent nephrotic pattern were classified in this category.

Regarding kidney infiltration malignancy, the presence of large kidneys without hydronephrosis on imaging in a patient with known lymphoma was suggestive of tumor infiltration. A rapid reduction in kidney size and improvement in kidney function within days after chemotherapy was started confirmed the diagnosis.

Urinary tract obstruction was defined as AKI associated with dilatation of the collecting system in one or both kidneys, assessed by imaging.

Clinical and Laboratory Parameters

The data in Tables 1-4 were abstracted from the medical records. Demographic parameters, medical history, presenting symptoms, and treatments were collected. All laboratory data in Table 2 were recorded at admission. Serum creatinine level was recorded within 3 months before admission and at admission, ICU discharge, 3 months, 6 months, and last follow-up. Recovery of kidney function was determined according to the AKI criteria, if serum creatinine level during follow-up was equal to the previous serum creatinine level $\pm$ 26.5 μmol/L (0.3 mg/dL). If hemodialysis therapy was withdrawn with return to baseline kidney function, recovery of kidney function was considered complete. Sequential Organ Failure Assessment (SOFA) parameters were collected on day 1.[30] Vital status at ICU discharge, hospital discharge, and last follow-up were determined from medical records and the outpatient clinic electronic database.

Treatment

All patients received full-code management. The period and duration of use of life-sustaining interventions (mechanical ventilation, vasoactive agents, and RRT) were collected. Chemotherapy was prescribed by the hematologist in charge of the patient, according to the best standard of care.

Statistical Analysis

Patient characteristics at ICU admission are described as median and interquartile range (IQR) for quantitative variables and