**Review**

# Acute kidney injury in the newborn: the role of the perinatal pathologist

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**Proceedings**

## Abstract

Neonatal acute kidney injury (AKI), that becomes acute renal failure (when renal replacement is needed), represents a common clinical problem in critically ill infants admitted to neonatal intensive care unit (NICU) centers. This article is aimed at reviewing the most important histological renal changes generally considered typical of AKI, useful to confirm, at morphological level, the structural and cell lesions responsible for the clinical picture. In the first part a simple schematic approach to the elementary lesions of the developing kidney will be proposed, aimed to decipher the renal lesions. In the second part, the typical lesions of AKI in the neonate will be presented and discussed. In the final part, we'll prospect the necessity for a more accurate microscopic analysis of the kidney in every neonate undergoing asphyxia or sepsis, in order to reveal subtle renal changes that might allow a pathological diagnosis of AKI even in newborns in which the clinical and laboratory pictures were not representative of a severe kidney damage. Finally, the role of the clinical-pathological discussion between the pathologist and the neonatologist will be underlined, in order to reach a final diagnosis, based on the clinical history, the laboratory findings, and the histological lesions. In this article, the role of the pathologist in the evaluation of a neonatal

kidney in a newborn with the clinical diagnosis of AKI is described, with particular attention to the differences existing between the preterm and the at term kidney, focusing on the differentiation between developmental changes occurring in the kidney in the perinatal period and the histological lesions induced by pathological events occurring around birth.

## Keywords

Neonatal acute kidney injury, neonatal intensive care unit, newborn, perinatal pathologist, neonatal kidney.

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## How to cite

## Introduction

Neonatal acute kidney injury (AKI), that becomes acute renal failure (when renal replacement is needed), represents a common clinical problem in critically ill infants admitted to neonatal intensive care unit (NICU) centers [1]. Previously defined as an abrupt severe decrease in glomerular filtration rate [2], emerging evidence in recent years suggests that even minor changes in serum creatinine levels may be associated with increased in-patient mortality [3]. As a consequence, the participants to a network involved in the study of this syndrome suggested that AKI should be better defined as a complex disorder for which currently there is no accepted uniform definition [4]. AKI is associated in most cases with a primary condition such as prematurity, perinatal asphyxia, sepsis, metabolic disease, feeding problems [5]. Perinatal asphyxia is generally considered the main cause of neonatal AKI, accounting for over 50% of cases [6]. Despite significant improvements over the past decades in obstetrics, delivery room and neonatal intensive care and despite improved understanding of pathophysiology and management of AKI in full term and preterm infants, the mortality remains as high as more than 60% [7].

The high mortality rate in infants affected by neonatal AKI, associated with the open problems on the pathogenesis of this syndrome gives a peculiar role to perinatal pathologists in the histopathological examination of kidneys in every autoptic case of neonatal AKI.

This article is aimed at reviewing the most important histological renal changes generally considered typical of AKI, useful to confirm, at morphological level, the structural and cell lesions responsible for the clinical picture. In the first part a simple schematic approach to the elementary lesions of the developing kidney will be proposed, aimed at helping a pathologist faced with a neonatal kidney to decipher the lesions that he sees, ending with a descriptive conclusion. In the second part, the typical lesions of AKI in the neonate will be presented and discussed. In the final part, we'll prospect the necessity for a more accurate microscopic analysis of the kidney in every neonate undergoing asphyxia or sepsis, in order to reveal subtle renal changes that might allow a pathological diagnosis of AKI even in newborns in which the clinical and laboratory pictures were not representative of a severe kidney damage. Finally, the role of the clinical-pathological discussion between the pathologist and the neonatologist will be underlined, in order to reach a final diagnosis, based on the clinical history, the laboratory findings, and the histological lesions.

In this article, the role of the pathologist in the evaluation of a neonatal kidney in a newborn with the clinical diagnosis of AKI is described, with particular attention to the differences existing between the preterm and the at term kidney, focusing on the differentiation between developmental changes occurring in the kidney in the perinatal period and the histological lesions induced by pathological events occurring around birth.

## Finding your way through histological examination of a neonatal kidney

### How to sample the neonatal kidney

The first difference between the newborn and the adult kidney is represented by the possibility to study the entire neonatal organ, due to its small volume at birth. In order to obtain the maximum of data regarding the different compartments of the newborn kidney, the following sampling method is recommended.

- A first tissue section, including the ureter, should be performed in the hilar region along the lower

diameter of the kidney. This kidney sample is necessary for the accurate study of the deepest renal regions where, in close proximity of the emergence of the ureter, a compartment of stem/progenitor cells is located, that is involved in the differentiation of the multiple cell types that give rise to the mature ureter. Moreover, the sections obtained from this polar sample allow a precise study of the relationships between cortical and medullary structures, of the collecting tubules and of the epithelium covering the apex of renal papillae.

- The two residual samples containing both renal poles should be subdivided into two parts, and included in the cut section. The histological study of these samples will allow a complete analysis of all the renal regions, including the capsule, the subcapsular nephrogenic zone, the cortex including glomeruli and proximal and distal tubules, the vessels at the cortico-medullary limit, the medulla including Henle loops and collecting tubules, and the hilar regions, including the renal papillae and the hilar progenitor cells.

*Evaluation of renal architecture in a newborn*

The neonatal kidney, and in particular the preterm kidney, is characterized at histology by a peculiar pattern, that renders its analysis completely different from that typically used for the study of the adult kidney. Moreover, given the continuous development of renal structures in the perinatal period, significant differences exist even among newborns of different gestational age at birth. The most striking differences regard the following compartments: a) the capsule, b) the nephrogenic zone, c) the ureteric bud tips, d) glomerular cells, and e) the presence of a huge amount of stem/progenitor cells.

**The capsule**

At panoramic view, the first structure appearing completely different is the renal capsule. Contrasting with the typical appearance of the adult capsule, the capsule of the newborn is characterized by the presence of numerous different cell types, characterized by large elongated nuclei with scarcely evident cytoplasm. The capsule in the newborn kidney is much thicker as compared to the adult one. Five to twenty layers of capsular cells may be frequently observed in the majority of neonatal

kidneys. A marked interindividual variability may be found among different neonates even at the same gestational age.

**The nephrogenic zone**

A blue strip localized in the subcapsular regions characterizes, in H&E-stained sections, the newborn kidney and, in particular, the fetal and preterm kidney. At higher power, cells of the blue strip are small undifferentiated cells, with roundish of oval nuclei, and scant cytoplasm. The width of the blue strip may change from one kidney to the next, even in infants with the same gestational age. Newly formed nephrons originate from the multipotent cells of the blue strip, giving rise through a process of mesenchymal-epithelial transition (MET) to the renal vesicles, comma-shaped bodies, S-shaped bodies, glomeruli, proximal and distal tubules that, eventually, fuse with the collecting tubules originating from the ureteric bud tips [8]. The width of the renal blue strip represents the actual stem cell burden in the neonatal kidney and its potential nephrogenic capacity, whereas the number of renal vesicles represents the actual nephrogenic activity of the kidney.

**The ureteric bud tips**

The ureteric bud proliferates dichotomously inside the metanephric mesenchyme, giving rise to a tubular tree connecting the renal hilum with the subcapsular regions, where the ureteric bud tips enter in strict contact with the blue strip cells. Whereas the undifferentiated blue strip cells appear diffusely and homogeneously distributed, progenitor cells in the peri-bud tip regions appear closer each other, and develop progressively intercellular junctions, giving rise to the cap mesenchymal cells, the first step of MET that will originate the renal vesicles. These are the first clearly identifiable epithelial structures originating from the metanephric mesenchymal cells: from each renal vesicle, a proximal nephron will take origin. The fusion process between the distal tubule of the newly formed nephron and the corresponding ureteric bud tip represent the final step of nephrogenesis, allowing the product of glomerular filtration to reach the ureter.

**Glomerular cells**

The glomerular count represents one of the most relevant datum in the evaluation of the

degree of maturation of the neonatal kidney. In the absence of better methods able to evaluate the real number of nephrons present in each kidney, the evaluation of the nephron burden is based on the radial glomerular count [9]. This method is based on the count of the number of glomeruli observed along a straight line extending from the capsule to the cortico-medullary junction. To this end, we suggest to utilize the hilar kidney sections, that allow a better orientation of the counting lines. The glomerular count is performed along 5 lines, in different kidney regions, and the mean value is assumed as representative of the mean radial glomerular value for each kidney. Previous works from our group [10] showed that the nephron burden, evaluated by the radial glomerular count, is related to the gestational age, but also evidenced marked interindividual variavility in the number of formed glomeruli, even in neonates with the same gestational age. These findings clearly indicate that even epigenetic factors acting during pregnancy, may interfere with the glomerulogenesis.

**The presence of a huge amount of stem/progenitor cells**

The presence of a high number of active endogenous stem/progenitor cells characterizes the newborn and, in particular, the preterm kidney, and characterizes the neonatal kidney as compared to the adult organ, where stem/progenitors identification necessitates an accurate search by an expert pathologist. The evaluation of the stem cell burden necessitates the knowledge of the multiple compartments in which stem/progenitors are present inside the neonatal kidney (**Fig. 1**).

a. The most important stem niche is probably represented by the capsule, particularly rich in undifferentiated mesenchymal stem cells. They may be evaluated by counting the number of layers of cells, varying significantly from one neonatal kidney to the next. The role of the renal capsule as the stem cell niche has been hypothesized to continue even after birth, putatively representing the major reserve of renal progenitors even in the adult kidney.
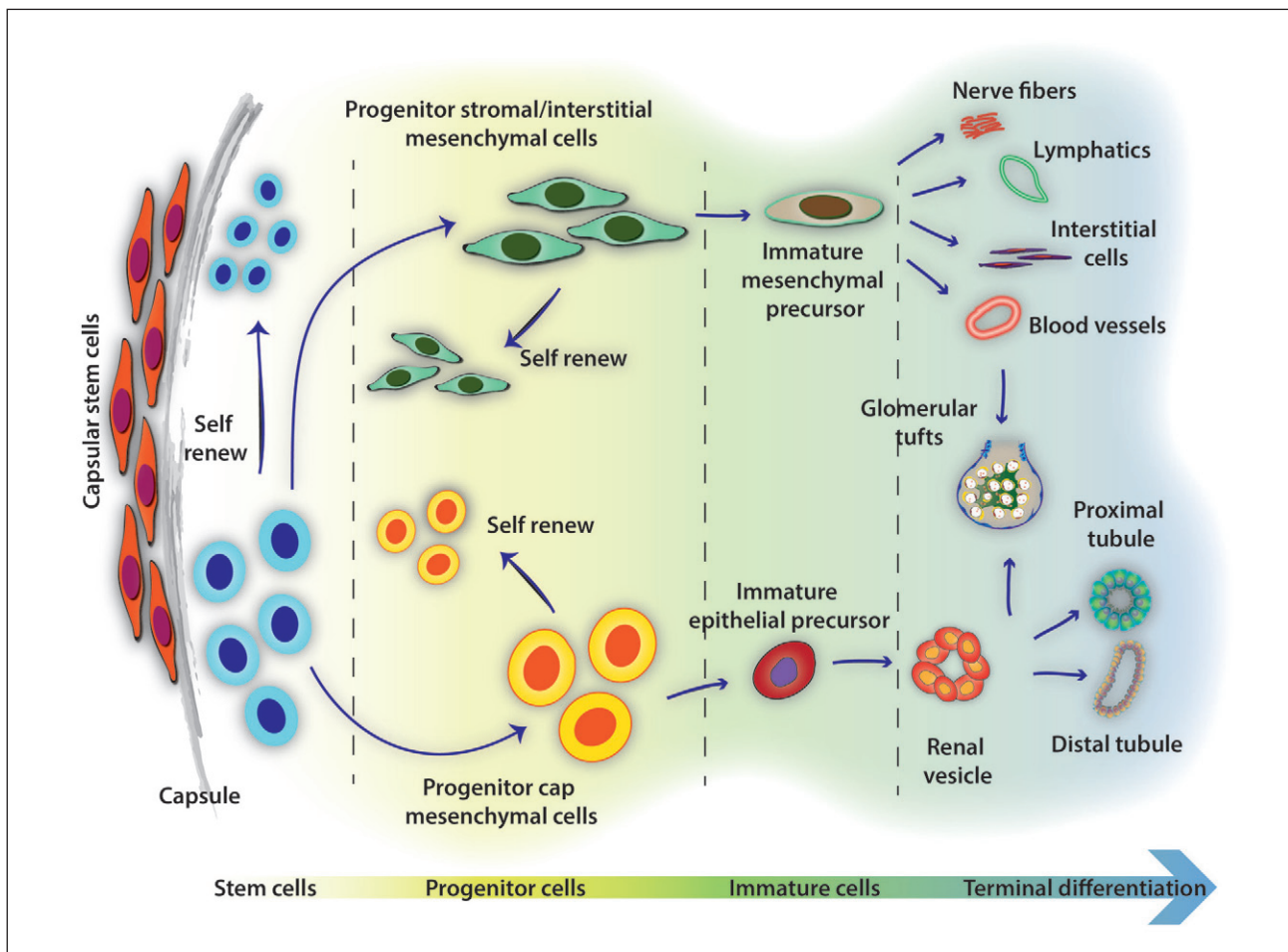


**Figure 1.** Schematic representation of the multiple compartments of stem/progenitor cells in the neonatal kidney.

b. The second, and often more prominent, source of stem/progenitor renal cells is well evidenced by the blue strip, representing an aggregate of undifferentiated cells occupying the subcapsular area. The width of the blue strip may represent an important datum in the evaluation of the stem cell burden in the neonatal kidney, representing the residual ability of the kidney to originate new nephrons after birth.

c. Cap aggregates (i.e. the stem progenitors condensating around the ureteric bud tips, committed toward the epithelial fate) represent another compartment of renal progenitors. Their accurate evaluation may give information on the entity of actual nephrogenesis, each cap mesenchymal aggregate representing a proximal nephron in its very early phase of differentiation. The count of the renal vesicles, and of comma-shaped and S-shaped bodies allows the pathologist to evaluate the actual efficacy of the ongoing nephrogenesis, all these structures representing intermediate steps in nephron formation.

d. A huge amount of undifferentiated mesen-chymal stem cells may be found in the deeper parts of the newborn kidney, in the deep medulla and in the peri-hilar regions. These progenitors are morphologically dif-ferent from the blue strip cells: they are characterized by an elongated nucleus and a elongated cell body, and are immersed in an abundant loose intercellular matrix. These cells are probably the remnants of the metanephric mesenchymal cells originally occupying the entire metanephros, before the invasion by the ureteric bud branching process.

e. A peculiar compartment of renal stem cells is represented by an aggregate of progenitor cells locate in close proximity of the insurgence of the ureter. These stem/progenitor cells play a fundamental role in the origin and organization of the ureteric channel, originating all the cell types that characterize the mature ureteric wall, including the pacemaker cells responsible for the ureteral peristalsis.

f. Stem/progenitors are also detectable inter-mingled among the parietal epithelial cells of the Bowman capsule in developing glomeruli. They are considered a reservoir of multipotent cells that might be maintained even in adulthhod, and that could be responsible for the ability of mature nephrons to restore cell death. These cells have been hypothesized to maintain their ability to differentiate into podocytes, and might represent the unique defense mechanism of the adult kidney to halt the progression of podocytopathies in childhood as well as in adulthood.

**Nephron elementary lesions**

*Glomerular elementary lesions*

The fetal developing glomeruli are characterized by marked differences as compared to the adult glomerulus. The first difference regards the mor-phology of podocytes, or better, of podocyte precursors. In the neonatal kidney, and in particular in preterm infants, podocytes appear as large cells with a large globoid dark nucleus, extending into the Bowman's capsular space. Podocyte precursors' chromatin is very dense, homogeneous and it is intensely stained by hematoxylin. The second difference regards the histochemical affinity of the basal membranes: probably due to its immaturity, glomerular basal membranes do not show the typical PAS-positivity normally present in the adult glomerulus. This finding results in a lower usefulness of PAS stain in the differentiation between the intracapillary (endothelial and mesangial cells) and extracapillary (visceral and parietal epithelial cells) compartments in the neonatal kidney. Also basement membrane lesions, including tickening, splitting and wrinkling are difficult to detect in the fetal glomerulus, due to the lower affinity of the immature basal membrane toward the silver stains, including the Jones method. Hyalinosis, scarring and glomerular obsolescence may be observed in few glomeruli, particularly in the deep cortical areas at the border with the medulla, probably representing the end stage of maldeveloped nephron, a phenomenon that should be normally observed due to the high number of nephrons built in each kidney.

*Elementary lesions of the tubules*

The first problem in the histological examination of the neonatal kidney is the differentiation of the different segments of the proximal and distal tubular structures (**Fig. 2**). The collecting tubules, extending from the hilum to the subcapsular regions, are characterized by epithelial cells with large and clear cytoplasm. PAS stain may be very useful in their detection, being collecting tubular cells intensely PAS-positive. Proximal tubules are characterized by the large eosinophilic cytoplasm
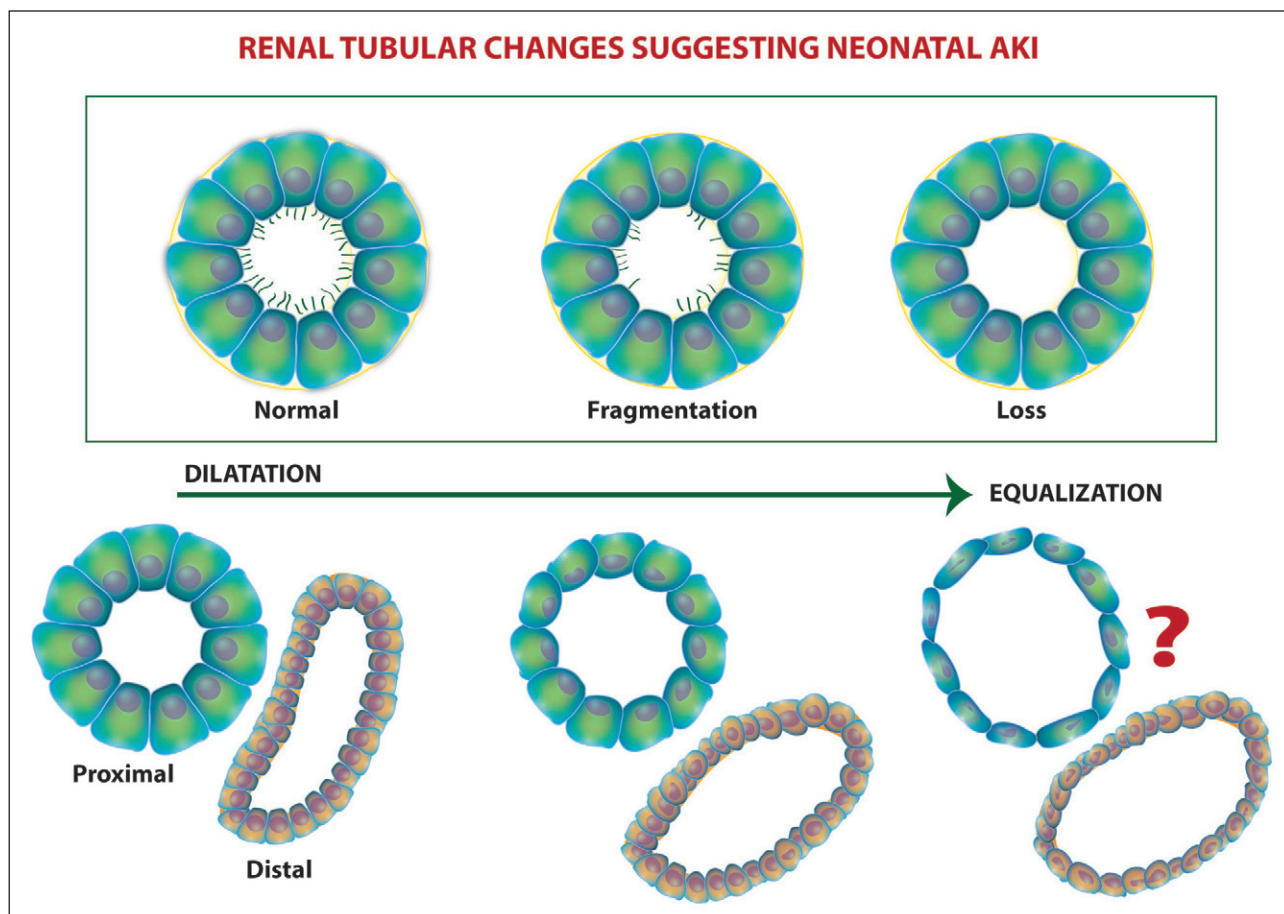
**Figure 2.** Loss of brushing border and tubular dilatation are the first pathological events suggesting AKI in neonatal kidney.

of the epithelium and by a small lumen. The brush border may be clearly evidenced in the proximal tubular epithelium, particularly in at term infants. The most frequent elementary lesions observed in tubular cells are reported below.

**Vacuolization**

Vacuolization of proximal and/or distal tubules may be seen in different clinical conditions, all characterized by proteinuria. A finely microvacuolar appearance restricted to proximal cells may be associated with osmotic nephrosis or, alternatively, with the administration of plasma expanders. The finding of coarse vacuoles mainly localized in epithelial cells of the distal tubules is often associated with hypokalemia.

**Dilatation**

Dilatation of proximal and distal tubules may be seen in all forms of severe acute renal damage, and it is often associated with dedifferentiation of the tubular epithelium, characterized by the decrease in the morphological differences between proximal and distal tubules (**Fig. 2**). Dilatation of tubular profiles is also found in small cysts formation. Cysts exclusively located in the collecting ducts are indicative of recessive polycystic kidney disease.

**Tubular cell death**

Cell death of tubular epithelium may occur in all forms of severe acute renal damage (**Fig. 3**). Multiple morphological forms of cell death may be detected in the neonatal kidney: i) coagulation necrosis is typical for toxic damage or for recent infarction; ii) decapitation means the loss of apical brush border of the proximal tubular epithelium, and it is the type of lesion typically observed in renal failure secondary to septic shock; iii) scattered apoptotic cells (**Fig. 4**) (appearing as eosinophilic roundish globules containing nuclear remnants, that progressively detach from the neighboring cells) are often seen in nephritic syndromes. Necrobiotic lesions of the proximal tubular cells are mainly
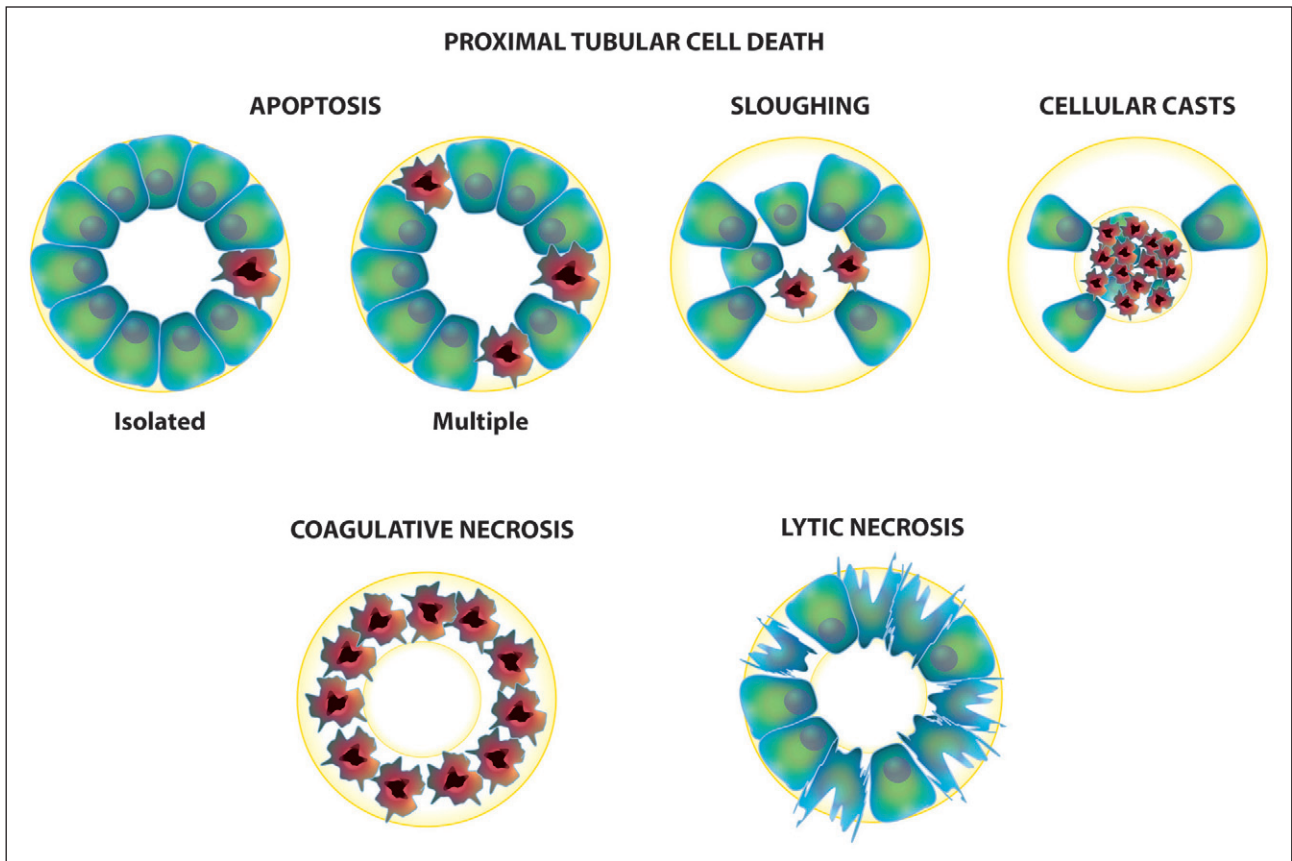
**Figure 3.** Schematic representation of pathological feature of apoptosis, sloughing and necrosis in neonatal AKI.
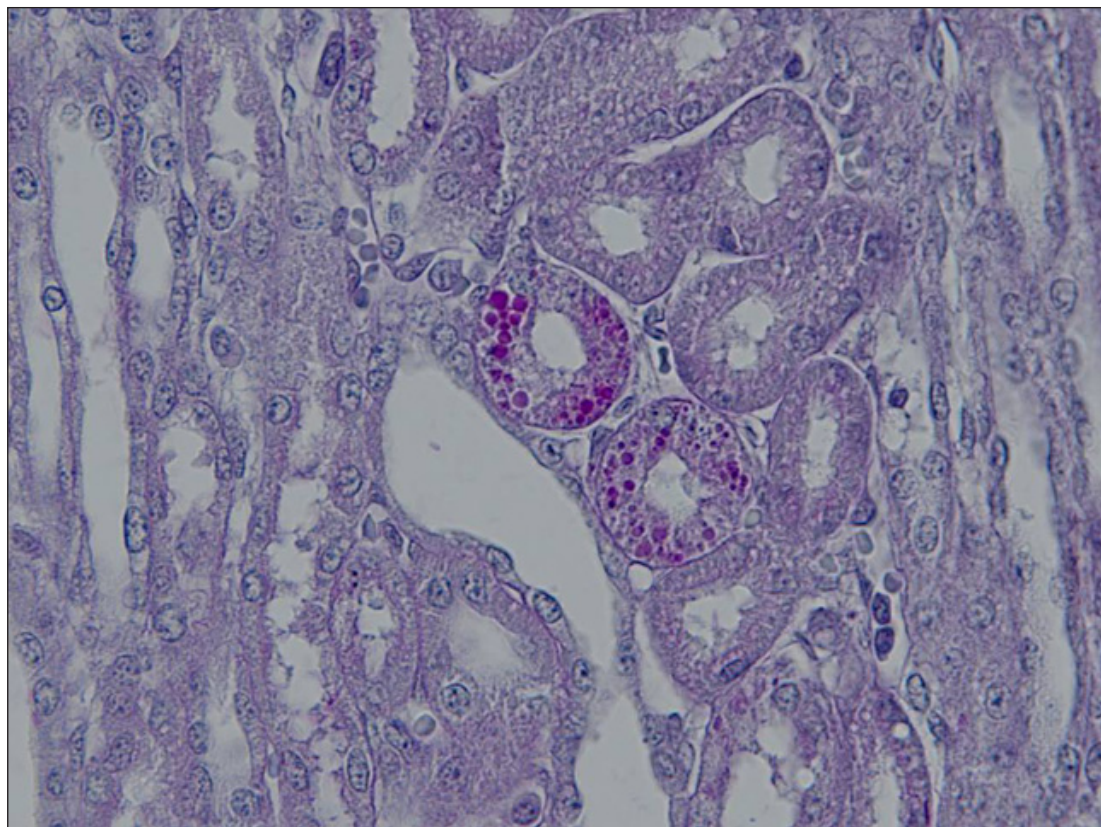


**Figure 4.** PAS-positive apoptotic bodies in proximal tubule.

associated with toxic drug reactions, including non steroid anti-inflammatory drugs (NSAIDs).

### Hyaline casts

Occasional hyaline casts have no clinical significance. Weakly eosinophilic and intensely PAS-positive casts in dilated tubules are frequently seen in acute renal failure.

### Epithelial casts

Epithelial casts are associated with tubular cell death and with sloughing of necrotic tubular epithelium into the tubular lumen.

### Red blood cell casts

The finding of red blood cell casts in the neonatal kidney is much rarer than in adult patients. Red blood cell casts may be associated to clear-cut tubular necrosis with different aetiologies.

### *Elementary lesions of the interstitium*

The interstitial space between the tubules and glomeruli is, in normal conditions, scarcely evidenced. As a consequence, the clear evidence of the intertubular interstitial space is always to be considered a pathological feature. Hereditary interstitial nephritis is characterized, at histology, by interstitial lymphocytic infiltration associated with tubular atrophy, whereas the remaining tubules are hypertrophic and dilated, with thickened basal membrane. In the papilla, cystically dilated tubules may be found. The disease may be associated with congenital liver fibrosis or with paucity of the intrahepatic bile ducts.

### *Elementary vascular lesions*

Endothelial lesions are frequently observed in the kidney of newborns affected by asphyxia or sepsis [11]. In both conditions, endothelial cells of the whole body, including renal arteries and veins, represent the target of multiple molecular pathways, ending with the production of high levels of tumor necrosis factor (TNF) and of multiple cytokines by activated circulating monocytes and dendritic cells. TNF induces endothelial cell apoptosis and detachment, ending with the loss of the endothelial barrier. Two main consequences are clearly detectable, at histology, in these kidneys: i) edema, with increase of the interstitial space; ii) intravascular coagulation and thrombosis. Endothelial dysfunction may be also observed inside the glomerular tuft: activated glomerular endothelial cells are characterized by nuclear swelling, followed by apoptosis, endothelial cell detachment, and glomerular thrombosis. Only rarely, thrombotic microangiopathy (TMA) occurs in the newborn, characterized at the histological level, by the presence of microthrombi, associated with collapse of the tuft and wrinkling of the basal membranes, all morphological markers of glomerular ischemia.

## Differences between the pre-term and the full term newborn kidney

Major changes occur in the human kidney during the last weeks of gestation, regarding the development and differentiation of the vast majority of progenitor cells giving rise to the typical cell types of the mature kidney. These developmental changes are responsible for major differences in the morphology of renal structures and cells in the preterm kidney, as compared with the kidney of at term infants. The first difference, at panoramic view, regards the blue strip. Well evident in preterm kidneys, and characterizing the entire renal architecture, the blue strip suddenly disappears between the 36th and the 38th week, being normally not detectable in the majority of at term babies. The second difference concerns the intermediate structures indicating the ongoing nephrogenesis, including renal vesicles, comma-shaped and S-shaped bodies. All these developmental structures are typical of the preterm kidney, whereas they are not detectable in term infants, clearly indicating that nephrogenesis does not continue after birth in at term infants. The most important stem cell niche, the renal capsule, shows major changes during gestation: it is very well represented and formed by multilayered cells (ranging from 4-5 up to 20 cell layers) in preterm kidneys, and progressively decreases in width during gestation, appearing in term babies as a thin layer with scattered residual progenitor cells. Even glomeruli are structurally different in the preterm kidney. The most evident difference between preterm and at term glomeruli regards podocytes, or better podocyte precursors. In preterms, podocyte precursors show roundish voluminous nuclei with dark condensed chromatin, surrounded by scant cytoplasm, encircling the whole glomerular tuft, and protruding into the capsular space. Podocyte

maturation is characterized, at morphology, by elongation and clearing of nuclei that progressively encircle the underlying capillaries of the tuft. The values obtained by the radial glomerular count progressively increases during gestation: values ranging between 4 and 6 are typical of preterms, whereas in kidneys of at term infants values range from 5-6 up to 8.

Taken all together, these data clearly indicate that the morphological picture of the kidney in preterms shows marked quantitative and qualitative differences as compared to the at term kidneys, allowing expert pathologists to "give an age" to each neonatal kidney, even when only based on morphological data.

**Helpful features for the diagnosis of acute kidney injury in the newborn**

The spectrum of morphological lesions observed in neonates with a clinical diagnosis of AKI is very broad. Architectural changes related to the disease are not present. Glomeruli are normally completely spared. No significant vascular change has been associated to AKI. The tubules represent the main target of the pathogenetic events leading to AKI in neonates. Different degrees of tubular cell involvement may be detected.

a. In the majority of cases, in our experience, no major pathological changes are detected in tubules which, at panoramic view show a normal architecture, with no evidence of the interstitium and normal-appearing tubular cells. In these cases, AKI-related lesions should be investigated at higher power, focusing on proximal tubules, that represent the main target for AKI-related pathogenetic factors.

b. Brush border changes in proximal tubules may represent the unique lesion detectable in renal tubules in the neonate. The interruption in the continuity of the brush border, followed by its loss in scattered tubules, ending with the complete brush border loss in the majority of proximal tubules is the principal lesion neonatal pathologists should look for, in order to confirm the clinical diagnosis (or suspicion) of AKI (**Fig. 2**). The same procedure should be applied in all newborns at autopsy, since AKI may be so subtle from a clinical and laboratory test point of view, that neonatal pathologists should always search for it, independently from the presence of a previous clinical diagnosis of the disease. In the search for subtle changes of the brush border, PAS stain may be useful. In cases of diffuse brush border loss, H&E-stained sections are sufficient to reach the pathological diagnosis.

c. Dilatation of the tubules occurs in all form of severe acute renal damage, often associated with some form of dedifferentiation of the tubular epithelium, with increased basophilia of proximal tubular cells and decrease in the histological differences between proximal and distal tubules. Dilatation may affect both proximal and distal tubules in the renal cortex (**Fig. 2**), whereas collecting tubules are generally spared.

d. Cell death of tubular epithelium also occurs in all forms of severe AKI, primarily affecting the epithelium of proximal tubules, and it is mostly associated with dilatation of the tubular lumen (**Fig. 3**). Different morphological markers of cell death of proximal tubular cells may be detected in the neonatal kidney: i) apoptosis (**Fig. 4**), appearing as scattered roundish eosinophilic cells, detaching from the neighboring cells and sloughing into the tubular lumen; ii) necrosis of tubular cells, appearing as coagulative or lytic necrosis affecting the vast majority of proximal tubules. In these cases, the presence of cellular casts is always associated (**Fig. 3**).

**Concluding remarks**

AKI is a complex disorder without a currently accepted uniform clinical-pathological definition. Having a standard for diagnosing and classifying AKI on a clinical and a histopathological ground would enhance our ability to improve the management of these patients.

The pathological data here reported based on the recent literature, as well on our experience, on the histological study of autoptic kidneys of neonates of different gestational ages, show that some points may be stated regarding the pathophysiology of this condition. First of all, concerning the classical classification of renal diseases into glomerular, tubular and vascular, according with our data AKI may be included in the "tubular" group, at least in the first stages. Secondly, given the predominant localization of pathological lesions in the epithelium of proximal tubules, AKI might be subclassified as a "proximal tubules disease", distal tubules being affected only in the advanced stages of the disease, when

dedifferentiation of tubular epithelium renders the differentiation of proximal and distal tubules problematic.

Interesting data emerge from our study regarding the pathological lesions that, although not specific, may suggest the diagnosis of neonatal AKI. The most interesting finding is the fact that subtle lesions, such as focal fragmentation of the brush border of proximal tubular epithelium, might represent the unique pathological lesion of the neonatal kidney undergoing AKI. This finding may induce to different considerations: on one hand, it underlines the prominent role of the proximal tubular epithelium in kidney physiology; on the other hand, for practical purposes, the identification of so subtle lesions of the brush border, in the absence of major architectural changes, necessitates of an accurate study at higher power of each neonatal kidney. We believe that these recommendations provide a stepping stone to standardizing the histological study of neonatal AKI and will greatly enhance our ability to design prospective studies to evaluate potential preventive and therapeutic strategies for this severe clinical condition.

## Future perspectives

Future clinical and translational research in AKI will require the development of collaborative networks of investigators drawn from various disciplines – including neonatologists, nephrologists, gynecologists, pathologists and clinical chemists – to facilitate the acquisition of evidence through well-designed and well-conducted clinical-pathological trials, dissemination of information via multidisciplinary joint conferences and publications, and improvement of the translation of knowledge from pre-clinical research. The triple-I approach (interactive, interdisciplinary, intersectorial) recently proposed for a better evaluation of metabolomic data and their correlation with histological data in the neonate [12] might help in this direction.

From a pathological point of view, future challenges regard the application of immunohistochemistry to the analysis of the neonatal kidney, to better study the intracellular modifications occurring in the proximal tubular epithelium and allowing a precocious identification of molecular changes leading to the disarrangement of the brush border, to renal dysfunction and to AKI insurgence [13].

## Declaration of interest

The Authors declare that there is no conflict of interest.

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