

Nicolas Lerolle
Dominique Nochy
Emmanuel Guérot
Patrick Bruneval
Jean-Yves Fagon
Jean-Luc Diehl
Gary Hill

Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration

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Present Address:

N. Lerolle (✉)
Département de Réanimation Médicale
et de Médecine Hyperbare,
Centre Hospitalo-Universitaire d'Angers,
49933 Angers Cedex, France
e-mail: nilerolle@chu-angers.fr
Tel.: +33-2-41354503
Fax: +33-2-41354083

N. Lerolle · D. Nochy · E. Guérot ·
P. Bruneval · J.-Y. Fagon · J.-L. Diehl
Faculté de Médecine, Université Paris
Descartes, Paris, France

N. Lerolle · E. Guérot · J.-Y. Fagon ·
J.-L. Diehl
Service de Réanimation Médicale, Hôpital
Européen Georges Pompidou, 20, rue
Leblanc, 75908 Paris Cedex 15, France
e-mail: nicolas.lerolle@egp.aphp.fr

D. Nochy · P. Bruneval · G. Hill
Laboratoire d'Anatomopathologie,
Assistance Publique-Hôpitaux de Paris,
Hôpital Européen Georges Pompidou, Paris,
France

Abstract *Purpose:* Septic shock is one of the leading causes of acute kidney injury. The mechanisms of this injury remain mostly unknown notably because of the lack of data on renal histological lesions in humans. *Methods:* Kidney biopsy was performed immediately post-mortem in consecutive patients who died of septic shock. Comparisons were made with specimens from eight patients who died of trauma on scene and nine ICU patients that died of non-septic causes. *Results:* Nineteen septic patients were included, 11 were male, and age was 72 ± 12 years. Anuria occurred in all patients 2.2 ± 1.4 days before death. Seven patients had disseminated intravascular coagulation. In all patients we observed (1) acute tubular lesions whose intensity correlated with blood lactate concentration; (2) intense infiltration by leukocytes, mainly monocytic, in glomeruli and interstitial capillaries as compared to

controls; (3) presence of tubular cell apoptosis proved by the presence of apoptotic bodies (2.9% of tubular cells) significantly more frequently than in controls and confirmed by TUNEL and activated caspase-3 staining. Arteriolar/arterial thromboses were observed in only 4 of 19 patients, without any association with presence of disseminated intravascular coagulation. *Conclusions:* Kidney lesions in septic shock go beyond those associated with simple acute tubular injury, notably capillary leukocytic infiltration and apoptosis. Vascular thrombosis, however, did not appear to play a major role in the majority of patients. The extent to which these lesions are specific to sepsis or are common to all multi-organ failure independent of its cause is yet to be elucidated.

Keywords Kidney pathology · Septic shock · Critical care medicine · Acute kidney injury · Apoptosis · Acute tubular necrosis

Introduction

Severe sepsis and septic shock are the leading causes for acute kidney injury (AKI) in critically ill patients [1, 2],

although there is little direct knowledge of the pathogenesis of this subset of AKI in humans. Notably, there is a paucity of histopathological data in humans, most coming from studies before 1980 that focused mainly on

tubular lesions [3–10]. Animal models have since directed attention to other lesions, such as apoptosis, leukocytic infiltration and thrombus formation [1, 11, 12]. However, the relevance of these features, notably apoptosis, to human organ dysfunction is debated [13]. Presence of occluding thrombi as a consequence of intense coagulation activation is frequently cited in the literature, but has seldom been shown in humans so far [14].

Therefore, in order to reassess the array of kidney lesions associated with septic shock and their correlation with clinical and biological parameters, we systematically performed immediate post-mortem kidney sampling in patients dying of septic shock.

Materials and methods

This prospective study was conducted in a 20-bed medical intensive care unit from December 2004 to April 2005. All patients who died of septic shock, as defined by the criteria of the Society for Critical Care Medicine/American College of Chest Physicians [15], and free of chronic renal insufficiency (serum creatinine $<105 \mu\text{mol/l}$ prior to shock onset) were considered. In accordance with French law, family members were questioned and the national file for refusal of post-mortem sampling investigated to determine if the deceased had previously disclosed refusal to allow procedures to be performed for research purposes. Written consent was obtained from the families. The study was registered with the French biomedical agency.

Kidney biopsy processing and histologic lesions

Percutaneous kidney biopsies were performed within 30 min following death with an automatic biopsy system (Achieve, Cardinal Health, Dublin, OH). Specimen processing and analysis are detailed in the Electronic Supplementary Material 1. In brief, after standard embedding and staining, all of the slides were reviewed by two experienced kidney pathologists (DN, GH) blinded to the clinical and laboratory data. A variety of morphological lesions, including glomerular, arterial, arteriolar, kidney tubular and interstitial, was assessed and evaluated semi-quantitatively or quantitatively. Presence of apoptosis was assessed by three different techniques: (1) routine microscopy, (2) TUNEL (terminal-deoxynucleotidyl-transferase-mediated dUTP–digoxigenin nick end labeling) and (3) activated caspase 3 labeling.

Characteristics of studied patients

Clinical and biological data were extracted from medical files. Specifically, initial severity at shock onset was

evaluated with the Simplified Acute Physiologic Score (SAPSI) and Organ Dysfunction and Infection (ODIN) score [16, 17]; fractional excretion of Na, urine/plasma creatinine ratio and proteinuria, based on the last urine sample available before death, were recorded. Disseminated intravascular coagulation (DIC) was evaluated based on the score of the International Society for Thrombosis and Hemostasis [18]. The worst score recorded during shock was used in this study. The length of terminal hypotension preceding death (systolic blood pressure below 60 mmHg) was recorded.

Kidney failure was diagnosed according to the RIFLE-Failure criteria: increase in serum creatinine (SCr) $\times 3$ or $\text{SCr} > 350 \mu\text{mol/l}$ or urine output $<0.3 \text{ ml/kg/h} \times 24 \text{ h}$ or anuria $\times 12 \text{ h}$ [19]. The decision to start renal replacement therapy (RRT) was based upon local guidelines: urine output $<20 \text{ ml/h} \times 12 \text{ h}$ or $\times 6 \text{ h}$ if serum potassium $>5.5 \text{ mmol/l}$, or $\text{SCr} >450 \mu\text{mol/l}$ on two consecutive determinations, despite adequate resuscitation. RRT was continuous hemodiafiltration in all cases.

Control patients

In an attempt to discriminate renal lesions relevant to the septic shock from agonal phenomena, we compared our septic patients with two groups of control patients. First, nine patients who had died in the ICU of other causes than septic shock and without multi-organ failure or severe AKI were biopsied in the same way as septic patients within 30 min following death (herein referred as “ICU control patients”). Second, eight autopsy specimens from eight patients who died suddenly of trauma (motor vehicle accident, gunshot wound) on scene were obtained from the Maryland Medical Examiners’ Office, Baltimore, Maryland (herein referred as “trauma patients”). The average post-mortem interval for these patients was $8 \pm 6 \text{ h}$. The specimens in both groups were analyzed in the same fashion as the biopsies from the septic shock patients, except for TUNEL and activated caspase-3 staining, which were performed in ICU control patients only.

Statistical analyses

Data are presented as mean \pm standard deviation (SD). Statistical analyses were performed using Statistica 6.0 (Statsoft, Tulsa, OK). Biological and clinical parameters that could be involved in the pathogenesis of kidney injury were tested for correlation with pathologic changes: infection site, type of microorganism, overall duration of shock (length of time on vasopressor), duration of terminal hypotension, presence of DIC, lactate concentration on the day before death, hydroxyethyl starch use, administration of iodinated contrast media and

RRT use. In another analysis, urinary parameters (creatinine, sodium, protein) were tested for association with kidney lesions as candidate markers of kidney injury. Correlations between continuous variables were tested using the Pearson correlation coefficient. Correlations involving categorical variables (e.g., use of RRT) were tested using Spearman rank order correlation. Only univariate analysis was performed. Finally, comparisons of histological lesions between septic patients and controls were performed using standard *t* tests. A value of $P < 0.05$ was considered significant.

Results

Kidney biopsy was performed in 19 patients who died of septic shock (Table 1). None received drotrecogin alpha. Epinephrine was the only vasopressor used in all cases. All patients met RIFLE-Failure criteria because of anuria for a mean of 2.2 ± 1.4 days before death. Although all patients reached the indications for RRT, only 11 were treated with RRT for 1.1 ± 1.4 days. The remaining eight patients showed marked hemodynamic instability and were felt to be moribund at the time RRT was considered, so that it was not undertaken.

Table 1 Characteristics of the 19 patients who died of septic shock

Characteristics	
Age (years)	72 ± 12
Males (<i>n</i>)	11
Comorbidities (<i>n</i>)	
Diabetes	3
Hypertension	6
Atherosclerosis (any location)	6
Neoplasia	5
Baseline serum creatinine ($\mu\text{mol/l}$)	65 ± 18
SAPS II at shock onset	77 ± 23
ODIN score at shock onset	4.4 ± 1
Site of infection (<i>n</i>)	
Pneumonia	12
Intra-abdominal	4
Meningococemia	1
Catheter-related septicemia	1
Limb fasciitis	1
Microorganism (<i>n</i>)	
Gram-negative bacilli	6
Gram-positive cocci	6
Association of both	4
Candida albicans	1
Neisseria meningitidis	1
None identified	1
Nosocomial infection (<i>n</i>)	10 (53%)
ISTH DIC ^a score ≥ 5 (<i>n</i>)	7 (37%)
Duration of vasopressor ^b (h)	60 ± 45
Terminal hypotension (h)	5 ± 2.6

^a International Society for Thrombosis and Hemostasis Disseminated Intravascular Coagulation

^b Vasopressor onset-death time interval

Pathologic observations

Glomerular lesions

The median number of glomeruli was 51 per biopsy (minimum 21). Glomerular capillaries showed prominent infiltration with monocyte/macrophages and PMNs (Fig. 1). Fibrin deposition (tactoids) in the capillary lumens was seen in eight (42%) patients. Only one patient had glomerular capillary thrombi.

Tubular lesions

Proximal and distal tubules in all patients showed the changes usually associated with acute tubular injury: loss of brush border, frank necrosis and dilatation of the tubules with variable flattening of the cytoplasm. Cytoplasmic debris, macrophages and hyaline casts were seen in tubular lumens without evidence of upstream tubular dilatation (see Electronic Supplementary Material 2). In 7/19 patients, tubular lesions were so severe as to give an appearance customarily associated with postmortem autolysis: tubular cytoplasmic degeneration and detachment from tubular basement membranes (Fig. 2). All patients showed tubular vacuolization.

Apoptosis

Apoptotic bodies, defined on routine light microscopy as cells having nuclear shrinkage and/or fragmentation and cytoplasmic condensation, usually with a hyaline quality, were observed in proximal and distal tubules of all septic

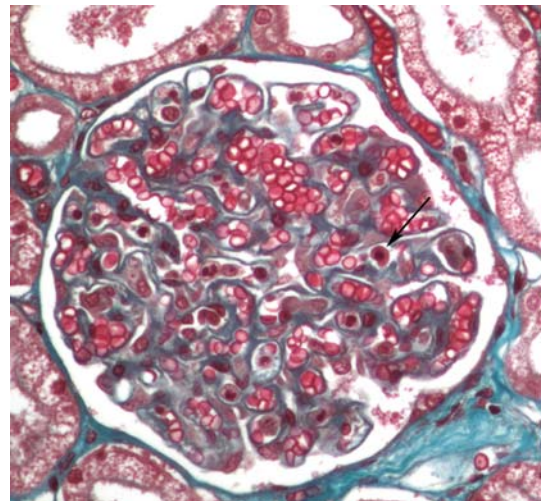


Fig. 1 Glomerulus with extensive capillary leukocytic infiltration; some leukocytes are apoptotic (arrow). In addition, vacuolization of proximal tubules with loss of brush border. Masson trichrome stain, magnification $\times 200$

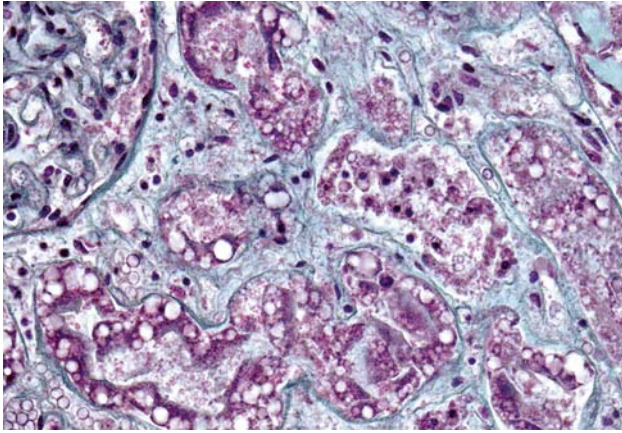


Fig. 2 Tubular epithelial cells with extensive degeneration and detachment from basement membranes, with numerous single detached cells and apoptotic bodies. Masson trichrome stain $\times 400$. Occurrence of these features in a patient biopsied immediately after death argues for “premortem autolysis.” This was encountered in seven patients; see Fig. 3 for comparison

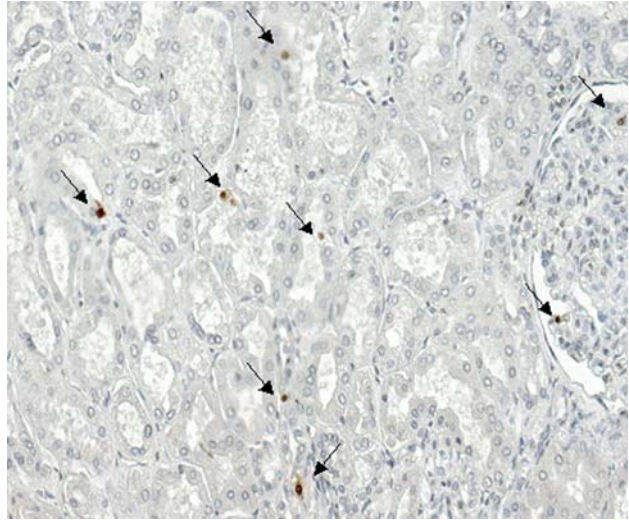


Fig. 4 TUNEL staining showing eight positive nuclei (six in tubules, two in a glomerulus). Magnification $\times 200$

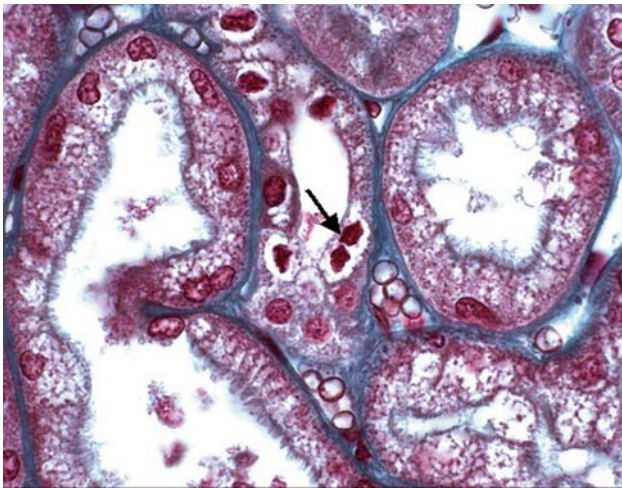


Fig. 3 At least three apoptotic bodies (*arrow*) are present in a distal tubule. Tubules, though vacuolated, are well preserved and have largely intact brush borders. Masson trichrome stain, magnification $\times 1,000$

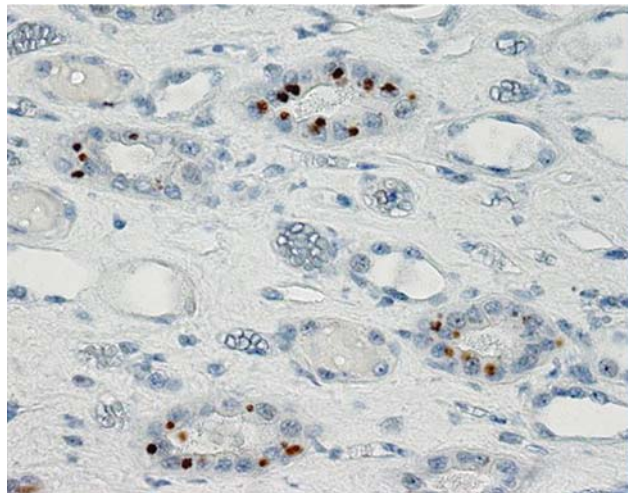


Fig. 5 Activated caspase 3 staining showing numerous positive tubular cells. Magnification $\times 400$

patients (Fig. 3). TUNEL and activated caspase 3-positive cells were identified in tubules of all biopsies (Figs. 4, 5) and occasionally in glomeruli with TUNEL.

Vascular lesions

Interstitial capillaries in the medulla showed congestion in 14/19 cases and dilatation in 11 cases. Both cortical and medullary peritubular capillaries contained increased numbers of monocyte/macrophages and PMNs. In four cases (21%), afferent arterioles showed partial or

complete thrombi (Fig. 6). In three of the four cases, there were associated arterial thrombi.

Interstitial

Interstitial inflammation was minimal or absent, in contrast to the often intense leukocytic infiltration of interstitial capillaries. Edema was severe in only 6 of 19 cases. Three patients had interstitial haemorrhage in the deep medulla. A single patient with *Candida* septicemia had evidence of pyelonephritis with small localized medullary abscesses with stainable *Candida* filaments.

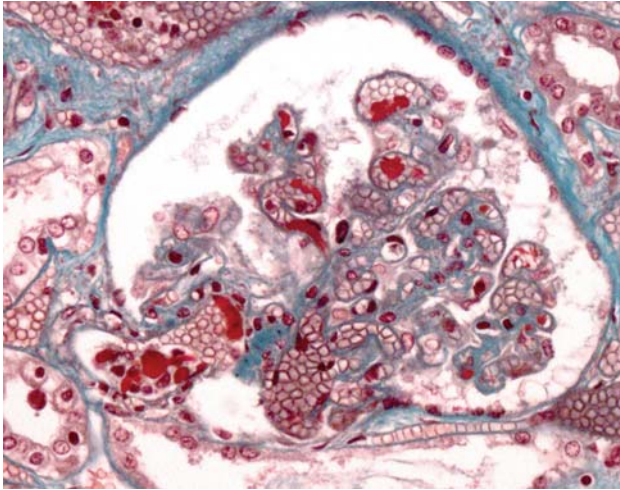


Fig. 6 Partial thrombi in an afferent arteriole and glomerular capillaries. Masson trichrome stain, magnification $\times 200$

Age-related lesions

Mild pre-existing tubular atrophy and interstitial fibrosis were present in all save one case, but seemed age-appropriate. Arteries showed age-appropriate lesions of arteriosclerosis, accompanied in 16/19 cases by typical hyaline arteriolosclerosis.

Clinical and biological correlations with pathologic lesions

Histologic lesions correlated strongly with only three parameters among those tested (Table 2). First, lactate concentration on the day before death correlated with the severity of “common” tubular injury lesions (proximal and distal necrosis, luminal debris) and with a particular subset of very severe tubular and vascular lesions (tubular

cytoplasmic degeneration, detachment from tubular basement membranes and capillary congestion), being classically considered post-mortem autolysis. Second, duration of terminal hypotension also correlated with this last subset of very severe lesions. Third, RRT use correlated with “common” tubular injury lesions. As the eight patients without RRT had the most severe hemodynamic compromise, such that RRT was considered futile at the time it was indicated, this association seems not to be related to selection of patients with a more severe shock. Patients with DIC did not differ from those without regarding thrombotic lesions (two with thrombotic lesions having DIC and the two others not) or the presence of fibrin tactoids (two with fibrin tactoids having DIC and six having no DIC). The administration of contrast media in the preceding 15 days (six patients) or starch-containing fluids for the treatment of shock (seven patients) was not associated with worse tubular lesions, notably vacuolization.

When the patients were divided into two groups according to U/P creatinine ratio >30 (nine patients) or <30 (ten patients) on the last urine sample, we observed no difference in morphological lesions. Similarly, there was no difference between patients with fractional excretion of Na $<1\%$ (nine patients) or $>1\%$ (ten patients). Conversely, proteinuria correlated significantly with the severity of several lesions (i.e., tubular necrosis $r = 0.45$, $P < 0.001$; capillary monocytes $r = 0.56$, $P < 0.001$; apoptotic bodies $r = 0.91$, $P < 0.0001$).

Comparison of trauma patients and ICU control patients

The age of trauma patients who died suddenly on scene (five males, three females) was 25 ± 4 years; none had known previous history of kidney failure. ICU control patients (five males, four females) were 69 ± 21 years

Table 2 Correlations between morphologic parameters, use of renal replacement therapy (RRT), duration of terminal hypotension and lactate arterial concentration on the day before death

	RRT (yes = 1; no = 0)		Lactate (mmol/l)		Terminal hypotension (h)	
	R ^a	P	r ^b	P	r ^b	P
“Common” tubular injury lesions						
Tubular brush border loss ^c	0.58	0.008	0.31	0.22	0.08	0.77
Tubular proximal necrosis ^c	0.46	0.05	0.56	0.02	0.34	0.18
Tubular distal necrosis ^c	0.51	0.03	0.60	0.01	0.21	0.42
Tubular luminal cytoplasmic debris ^c	0.57	0.01	0.77	<0.001	0.29	0.27
“Very severe” injury lesions						
Tubular cytoplasmic degeneration ^c	0.27	0.25	0.69	0.002	0.53	0.02
Cellular detachment from TBM ^{c,d}	0.36	0.12	0.68	0.002	0.48	0.05
Capillary congestion ^c	0.12	0.62	0.41	0.10	0.60	0.01

^a Spearman rank R correlations

^b Pearson r correlations

^c Lesions graded semiquantitatively 0–4

^d Tubular basement membrane

old. Six died from cerebral anoxia after successful resuscitation after out-of-hospital cardiac arrest, and three died after cerebral hemorrhage. They were ventilated for 6 ± 5 days before death, which occurred in the few hours following terminal ventilator weaning after a withdrawal of care decision. None of these patients had evidence of severe sepsis in the preceding month, or hemodynamic instability requiring vasopressor in the preceding 3 days or severe AKI (RIFLE failure) on the day before death. Serum creatinine in the day before death was $117 \pm 36 \mu\text{mol/l}$ (only two patients having values $>130 \mu\text{mol/l}$).

Tubular injury lesions were present in these patients but to a much lesser extent than in septic shock patients (Electronic Supplementary Material 3). Tactoids of fibrin and vascular thrombi were not observed at all in ICU control patients or in trauma patients. By contrast, age-related lesions were not different between septic shock patients and ICU control patients. Monocyte/macrophage, PMNs, apoptotic bodies, TUNEL- and activated caspase 3-positive cells were significantly more frequent in septic shock patients than in the two other groups (Table 3). Of note, no difference was observed for monocyte blood counts between sepsis shock patients and ICU controls, such as the increase in capillary leukocytes observed in the former patients cannot be attributed to a difference in circulating cells (data not shown). Regarding circulating PMNs, only a twofold difference was observed between the two groups, which cannot account for the tenfold difference in medullary and cortical capillaries PMNs (data not shown).

Discussion

This study examines renal biopsies taken immediately after death in 19 patients dying of septic shock with anuric AKI. A number of observations were common to all of these patients: (1) differing degrees of acute tubular lesions, typically grouped under the entity acute tubular injury or necrosis [3–5, 7–9]; (2) intense infiltration of glomeruli, interstitial capillaries and occasionally tubular lumens by leucocytes, predominantly monocytic; (3) apoptosis of tubular cells and occasionally glomerular cells. By contrast, thrombotic lesions were identified in less than half the cases being confined to glomerular fibrin tactoids in five cases with thrombi in only four cases. Acute tubular lesions also occurred, although to a limited extent in the ICU control patients without severe AKI. The marked increase in apoptosis and capillary leukocytic infiltration in comparison with ICU controls and trauma patients, however, argues strongly for a role for them in the pathogenesis of AKI in septic shock.

This array of lesions goes beyond the acute tubular lesions usually cited in those few articles describing kidney change in patients with shock, including some with sepsis [3–5, 7, 8, 10]. Most were published before 1980 and are not specifically dedicated to sepsis or septic shock, displaying little clinical data and focusing mainly on tubular lesions, and finally did not include control patients [3–5, 7, 8, 10]. One more recent study of patients dying with septic shock found only few renal abnormalities and no apoptosis using routine microscopy [6]. However, interest in that

Table 3 Comparisons of lesions in septic shock patients with ICU control patients dying of nonseptic causes and subjects with sudden death due to trauma

	Septic shock patients (<i>n</i> = 19)	ICU control patients (<i>n</i> = 9)	<i>P</i> ^a	Trauma patients (<i>n</i> = 8)	<i>P</i> ^a
Monocyte/macrophage					
Glomerular (/glomerulus)	3.3 ± 1.7	1.9 ± 1.9	0.045	0.8 ± 0.2	<0.001
Cortical capillaries ^b	5.6 ± 4.5	1.1 ± 0.7	<0.001	1.3 ± 0.5	0.01
Medullary capillaries ^b	8.7 ± 5.8	1.1 ± 0.4	<0.001	1.2 ± 0.6	0.001
Polymorphonuclear leucocytes					
Glomerular (/glomerulus)	0.5 ± 0.4	0.2 ± 0.2	0.03	0.1 ± 0.1	0.005
Cortical capillaries ^b	1.0 ± 1.0	0.1 ± 0.2	0.02	0.1 ± 0.1	0.01
Medullary capillaries ^b	0.9 ± 1.2	0.07 ± 0.07	<0.05	0.1 ± 0.1	0.04
Tubular apoptotic bodies					
No. of tubules counted	1,707	1,043		424	
No. of nuclei counted	12,232	7,064		3,891	
Apoptotic bodies counted	353	10		48	
Frequency: % apoptotic bodies	2.9 ± 3.41	0.17 ± 0.32	0.002	0.54 ± 0.43	0.002
TUNEL					
Positive cells/photo	6.4 ± 6.6	1.7 ± 1.2	<0.0001	ND	
Activated caspase 3 staining					
Positive cells/photo	6.0 ± 2.6	3.5 ± 1.7	<0.0001	ND	

^a For comparison with septic shock patients

^b Per ten high power fields

study was focused on the spleen, colon and ileum. In our study, we paid special attention to confirm apoptosis in our renal samples by using three different techniques, all confirming the presence of apoptosis. Using the most specific method, we observed that apoptosis involved nearly 3% of tubular cells. Apoptosis and capillary leukocytic infiltration in patients are in accordance with animal septic models in which they emerged as central factors in the pathogenesis of kidney failure [11, 20–22]. Our results confirm that the observations made in these models are relevant for understanding the pathophysiology of septic AKI in humans.

Thrombi were not a prominent feature in our patients either in terms of frequency or in the small numbers of occluded vessels per given patient. The relevance to kidney failure of tactoids of fibrin, which represent an intermediate between weakly-polymerized fibrin deposits and organized thrombus, is difficult to establish [23]. The discrepancy between thrombotic lesions and biological DIC raises the questions of the relationship between peripheral blood measurements and potential anomalies of coagulation compartmentalized in organs, and also of the pathways connecting activation of coagulation and increased mortality in sepsis [24].

The acute tubular lesions were correlated with the arterial lactate concentration the day before death. Arterial lactate concentration is a parameter of severity in shock, correlating with mortality and reflecting metabolic alterations associated with hemodynamic compromise and other factors. Thus, the association observed in our patients is not surprising and indicates that the kidney lesions are integral to the severity of the shock and of multi-organ failure. In addition, epinephrine infusion enhances lactate production also by itself; the higher epinephrine dose required in the more severe patients may also have contributed to this association. The association between the use of RRT and more severe lesions of tubular injury, by contrast, raises the question of the technique itself being responsible for aggravation of the lesions. Indeed, several studies that have shown that passage of blood in an extracorporeal circuit activates complement pathways and leukocytes, which may lead to kidney damage [25]. Due to the study design we can only hypothesize on this potential side effect of this otherwise life-saving technique.

The correlation between tubular cytoplasmic degeneration, detachment from basement membranes and capillary congestion with terminal hypotension and lactate concentration suggests that these lesions are probably agonal phenomena. Some of these lesions, such as dissolution and detachment of tubular epithelial cells, have traditionally been assumed to be related to post-mortem autolysis. The premortem occurrence of these lesions, since the biopsies were taken immediately post-mortem, raises the hypothesis that the kidneys might well “die” before the diagnosis of clinical death, with occurrence of

“premortem autolysis.” This pattern of very severe lesions was encountered in “only” seven patients. By contrast, the 12 others died with no evidence of irreversible kidney damage on microscopic evaluation.

Starch or contrast-media administration had no association with any lesion, but all patients received hypertonic glucose solute to treat hypoglycemia in the hours preceding death, which may have overwhelmed any consequence of these products. In accordance with previously published studies, usual indices of intrinsic kidney failure performed poorly in predicting the observed lesions [26]. By contrast, proteinuria on a random sample may be a relevant index of the intensity of renal lesions in septic shock.

Our series consists only of patients who died and thus likely represents the maximal intensity of renal lesions in septic shock; it is not possible to determine which lesions were responsible for the appearance of kidney failure, especially as we observed that most tubular lesions were also observed, although to a lesser extent, in ICU patients without severe kidney failure. Conversely, it is possible that lesions that participated in the onset of kidney insufficiency have since disappeared, notably minor thrombi under the influence of natural fibrinolysis [27]. Unfortunately, given the natural history of septic shock, it is impossible to find patients dying of septic shock but without kidney failure, the vast majority of patients dying of multiorgan failure with a prominent renal component. Renal biopsy during septic shock is not practiced because, given our present state of knowledge, therapy would not be changed by the results, and there are significant risks owing to derangements of hemostasis and patient instability.

Importantly, our patients were not compared to patients dying of shock of non-septic origin, and it is likely that some of these lesions may be common to any multiorgan failure syndrome, whatever the cause, or even to other causes of AKI outside the ICU. However, this limitation does not impair the relevance of our observations regarding the pathophysiology of sepsis. In addition, the lesions observed in our patients are probably not only the consequences of the initiating disease, but also of the adverse effects of treatments: vasopressor, antibiotics, RRT, etc. Thus, our data may not be entirely applicable to patients with different therapeutic approaches especially as regards the choice of the vasopressor agent.

Overall, our observations indicate that the renal lesions associated with AKI in septic shock are more complex than the simple acute tubular injury previously cited, involving intense capillary leukocytic infiltration, apoptosis and rare thrombi. Apoptosis and leukocytic infiltration, predominantly mononuclear, seem likely to be of major importance. This may be a potential target in human septic shock to impact favorably on the development of AKI [28]; conversely, thrombus formation may be a relevant target only in a minority of patients.

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