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The complexity of hemorrhage-generating factors in various organs in acute kidney injury

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Abstract

Bleeding disorders, associated with macroscopic and microscopic lesions in different organs are frequently found in acute kidney injury (AKI), in the third stage of the RIFLE (risk, injury, failure, loss, end-stage kidney disease) classification, treated by hemodialysis. The study included 81 cases of AKI of various causes (septic, posttraumatic, postoperative, toxic, medical nephropathies). 59.25% of the patients presented various forms of bleeding disorders (gastrointestinal bleeding, meningo-cerebral hemorrhage, epistaxis, hemodialysis vascular access bleeding, etc.). In the deceased patients that underwent necropsy, various bleeding lesions were found, involving the lungs, kidneys, brain, gastrointestinal tract and liver. A physiopathological interpretation of the factors generating these lesions and their impact on the evolution and prognosis was performed. These factors are related to the AKI's etiology, as well as the physiopathological disorders regarding the uremic syndrome and the various therapies required (blood transfusions, hemodialisys, heparin administration, surgery, macromolecule perfusion). In conclusion, multiple factors are involved in causing bleeding disorders in various organs with a major impact on the evolution and prognosis of AKI patients.

Keywords: acute kidney injury, coagulation, hemodialysis, uremic syndrome.

Introduction

Acute kidney injury (AKI) is a polyetiological syndrome that involves a coagulation balance disruption, among other clinical symptoms, concerning various organs, as microscopic and macroscopic lesions can be found in the liver, brain, gastrointestinal tract and cardiovascular system. Our study is important because AKI still has a very high mortality rate (around 50%), in spite of the latest renal replacement therapy. Most deaths occur due to multiple organ failure. One of the negative prognosis factors is represented by a series of bleeding disorders with various clinical aspects, causing therapeutic difficulties and requiring the involvement of many physicians (intensive care specialists, nephrologists, hematologists, surgeons, etc.). Many factors cause macroscopic and microscopic hemorrhagic lesions in various organs, such as the liver, brain and cardiovascular system [1–5].

The analysis of the factors that cause bleeding disorders may be difficult, because usually more than one are involved: factors regarding the etiology [4], factors regarding the uremic syndrome [5], factors regarding the therapy [6] and other organ failure (liver failure).

The purpose of this study is to correlate the bleeding lesions with the various factors generating these lesions, as well as to underline their impact on the evolution and prognosis.

Patients and Methods

Our study included 81 cases of RIFLE (risk, injury, failure, loss, end-stage kidney disease) stage III acute kidney injury [7] patients undergoing hemodialysis. Table 1 presents the etiology of the AKI. It is obvious that most cases had septic etiology (septic shock and severe sepsis). Other causes were also identified (trauma, surgery, severe pancreatitis, intoxication, etc.).

Table 1 – ***The acute kidney injury's etiology in patients undergoing hemodialysis***

AKI's etiology	No. of cases	Percent
Severe sepsis	18	22.22%
Trauma	11	13.58%
Surgery	10	12.34%
Severe pancreatitis	12	14.81%
Intoxication	7	8.64%
Leptospirosis	1	1.23%
Chronic nephropathies	12	14.81%
Total	81	100%

All patients were investigated in order to establish the diagnosis of AKI and to determine its stage. Therefore, we ran the following blood tests: blood nitrogen retention (blood urea, serum creatinine), ionogram (focusing on the potassium levels) and acid–base balance. The clinical aspects of our patients were also important, because sometimes-clinical conditions require hemodialysis, in spite of the nitrogen retention.

Inclusion criteria: the study included only RIFLE stage III (failure stage) AKI patients. RIFLE stage I and II (risk and injury) patients that required only medical treatment were excluded, as well as RIFLE stage IV and V (loss and end-stage kidney disease) patients that were included in an intermittent hemodialysis program.

The biological material collected from the autopsy of patients was fixed for 24 hours in 10% neutral buffered formalin, the tissue fragments used for histopathological analysis being then processed by classical paraffin embedding technique and Hematoxylin–Eosin (HE) staining.

Results

Out of the 81 cases, 48 (59.25%) presented various bleeding disorders (Table 2). The clinical forms of bleeding disorders found were: vascular access bleeding, gastro-intestinal bleeding, airway bleeding, epistaxis, meningo-cerebral bleeding, etc.

The mortality rate correlated with the acute kidney injury's etiology is shown in Table 3.

Table 2 – ***Clinical aspects of bleeding disorders***

Clinical aspects of bleeding disorders	No. of cases	Percent
Vascular access hemorrhage	10	12.34%
Gastrointestinal bleeding	9	11.11%
Meningo-cerebral bleeding	3	3.7%
Airway bleeding	4	4.93%
Epistaxis	3	3.7%
Hemorrhagic conjunctivitis	4	4.93%
Hematoma	4	4.93%
Multiple hemorrhage	11	13.58%
Total bleeding disorders	48	59.25%
Total AKI cases	81	100%

Table 3 – ***Acute kidney injury's mortality rate***

AKI's etiology	No. of cases	Deaths	Percent
Severe sepsis	28	14	50%
Trauma	11	6	54.5%
Surgery	10	6	60%
Severe pancreatitis	12	7	58.33%
Toxic	7	2	28.57%
Leptospirosis	1	0	0%
Chronic nephropathies	12	0	0%
Total	81	35	43.2%

The morphological changes of acute renal lesions were identified in the autopsies and microscopic examination of the fragments harvested and consisted primarily in the presence of systemic circulatory damage, as meningo-cerebral, cardiac, respiratory, digestive and urinary tracts damage.

The macroscopic appearance of the kidneys indicated sclerolipomatosis and a high cortico-medullary contrast, with pronounced medulla stasis and pale cortex (Figure 1).

Microscopically large areas of acute tubular necrosis and glomerular and interstitial stasis, and accumulation of mononuclear inflammatory elements in the interstitium were observed (Figure 2).

The lungs were distended in volume, with purplish color, smooth and wet surface section, and spontaneous leakage of increased amounts of red-purple blood. In microscopy, we found interalveolar capillaries congestion with hematic infiltration of the septum and the presence of intra-alverolar edema fluid and red blood cells (Figure 3). Focal necrosis of alveolar epithelial cells and arterioles microthrombosis were also observed.

In the heart, especially in the left ventricular wall, in some cases hemorrhagic or pale areas with well-defined, slightly raised, hemorrhagic border, suggestive for recent myocardial infarction were present. These were later confirmed by microscopic examination as structured or unstructured necrosis areas with inflammatory demarcation border (Figure 4).

Macroscopic analysis of the digestive organs revealed gastric, duodenal and/or jejunal hyperemia and superficial ulcerations, as well as well defined, single or multiple, acute stress ulcers in stomach mucosa, with the base covered with brown-red material (Figure 5). Microscopic focal areas of ulceration and necrosis were found.

In the investigated cases, the liver presented tensioned capsule, with increased volume, high consistency and increased amounts of red-violet blood leaking on the section surface. Microscopically, we found centrilobular, sinusoidal and portal stasis (Figure 6). The presence of steatosis and focal hepatocyte necrosis were also common.

In the brain, we found edema and meningeal and intracerebral hyperemia and sometimes white matter petechiae. Hemorrhagic stroke was also found, a situation in which the brain parenchyma appeared distended, with the presence of a retracted clot and nervous substance dilaceration (Figure 7). Microscopically, in these cases, in addition to heavy bleeding, we noticed small annular hemorrhages in the periphery and glial reaction.

A high number of patients presented coagulation disorders due to other organ failure, such as liver failure. Table 4 shows the rate of liver failure correlated with the acute kidney injury's etiology.

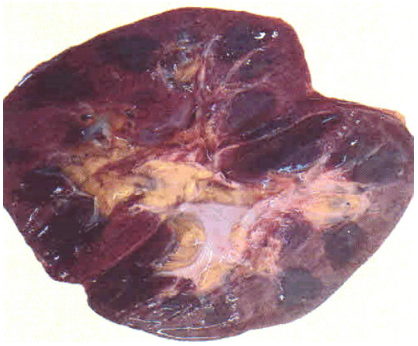

Figure 1 – ***Macroscopic aspect of acute kidney injury.***

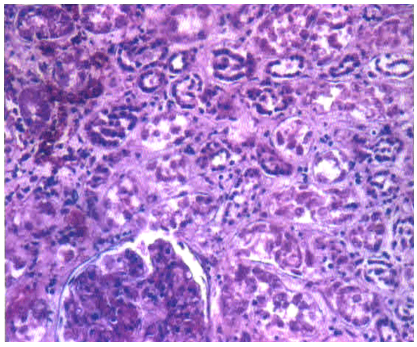

Figure 2 – ***Kidney with extensive acute tubular necrosis (HE staining, ×100).***

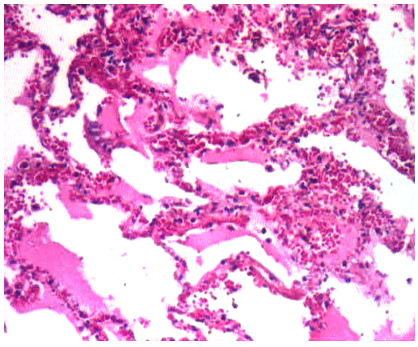

Figure 3 – ***Stasis and edema in pulmonary tissue (HE staining, ×100).***

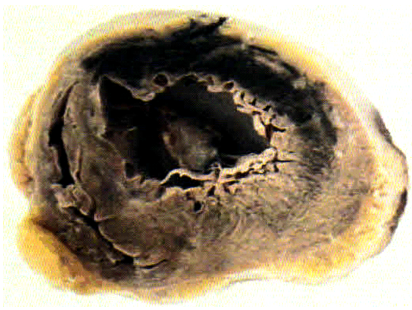

Figure 4 – ***Recent anterior transmural left ventricle infarction.***

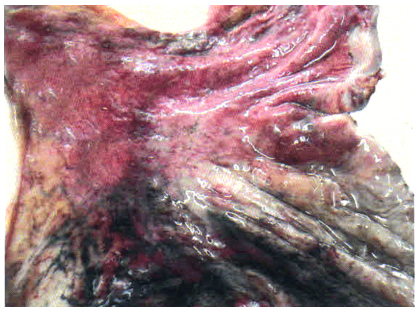

Figure 5 – ***Gastric hyperemia and superficial ulcerations.***

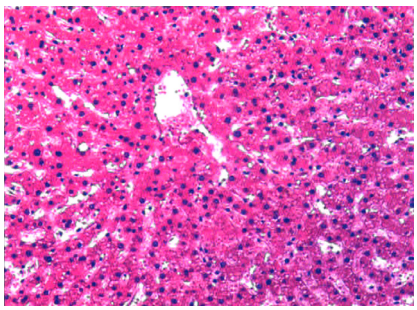

Figure 6 – ***Liver centrolobular and sinusoidal stasis (HE staining, ×100).***

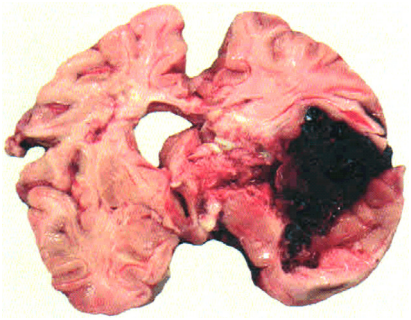

Figure 7 – ***Brain: hemorrhagic stroke associated with acute kidney injury.***

Table 4 – ***Liver failure associated with the AKI's etiology***

AKI's etiology	No. of cases	Liver failure	Percent
Severe sepsis	28	25	89.28%
Trauma	11	3	27.27%
Surgery	10	3	30%
Severe pancreatitis	12	4	30%
Intoxication	7 (4 caused by carbon tetrachloride)	4	57.14%
Leptospirosis	1	1	100%
Chronic nephropathies	12	0	0%
Total	81	40	49.38%

Discussion

Particular features of our AKI patients that required hemodialysis allowed us to explain the aspects of their bleeding disorders and of hemorrhagic lesions in various organs. We managed to establish a correlation between the prevalence and gravity of hemorrhagic disorders and the AKI's etiology, as well as other organ failure and the impact of the uremic syndrome and the applied therapy. Our group of patients was very diverse, with patients recruited from various medical fields: surgery, traumatology, infectious diseases (severe sepsis and septic shock patients), toxicology and nephrology. This allowed us to outline the various etiological causes that affect the coagulation balance, causing macroscopic and microscopic hemorrhagic lesions, apart from the renal failure.

We intended to generate a large view on the complexity and multitude of hemorrhagic syndromes that occur in AKI patients and to analyze their particular aspects in various organs. Our goal was to outline the most important causes that produce coagulation disorders in various organs in our group of AKI patients. Hemorrhage-generating factors were different depending on the AKI's etiology (severe sepsis, trauma, surgery, chronic nephropathies, etc.). There are individual factors for each etiology, but there are also common factors, each in a different ratio. Among the common factors, the most usual is the uremic factor, as it is found in all forms of AKI. It is the only factor found in aggravated medical nephropathies and it is an aggravating factor in other forms of AKI.

Severe sepsis was the main cause of AKI in our group of patients (24.56%), explaining the high number of bleeding disorders that occurred even from the condition's onset. This situation is explained by the fact that disseminated intravascular coagulation (DIC) is present from the AKI's onset, with a local impact, on the vascular endothelium, and a systemic impact, caused by enzyme, cytokine, complement, protein and lipid imbalance [8]. DIC was identified at clinical examination, as well as using coagulation tests.

The hepatorenal syndrome is another cause of hemorrhagic lesions mentioned in literature [9, 10]. In our group of patients, hepatic damage in association with kidney damage was found in 89.28% of our septic patients, disrupting the coagulation balance by a lack of clotting factors synthesis.

Our study also included other forms of AKI, with a lower rate than the sepsis-induced one (Table 1). Each one of these forms revealed etiological factors involved in coagulation disruption. Therefore, in AKI secondary to severe necrotizing pancreatitis, the coagulation balance was altered due to circulating enzymes and inflammation chemical mediators, as well as the frequent shock status, DIC and septic complications. These cases show the complexity of hemorrhage-generating factors in various organs in AKI, explaining the high mortality rate (28.57%).

Regarding intoxication-induced AKI, the nature of the toxic substance involved was very important. In our group of patients, carbon tetrachloride was involved in over 50% of these cases. Other toxic substances were also involved. Chemotherapy caused tumor lysis syndrome, producing AKI and affecting the coagulation balance [11].

Posttraumatic AKI caused coagulation disorders through rhabdomyolysis [12], being accompanied by a high mortality rate (54.5%). Posttraumatic AKI affected the coagulation balance through multiple factors (tissue trauma, septic complications and preserved blood and macromolecule transfusions) [13].

In contrast with the previously mentioned form of AKI, aggravated chronic kidney disease had the most favorable outcome, without any mortality. The AKI's etiological factors that can affect the coagulation balance were absent in this situation. The only physiopathological factor that affected the coagulation was the uremic

syndrome that disrupts the coagulation balance because of nitrogen retention, increased NO and prostaglandin levels and primary platelet damage [14].

The uremic factor was also involved in all the other forms of AKI, being a common factor that contributed to causing an imbalance of the coagulation. Another common element found in all our patients was represented by the anticoagulant medication used during hemodialysis [3].

Regarding the microscopic and macroscopic hemorrhagic lesions found in our group of patients, these were located in various organs (gastrointestinal tract, liver, kidney, brain, etc.) and presented different aspects. For example, in the gastrointestinal tract we identified multiple stress ulcerations using endoscopy. These ulcerations are caused by the following factors: cortisone, histamine, catecholamines and sepsis-related factors [15]. An aggravating element is represented by the lack of clearance for these substances due to acute renal failure.

Pulmonary hemorrhage was in the context of pulmonary damage that occurs during AKI [2]. Pulmonary manifestations of AKI consisted in acute respiratory distress syndrome (ARDS) and non-cardiogenic pulmonary edema. Primary pulmonary lesions also occurred in the context of posttraumatic acute kidney injury.

Pulmonary hemorrhage can sometimes occur in the context of medical nephropathies [2, 16], but we did not have any of these cases in our group of patients.

Neurological lesions consisted in meningo-cerebral hemorrhage and even hemorrhagic stroke, in the context of the coagulation balance disruption. Cerebral hemorrhages had a poor outcome. An important difficulty was to maintain the hemodialysis treatment, considering the required anticoagulant therapy and the impact of the extracorporeal circuit on the coagulation.

Conclusions

There are multiple factors that cause hemorrhagic lesions in acute kidney injury patients, with a different contribution, depending on the condition's etiology. The etiologic factor that triggered the acute kidney injury was very important. Most frequent and severe hemorrhagic lesions were found in patients with septic, posttraumatic, toxic and postoperative acute kidney injury. On the contrary, patients with aggravated chronic kidney disease presented fewer and less severe hemorrhagic lesions, as these lesions were determined only by the uremic syndrome and other kind of damage was not present (surgery, trauma, intoxication or infections).

Conflict of interests

The authors declare that they have no conflict of interests.

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