Pathological findings of kidney tissue in deceased COVID-19 patients.

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Introduction:

Since the pandemic state was declared in March 2020 by WHO, millions of people worldwide became infected by SARS-CoV-2 virus (1). This novel coronavirus inducing COVID-19 disease primarily targeting the lungs is also known to involve multiple organs and tissues. As many people don't survive the infection, this disease became one of the leading causes of death in several countries, especially in the U.S. (2). Numerous studies revealed that underlying health conditions and comorbidities are significant risk factors regarding the course of the infection. There is a six-time higher rate of hospitalization of patients suffering from underlying health conditions compared to the patients without comorbidities (3). The kidney involvement in COVID-19 has been frequently reported. Previous studies revealed COVID-19-associated acute kidney insufficiency (AKI) (4). Post-mortem findings commonly revealed epithelial necrosis and acute tubular injury (5,6). The main focus in the presented research is to evaluate morphological changes of renal tissue in COVID-19 patients in relation to clinical data.

Methods:

Renal tissue samples from 42 patients suffering from COVID-19, who died between April 2020 and February 2021 in Slovakia have been evaluated by light microscopy. The diagnosis of SARS-CoV-2 infection was confirmed by nucleic acid testing of nasopharyngeal secretion as a PCR test or as an antigen test based on immunochromatography. The kidney tissue was sampled during autopsy after fixation in 4 % formaldehyde processed into paraffin, sliced and histological slides were stained with hematoxylin and eosin. Histomorphological findings of glomerulosclerosis, glomerular capillary thrombosis, thrombosis of large vessels, canalicular epithelium necrosis and interstitial inflammatory infiltrate, were assessed semiquantitatively in the following grades: negative; <10%; 11-50%; 51-100%. Evaluation of the presence and intensity of large vessels arteriosclerosis, arteriolosclerosis and mesangial thickening was from light, moderate to prominent. Further, clinical data from the patient were collected including hospitalization period, death-autopsy time interval, Creatinine blood levels and eGFR by using CKD-EPI equation. Also, pre-diagnosed comorbidities such as arterial hypertension, Diabetes mellitus, obesity and acute or chronic renal insufficiency have been assessed. All data and results were collected and further investigated by analysis of variance.

Results:

Overall, 42 samples from SARS-CoV-2 infected patients were investigated and included 22 females and 20 males with an average age of 74,4 years (range: 32–95 years). The average hospitalization period amounts approx. 9 days and the interval between the time of death and subsequent autopsy is 31,2 hours in average. Regarding the comorbidities, 73,8% of all patients were diagnosed with arterial hypertension, 33,3% with Diabetes mellitus (DM) and 30,9% with obesity. Acute renal insufficiency was reported in one third of cases (33%) and chronic renal insufficiency in 30,9%.

In all samples arteriosclerosis of large vessels was present and in six of these cases the feature was evaluated as severe. Common findings from histological examination were arteriolosclerosis in 80,9% of cases, followed by glomerulosclerosis (76,2%) and mesangial thickening (71,4%). The arteriolosclerosis was evaluated from light to prominent and is described of medium severity degree in seven cases (Fig. 1).

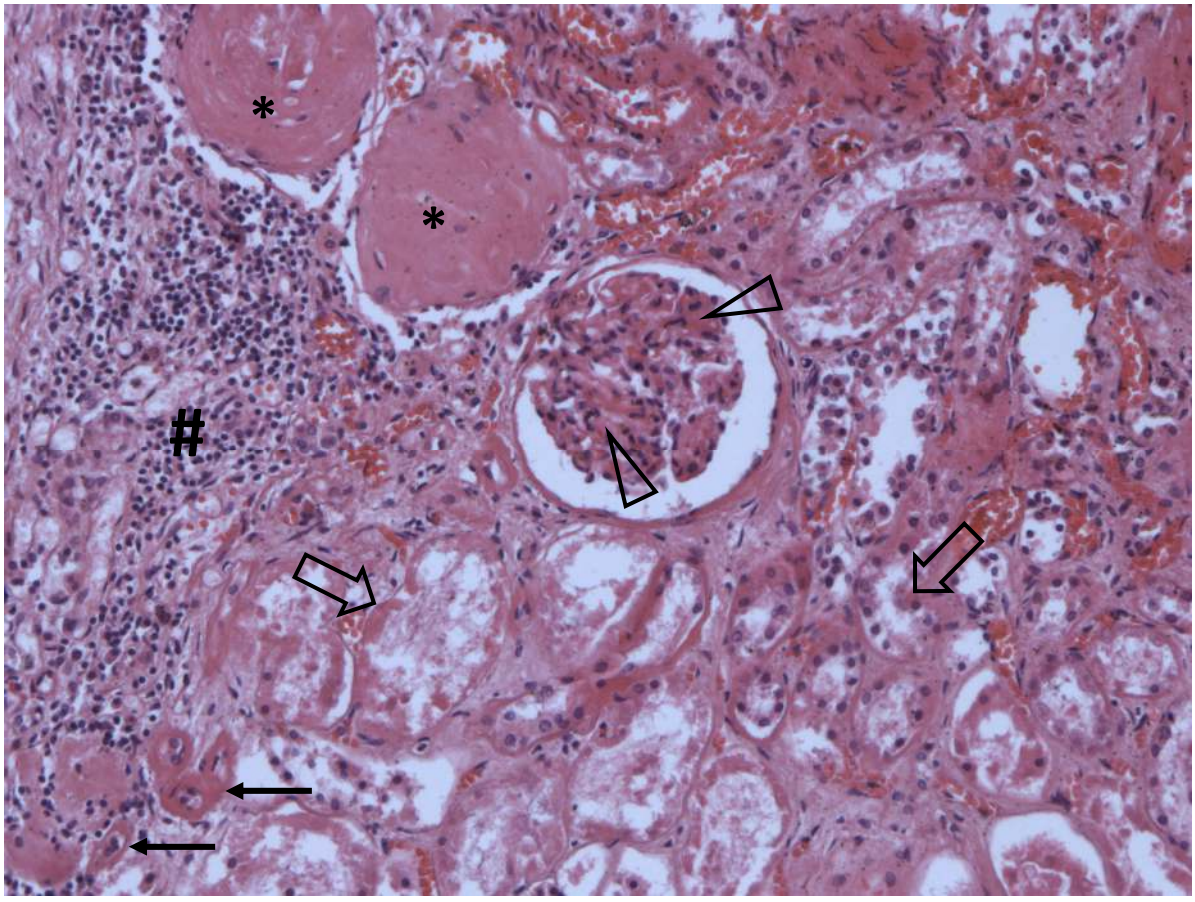

Figure 1. Kidney of a patient with hypertension and diabetes mellitus, who died of COVID-19. Thickened arterioles show signs of arteriolosclerosis (arrow), mesangium of glomerulus (arrowhead) is thickened, high portion of glomeruli was fibrotized (*), focal lymphocytic interstitial infiltrate (#), some epithelial cells of proximal canaliculi were alive with visible nuclei (open arrow, right), most of the canaliculi were necrotic (open arrow, left). Hematoxylin and eosin, 200x.

Moderate glomerulosclerosis, (11 - 50%) of the tissue sample was found in four cases and serious (>51% of glomeruli) glomerulosclerosis was in two patients. The mesangial thickness was of moderate intensity in five cases.

The morphological changes which can be linked to clinical data are summarized in Table 1. Some of the morphological findings represent expected manifestations of the underlying clinical conditions. All of the pathological morphological changes corresponded to situations worsening the clinical condition of COVID-19.

Morphological changes	Associated clinical data	p value
canalicular necrosis of epithelium	death-autopsy interval	p<0,01
arteriosclerosis of large vessels	max. Creatinine levels	p<0,01
interstitial inflammatory infiltrate	max. Creatinine levels	p<0,05
glomerulosclerosis	Acute renal insufficiency	p<0,05
glomerulosclerosis	Chronic renal insufficiency	p<0,05
interstitial inflammatory infiltrate	Diabetes mellitus	p<0,01
mesangial thickness	Diabetes mellitus	p<0,05
arteriolosclerosis	Diabetes mellitus	p<0,05
canalicular necrosis of epithelium	Obesity	p<0,05
Arteriolosclerosis	Arterial hypertension	p=0,083
canalicular necrosis of epithelium	Diabetes mellitus	p=0,063
arteriosclerosis of large vessels	Diabetes mellitus	p=0,057
glomerulosclerosis	max. CKD-EPI	p=0,1

Table1.: Morphological changes associated with some of the clinical data and their significance

Discussion:

Post-mortem studies represent an unreplaceable source of knowledge about the impact of SARS-CoV-2 virus infection. Most of the studies focus on lung tissue changes, however, other tissues and organs may be significantly damaged and can contribute to the negative outcome of the disease. The present post-mortem study is based on these histopathologic findings from 42 autopsies of patients, who died due to COVID-19. The autopsy results focus on changes within the renal tissue, that are correlated with clinical data and comorbidities. Therefore, this study may provide important information for future research in the field of clinical pathology dealing with COVID-19 infection and kidney damage.

One of the prominent findings are the strong connections between the canalicular epithelium necrosis and the death-autopsy interval. This strong correlation can only partly be explained by autolysis. As autolysis is exhibiting similar histologic features as ATN, it is difficult to differentiate between them. This is also supported by the study by Santoriello et al. with the post-mortem interval of 21,8h in average and their main finding, that ATI was obscured by post-mortal autolysis (7). Similar picture of acute tubular injury revealed the study from China in 2020 (8). The death-autopsy interval was one to six hours and therefore no association between death-autopsy interval and acute tubular necrosis can be drawn. Another retrospective analysis revealed tubular damage as the main finding with the post-mortem interval of less than 24 hours (9). It is evident, that autolysis is participating at the tubular damage histological picture but the underlying disease is the principal cause of the change.

Su et al. (5) further pointed out mesangial expanding, arteriosclerosis of medium-sized blood vessels and focal segmental glomerulosclerosis. Other findings refer to glomerular and peritubular occlusion by erythrocytes without platelets or thrombi. As the mean age with 69 is

very close to that of our study and 11 of the 26 investigated patients were diagnosed with DM, arterial hypertension or both (8), similar results to those found in our study can be explained.

The max. creatinine level in our study revealed to be related to interstitial inflammatory infiltrate as well as to arteriosclerosis of large vessels. In a study from Slovenia, there was confirmed the association between serum creatinine levels and the degree of coronary arteriosclerosis. The study discovered that elevated serum creatinine could be also associated with renal artery stenosis (10). Their conclusion, that creatinine could be a marker of nephrovasculopathy featuring structural tissue changes, support our findings.

Further, we found out that patients diagnosed with Diabetes mellitus commonly show interstitial inflammatory infiltrate as well as arteriosclerosis and mesangial thickening. This is supported by findings from previous studies, in which the majority of glomeruli showed structural changes in cases having comorbidities such as diabetes and long-standing hypertension (6). The relation to the inflammatory infiltrate, which was found in diabetic patients, cannot be emphasised by other studies.

Our study pointed out, that the association between obesity and canalicular necrosis of the epithelium cannot be underlined by previous studies. They showed that obesity is one of the major causes of the development of chronic kidney disease, referring to glomerulopathy and nephrolithiasis (11). Since obesity represents an important factor for development of cardiovascular diseases and is closely related to diabetes mellitus (12), our finding of correlation of obesity with the morphological picture of acute renal failure with canalicular epithelium necrosis, is not surprising.

The reported results should be interpreted considering following limitations. The number of investigated cases which amounts 42 is small and there is also a lack of a control group. Since the group of patients was hospitalized in several different centres, the clinical data may represent COVID-19 patients in general.

More extended research is still necessary for characterizing and understanding pathophysiology of COVID-19, especially regarding the impact on kidneys.

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References:

1 Khan, Mujeeb et al. (2020) “COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far,” Molecules (Basel, Switzerland). NLM (Medline). doi:10.3390/molecules26010039.

2 Ahmad, F.B. et al. (2022) “Provisional Mortality Data — United States, 2020,” MMWR. Morbidity and Mortality Weekly Report, 70(14), pp. 519–522. doi:10.15585/MMWR.MM7014E1.

3 Stokes, E.K. et al. (2020) “Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020,” Morbidity and Mortality Weekly Report, 69(24), p. 759. doi:10.15585/MMWR.MM6924E2.

4 Smarz-Widelska, I. *et al.* (2021) “Pathophysiology and Clinical Manifestations of COVID-19-Related Acute Kidney Injury—The Current State of Knowledge and Future Perspectives,” *International Journal of Molecular Sciences*, 22(13). doi:10.3390/IJMS22137082.

5 Menter, T. *et al.* (2020) “Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction,” *Histopathology*, 77(2), p. 198. doi:10.1111/HIS.14134.

6 Golmai, P. *et al.* (2020) “Histopathologic and Ultrastructural Findings in Postmortem Kidney Biopsy Material in 12 Patients with AKI and COVID-19,” *Journal of the American Society of Nephrology*, 31(9), pp. 1944–1947. doi:10.1681/ASN.2020050683/-/DCSUPPLEMENTAL.

7 Santoriello, D. et al. (2020) “Postmortem Kidney Pathology Findings in Patients with COVID-19,” Journal of the American Society of Nephrology, 31(9), pp. 2158–2167. doi:10.1681/ASN.2020050744/-/DCSUPPLEMENTAL.

8 Su, H., Yang, M., Wan, C., Yi, L. X., Tang, F., Zhu, H. Y., Yi, F., Yang, H. C., Fogo, A. B., Nie, X., & Zhang, C. (2020). Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney international, 98(1), 219–227. doi.org/10.1016/j.kint.2020.04.003

9 Diao, B. et al. (2021) “Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection,” Nature Communications, 12(1). doi:10.1038/S41467-021-22781-1.

10 Cerne, D. et al. (2000) “Mildly elevated serum creatinine concentration correlates with the extent of coronary atherosclerosis,” Renal failure, 22(6), pp. 799–808. doi:10.1081/JDI-100101965.

11 Silva Junior, G.B. da et al. (2017) “Obesity and kidney disease,” Jornal brasileiro de nefrologia : ’orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia, 39(1), pp. 65–69. doi:10.5935/0101-2800.20170011.

12 García-Carro, C. *et al.* (2021) “A Nephrologist Perspective on Obesity: From Kidney Injury to Clinical Management,” *Frontiers in Medicine*, 8, p. 418. doi:10.3389/FMED.2021.655871/BIBTEX.