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Review

# Multiple organ failure in the newborn: the point of view of the pathologist

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*The role of the clinical pathological dialogue in problem solving*
**Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken**

## Abstract

One of the most severe events occurring in critically ill patients admitted to a neonatal intensive care unit (NICU) center is represented by the multiple organ failure (MOF), a systemic inflammatory response leading to a progressive organ dysfunction and mortality in newborns. MOF may occur in newborns primarily affected by multiple single organ diseases, including respiratory distress syndrome neonatal sepsis with acute kidney injury, post-asphyxial hypoxic-ischemic encephalopathy and pandemic influenza A (H1N1) infection. In a previous article from our group, based on the histological examination of all organs at autopsy of newborns affected by MOF, all organs studied did not escape to be damaged, including thymus and pancreas normally not mentioned in the literature of MOF. The aim of this article is to review the most important pathological changes pathologists should look for in every case of MOF occurring in the perinatal period, with particular attention to systemic endothelial changes occurring in blood vessels in all organs and sytems. On the basis of our experience, matching data during the last phases of the clinicopathological diagnosis represents a useful method, much more productive as compared to the method based on giving pathological answers to the clinical questions prospected before autopsy. As for the pathological features observed in neonatal MOF, one of them deserves a particular attention: the vascular lesions, and in particular the multiple changes occurring during MOF development in endothelial cells, ending with the loss of the endothelial barrier, probably the most relevant histological lesion followed by the insurgence of interstitial edema and disseminated

intravascular coagulation. Small vessels should be observed at high power, with particular attention to the size and shape of endothelial nuclei, in order to evidence endothelial swelling, probably the initial modification of the endothelial cells leading to their death. Finally, only the clinical pathological discussion may lead to a good diagnosis, correlating the morphological evidences with the clinical history and the sequence of clinical events that, at the best of our experience, are always different in a new case of MOF.

### Keywords

MOF, endothelial changes, hypoxia, neonatal respiratory distress syndrome, newborn.

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### Introduction

One of the most severe events occurring in critically ill patients admitted to a neonatal intensive care unit (NICU) is represented by the multiple organ failure (MOF), a systemic inflammatory response leading to a progressive organ dysfunction and mortality in newborns [1]. MOF may occur in newborns primarily affected by multiple single organ diseases, including respiratory distress syndrome [2] neonatal sepsis with acute kidney injury (AKI) [3], post-asphyxial hypoxic-ischemic encephalopathy [4] and pandemic influenza A (H1N1) infection [5]. The whole process is characterized by progression of a persistent hyperdinamic, hypermetabolic state towards a gradual functional deterioration of multiple organs and systems [6]. The involvement of seven systems has been generally considered typical of MOF, including cardiovascular, respiratory, renal, suprarenal, hepatic, hematologic and central nervous system [7]. As compared with MOF occurring in adults, neonatal multisystem organ failure has been reported to be characterized by a different sequence of organ involvement [8, 9]. In particular, the earliest organ involvement in neonates was the kidney, followed by microvascular, hematologic, hepatic, pulmonary and cardiac failure [10]. In another study, the sequence of organ involvement in neonatal MOF was slightly different, liver representing the first organ involved in the majority of newborns affected by MOF [6]. A possible explanation for the earlier development of liver function derangement in this study might be the higher proportion of premature infants, being the premature liver more susceptible to toxic exposure than the mature liver.

In a previous article from our group, based on the histological examination of all organs at autopsy of two newborns affected by MOF, all organs studied did not escape to be damaged, including thymus and pancreas normally not mentioned in the literature of MOF [11]. In that study, relevant pathological changes were detected in the blood vessels of the intestinal mucosa, as well as of all the organs examined. According with our data, we hypothesized that the loss of the endothelial barrier might represent the most important pathological change in neonates affected by MOF, followed by disseminated intravascular coagulation, confirming previous data on nonhuman primates [12].

The aim of this article is to review the most important pathological changes pathologists should look for in every case of MOF occurring in the perinatal period, with particular attention to systemic endothelial changes occurring in blood vessels in all organs and sytems.

### Gastrointestinal tract

The accurate study of the intestinal mucosa plays a fundamental role in the histological analysis of every case of MOF. This is mainly due to the hypothesis that the loss of the neonatal gut barrier could represent the primary pathological event in many cases of MOF, followed by endotoxemia and release in the blood of proinflammatory cytokines [13]. This hypothesis has been confirmed by our previous study on two neonates affected by MOF, in which the histological examination of colon and ileum samples revealed frequent areas of epithelial loss, characterized by disappearance of enterocytes, associated with inflammation of the mucosa and intravascular coagulation in the mucosal blood vessels [11]. On the basis of these data, an accurate examination of multiple samples of the ileum and colon appears mandatory in every case of neonatal MOF. In order to obtain optimal histological images of the subtle pathological changes occurring

in the gut during MOF development, the entire intestinal tube should be carefully fixed at autopsy, introducing adequate amounts of 10% formalin inside the intestinal lumen and closing the resection margins, in order to allow an optimal fixation of the enterocytes and of the entire intestinal wall. 24 hours after fixation, multiple specimens should be obtained from different segments of the small intestine, including proximal and distal ileum, from colon, including ascendant, transversum and distal colon, and from sigma and rectum. At microscopy, the following elementary lesions should be checked: the status of enterocytes bordering the intestinal lumen; the presence of inflammatory cells in the intestinal mucosa; the endothelium of the mucosal and submucosal intestinal vessels, with particular attention to the presence of endothelial apoptosis, swelling, detachment (**Fig. 1A**), ending with the loss of the endothelial barrier; the presence of intravascular coagulation. The presence of all these pathological changes should be graded, according with their occurrence in one or in multiple segments of the gut, and according with the intensity of the lesions (for example: lymphocytic infiltration brisk, or diffuse). In the diagnostic report, the presence (or absence of significant lesions of the intestinal barrier and of the endothelial barrier) should be clearly mentioned, as well as the occurrence or the absence of disseminated intravascular coagulation and its extent. The endothelial dysfunction and the loss of the endothelial barrier represent the pathological changes favouring leakage of liquids from the vascular lumen inside the intestinal wall. For this reason, the presence of edema in the intestinal wall should be mentioned, and considered in the final evaluation of the intestinal changes as a confirmative factor of the endothelial dysfunction during MOF development.

## Heart

The first factor to be searched for in the panoramic examination of the heart samples is represented by interstitial edema. Edematous cardiac tissue is characterized by a decrease in its eosinophilia, due to the increase of interstitial liquids without any reactivity for eosin. Edema represents a severe lesion, the increased interstitial fluid increasing the intercellular distance among cardiomyocytes, leading to altered diffusion of the electric wave and to functional disturbances of cardiac function [14]. The presence of edema should induce to a careful examination of the coronary arteries and vein, looking for endothelial changes and for the loss of their endothelial barrier, as a possible pathogenetic factor of interstitial edema. Severe changes in the endothelial barrier of coronary vessels are frequently associated with disseminated intravascular coagulation (**Fig. 1B**), that should be reported and, when possible, graded. The study of cardiomyocytes is mandatory: cytoplasmic vacuolization, increased eosinophilia, cardiomyocyte apoptosis and, more rarely, foci of coagulative necrosis may be also detected.

## Lungs

A careful examination of the status of the respiratory barrier should start with the histological examination of the tracheal and bronchial epithelium. Apoptosis of epithelial cells covering the bronchial mucosa have been reported in neonatal MOF [11]. The presence of mild focal apoptosis may be associated with the general integrity of the respiratory barrier, but diffuse apoptosis of chief and mucosal cells may lead to a complete disruption of the respiratory barrier (**Fig. 1C**) This lesion should be underlined in the autoptic report, representing a possible site of entrance of endotoxins leading to the systemic inflammatory response typical of MOF. The presence of endothelial damage and of disseminated intravascular coagulation in blood vessels of the respiratory mucosa should also be reported. It should be stressed that, in the interpretation of the role played by the different histological changes in the development of MOF in any single case, the association between a loss of the respiratory barrier and the presence of histological lesions suggestive for endothelial dysfunction in the underlying blood vessels may represent a significant association. This suggests the hypothesis that endotoxins entered in the respiratory wall through the fragmented respiratory barrier might have reached the underlying vessels causing apoptosis of the endothelial cells followed by intravascular coagulation and thrombosis. Distal vessels should be carefully examined in different samples of lung parenchyma, looking for signs of endothelial dysfunction and loss. The presence of interstitial edema in close proximity of affected vessels should represent a valuable confirmative finding to support the pathogenetic role played by endothelial dysfunction in the increase of fluids in the lung parenchyma, ending with lung failure in the development of MOF.

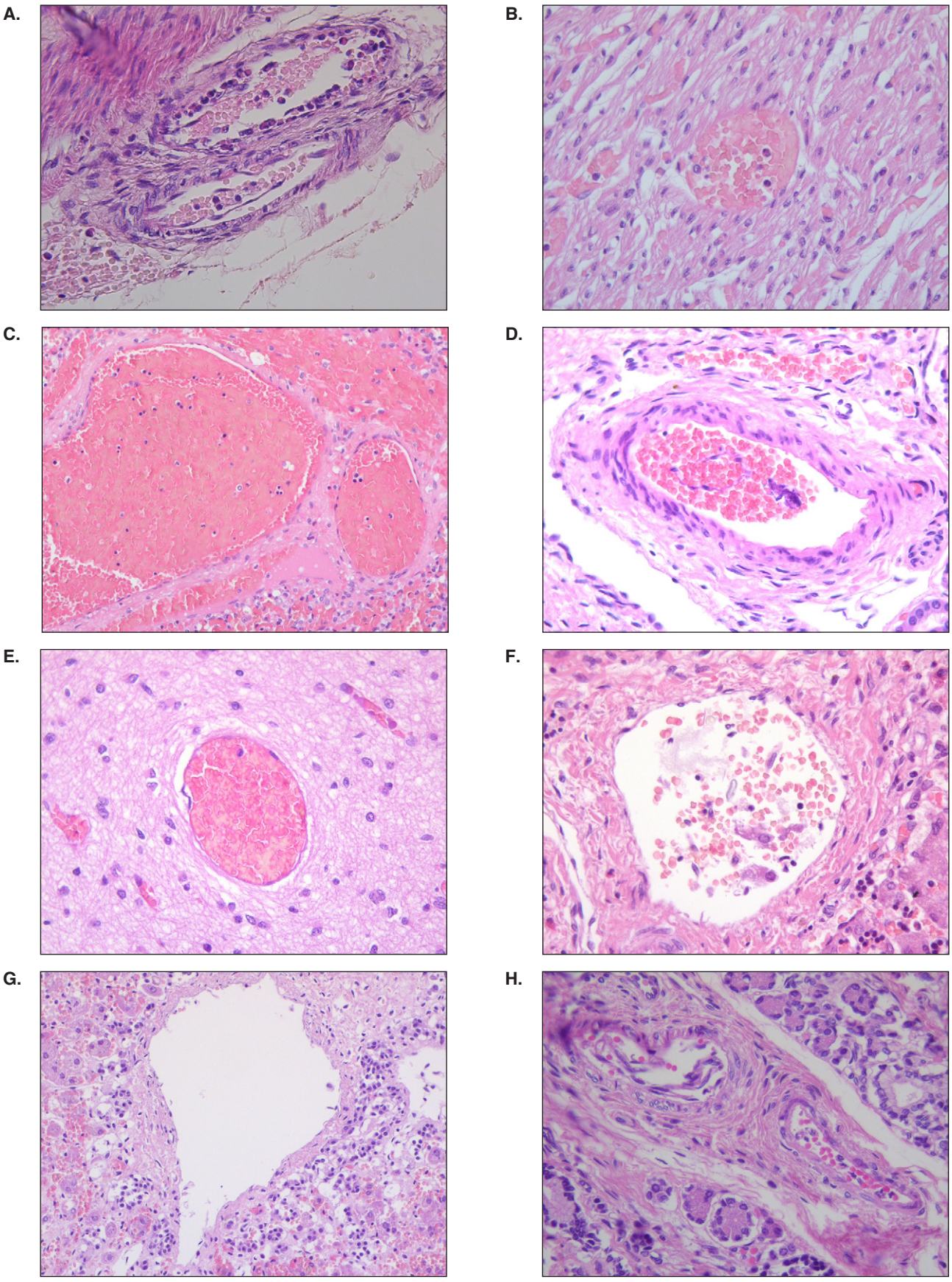


**Figure 1.** Endothelial changes in blood vessels of major organs. **A.** Colon: endothelial swelling and detachment. **B.** Heart: intravascular thrombosis. **C.** Lungs: loss of endothelial barrier. **D.** Kidney: loss of endothelial barrier. **E.** Brain: loss of endothelial barrier. **F.** Liver: endothelial detachment. **G.** Adrenal: apoptosis and loss of endothelial barrier. **H.** Pancreas: endothelial detachment.

## Kidneys

AKI is a common clinical syndrome in critically ill neonates, complicating 30% of admissions to NICU centers, mortality from AKI remaining over 60% when part of MOF [15]. These data clearly indicate the necessity of an accurate histological examination of kidneys in every case of MOF. Attention of pathologists should be focused on the following cells and structures.

a. Endothelial changes in all vascular structures, including endothelial regressive changes, endothelial detachment and disseminated intravascular coagulation (**Fig. 1D**).
b. Interstitial edema, often causing the appearance of a clear space between the proximal and distal tubules.
c. Regressive changes of the proximal tubular cells, including loss of the brush border, cytoplasmic vacuolization, hypereosinophilia, apoptosis, sloughing, tubular casts, ending with diffuse epithelial loss of proximal epithelial cells.
d. Glomerular changes, including retraction of the glomerular tuft (of ten associated with thrombosis of the afferent artery), dilatation of the capillary tuft (often associated with thrombosis of the efferent artery), podocyte precursor loss, glomerular endothelial swelling and/or apoptosis.
e. Medullary changes, including interstitial edema and regressive changes of the collecting duct epithelium.
f. A particular attention should be deserved, in preterm infants, to the subcapsular zone, where stem/progenitor cells are particularly abundant, to evaluate a possible damage occurring in the renal progenitors during MOF development.

## Brain

MOF may be the end result of a post-asphyxial hypoxic-ischemic encephalopathy [4]. In these cases, all pathological changes related to the original cerebral damage should be investigated. The following structures should be carefully analyzed in the brain in all cases of neonatal MOF.

a. Cerebral vessels, both superficial and intracerebral blood vessels. The morphology of endothelial cells, and in particular of endothelial nuclei, should be analyzed at high power. The most frequent lesion is represented by endothelial swelling, with enlarged elongated endothelial nuclei extending into the vascular lumen. In some vessel, two nuclei may touch each other, significantly reducing the vascular lumen and possibly causing functional changes in the intracerebral circulation. Another endothelial lesion is represented by apoptosis: nuclei of affected endothelial cells appear shrunken, hyperchromic, and endothelial cells detach from each other. The complete detachment of endothelial cells by the vascular wall is constantly associate with perivascular edema, appearing as roundish clear halos around the affected vascular structures (**Fig. 1E**).
b. Cerebral edema is the typical consequence of the endothelial barrier loss. When edema develops, the white and/or the grey matter appear clear and less eosinophilic, due to the increased amounts of liquid in the interstitial spaces.
c. Neurons undergoing apoptosis appear as shrunken, dark, spicular cells intermingled with normal-appearing neurons. The neuronal nucleus undergoes shrinkage, followed by fragmentation. Apoptotic cells are often surrounded by activated glial cells. Neuronal apoptosis is not restricted to cortical neurons. At autopsy, the brain should be extensively sampled, including the hippocampus, cerebellum, the pons and medulla. In our experience, it is not rare to find the higher degree of apoptotic cells in these regions, as compared to the cortical brain areas.

## Liver

The histological study of liver samples may give relevant data useful for a better comprehension of MOF development. The first suggestion is to frozen a liver specimen at autopsy: frozen sections by preserving fat droplets possibly present in the cytoplasm of hepatocytes, will allow the evaluation of steatosis, with the Sudan orange stain. The evaluation of steatosis is much more complex and often impossible in formalin-fixed and paraffin-embedded sections, in which the differential diagnosis between vacuolar degenerazion and lipid droplets accumulation is very difficult. A second trick is the execution of some appositions gently putting a liver section on a glass. This simple technique permits the immediate cytological examination of liver cells, allowing a morphological examination of hepatocytes and of hematopoietic cells, as well

as histochemical (Sudan orange for lipids) and immunohistochemical analyses for identifying subpopulations of hematopoietic cells. The histological examination of H&E-stained sections shoud be focused on the hepatic vessels, looking for the presence of endothelial changes both in portal arteries and veins and in terminal (central) veins (**Fig. 1F**). Sinusoidal dilatation is often observed, and when associated with atrophy of liver cell plates, is indicative of chronic disturbances in the intrahepatic circulation. Sinusoidal dilatation may be associated with enlargement of Disse spaces, that become evident at high powers. Significant information may be also obtained by the evaluation of the amount of hematopoietic cells in the liver of neonates affected by MOF. In cases of asphyxia, the hematopoietic cell burden may be increased, possibly due to the increased levels of the hypoxia inducible factor (HIF). In other patients, hepatic hematopoiesis may be severely reduced, due to a failure of the hematopoietic system in the set of developing MOF.

### Adrenals

Adrenal glands are often reported to be involved in neonatal MOF, adrenal hemorrhage being the most frequent lesion of suprarenal glands in the perinatal period [16]. Our preliminary data [17] show that pathological changes may occur in adrenal glands in newborns undergoing MOF. Adrenal arteries may show histological signs of endothelial dysfunction, leading to loss of the endothelial barrier and to adrenal cortex edema (**Fig. 1G**). Moreover, some delay in adrenal gland maturation was observed in MOF, affecting both the definitive and fetal cortical zones, as well as the developing medullary zone.

### Pancreas

Even though pancreas is not generally enlisted among the organs primarily affected by MOF, pancreatic damage has been reported to occur in critically ill children undergoing MOF [18]. According with our experience, pancreas is often damaged in MOF [11]. Endothelial damage (**Fig. 1H**) in intrapancreatic vessels represent the first pathological lesion to look for in every pancreas in the set of a MOF, possibly associated with intravascular coagulation and/or with edema of the pancreatic exocrine pancreas.

## Conclusions

The macroscopic and microscopic analysis of every newborn with a clinical diagnosis of MOF represents for perinatal pathologists a continuous challenge, finalized to confirm, at tissue level, the clinical diagnosis of multiple organ involvement, and aimed at revealing at microscopical level subtle pathological changes that could not be evident in the complex clinical setting typical of neonatal MOF. In this diagnostic procedure, on the basis of the 30 year-old cooperation between the Institute of Pathology and the NICU of AOU and University of Cagliari, we suggest the following method. The pathologist should perform his best morphological diagnosis, mainly based on morphological and, occasionally, histochemical and immunohistochemical data. At this point, the clinical pathological discussion is mandatory, putting on the table the clinical and laboratory data regarding the prenatal and the postnatal life and comparing them with pathological data emerging from autopsy and from histological analysis of tissue samples from all the organs. On the basis of our experience, matching data during the last phases of the clinicopathological diagnosis, represents a useful method, much more productive as compared to the method based on giving pathological answers to the clinical questions prospected before autopsy. As an example, no neonatologist even when extremely expert, will ask the pathologist to look carefully at thymus, or at thyroid gland or at other organs and systems normally not involved, or better normally not reported to be damaged in the clinical setting of MOF. On the contrary, our experience shows that a careful pathological examination of all organs and systems may give useful information that may result of some relevance in the final clinico-pathological diagnosis of every case of MOF.

From a practical point of view, a complete and fruitful pathological examination of every newborn affected by MOF necessitates a particular training in perinatal pathology. The macroscopic and microscopic features, including the architecture of all organs in the newborn is characterized by marked differences, as compared to the adult organism, in physiological conditions. This diversity is enhanced in pathology and particularly in the setting of MOF, when multiple organs undergo major structural changes ending with severe dysfunctions.

As for the pathological features observed in neonatal MOF, one of them deserves a particular attention: the vascular lesions, and in particular

the multiple changes occurring during MOF development in endothelial cells, ending with the loss of the endothelial barrier, probably the most relevant histological lesion followed by the insurgence of interstitial edema and disseminated intravascular coagulation. This finding necessitates a particular training for pathologists interested to focus on perinatal pathology and, specifically, on the fine interpretations of MOF. Small vessels should be observed at high power, with particular attention to the size and shape of endothelial nuclei, to evidence endothelial swelling, probably the initial modification of the endothelial cells leading to their death. Since endothelial lesions are, on the basis of our experience, very similar in vessels from different organs, their recognition might allow the pathologist in training to evaluate MOF-related damage in all different organs.

Finally, only the clinicopathological discussion may lead to a good diagnosis, correlating the morphological evidences with the clinical history and the sequence of clinical events that, at the best of our experience, are always different in any new case of MOF.

## Declaration of interest

The Authors declare that there is no conflict of interest.

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