

Pathomorphology of the Zona Glomerulosa of the Adrenal Glands in COVID-19

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Abstract In this article, pathomorphological changes of the cortical columnar area of the adrenal gland in COVID-19 infection are studied. The results showed that the interstitial tissue and blood vessels of the columnar region of the adrenal cortex during the COVID-19 infection exhibited severe discirculation, edema, haemorrhage and inflammatory infiltrates. It was found that in those patients who died from COVID-19, severe interstitial edema and destruction developed in the outer membrane and zona glomerulosa of the adrenal cortex, and in the columnar zone, the cytoplasm of parenchymal cells expanded and swollen due to vacuolar and fatty degeneration. It has been determined that necrobiosis, necrosis and infarction foci occur in the columnar region of the adrenal cortex due to various mechanisms, including discirculation, dystrophy, hypoxia and ischemia. Foci of necrosis and infarction undergo reparative regeneration over time and are morphologically infiltrated by macrophages, other histiocytic cells and lymphocytes.

Keywords COVID-19, Adrenal glands, Zona glomerulosa, Columnar region, Fibrinoid necrosis, Thrombosis, Infarction

1. Introduction

The columnar zone of the adrenal cortex occupies two-thirds of the gland and consists of large adrenocorticocytes that form long columns. They predominantly synthesize glucocorticoid hormones, such as cortisol and cortisone, affect the immune system, slow down the growth of connective tissue, and reduce the rate of inflammatory and allergic processes. Today, more than 50 steroid compounds synthesized by the adrenal cortex have been identified. They are divided into two groups: glucocorticoids and mineralocorticoids, the first mainly affects the metabolism of carbohydrates, and the second controls the metabolism of minerals. Cortisol, cortisone and corticosterone from glucocorticoid hormones are synthesized in the columnar region of the adrenal cortex. In particular, hydrocortisone ensures the accumulation of glycogen in the liver and skeletal muscles, and also slows it down in other tissues. Aldosterone is responsible for water-salt metabolism and maintains the ratio of potassium and sodium salts to each other. Cortisol stimulates the immune system. If the body is exposed to unexpected stress, cortisol begins to be produced. As a result, brain function improves, heart muscles are strengthened, and the body can withstand any stress load.

Cortisol is one of the glucocorticoids and is produced in the zona fasciculata of the adrenal cortex. It controls blood pressure, participates in protein, fat and carbohydrate metabolism, and protects the body from stressful situations.

The synthesis and secretion of cortisol is controlled by adrenocorticotrophic hormone (ACTH) through the opposite mechanism. ACTH is a hormone of the anterior pituitary gland, produced under the influence of tropic factors of the hypothalamus and having its own daily rhythmic cycle. Cushing's syndrome develops when the amount of cortisol in the blood increases. The development of this disease is observed with tumor diseases of the glands and the use of glucocorticosteroid hormones in large quantities. If the synthesis of glucocorticoids and mineralocorticoids by the gland is reduced, Addison's disease develops.

It has been established that during infection with COVID-19, the blood vessels of the adrenal glands can be damaged, and then the parenchymal cells. Fibrinoid necrosis of the vascular wall in the gland tissue, the development of thrombosis and infarctions continue with irreversible damage to the adrenal parenchyma, the synthesis of hormones is disrupted, and metabolism in the internal organs is disrupted. Therefore, the problem of studying damage to the adrenal glands, including pathomorphological changes developing in the zona fasciculata of the cortex during COVID-19 disease, is relevant.

2. Material and Methods

During the 2020-2021 pandemic, the adrenal glands were removed during autopsies of people who died from COVID-19 in 42 cases. Pieces of glands were frozen in a neutralized solution of 10% formaldehyde for 72 hours. They were washed in running water for 3-4 hours, dehydrated in

alcohols of increasing concentrations, paraffin and wax were added and blocks were prepared. Histological sections 5-7 μm thick were prepared from paraffin blocks, deparaffinized and stained with hematoxylin and eosin. The state of connective tissue fibers in the tissue was studied with picrofuchsin using the Van Gieson method, and the accumulation of acid glycosaminoglycans was studied with Alcian blue staining.

3. Results

The results of the study showed that the morphofunctional areas of the adrenal cortex of patients who died from COVID-19 underwent various morphological changes, including vasodilation, the development of plethora, and the development of perivascular hemorrhages in some areas. It has been established that the histotopographic area where the blood vessels are located, i.e. interstitial tissue is highly edematous and susceptible to hydration, especially in the subcapsular region, glomerular and fascicular zones, focal development of the edema process is noted. It was established that in some areas of the zona fasciculata the process of edema predominated, in others hemorrhages and necrotic processes took up a lot of space, and in others inflammatory lymphohistiocytic infiltration appeared. During COVID-19, under the influence of the SARS-CoV-2 virus, first the arteries and arterioles of the outer shell undergo fibrinoid edema, some of them undergo thrombosis, resulting in acute discirculation in the blood vessels that penetrate the parenchyma of the gland, as a result of damage to the intermediate tissue, acidic substances accumulate glycosaminoglycans, the tissue was hydrated and edematous. To determine the accumulation of acidic glycosaminoglycans, when staining a tissue section with Alcian blue, acidic interstitial tissue was stained dark blue, and this process was manifested by positive staining of the interstitial tissue of the outer membrane and the zona glomerulosa of the subcapsular region (Figure 1).

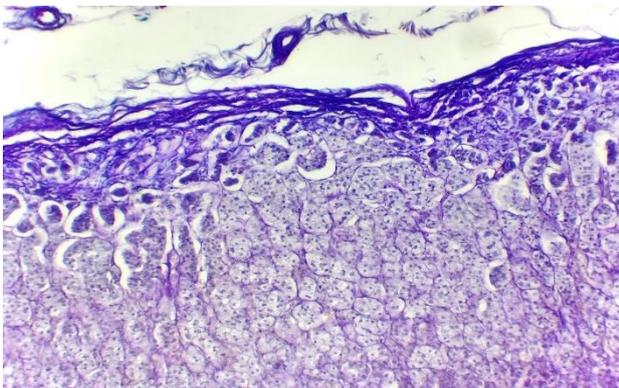


Figure 1. E, 37-year-old man who died of COVID-19, blue staining of the adrenal gland, outer connective tissue membrane, and interstitium of the glomerulosa region. Alcian blue(10x20)

When infected with COVID-19, severe discirculation and interstitial edema developed in the glomerular region of the

adrenal cortex, and in the fascicular region, on the contrary, the cytoplasm of parenchymal cells sharply increased due to edema and accumulation of fatty substances. As a result, it was found that adrenocorticocyte cells in this area violate the bundle arrangement, are located close to each other, are relatively lightly colored, and have a disordered appearance with expanded cytoplasm (Fig. 2). It has been established that the nuclei of adrenocorticocytes are round, located in the middle of the cell, some of them are hypertrophied and hyperchromic. It was found that the blood vessels in the interstitial tissue of this area are sharply dilated and thickened in places. By staining with picrofuchsin the connective tissue fibrous structures in the wall of the blood vessel and the interstitial tissue of the adrenal gland, it is determined that the connective tissue fibers and blood vessels in the outer membrane have passed through the zona glomerulosa and spread between the zona fasciculata and the innermost reticular zone. When examining the zona fasciculata of the adrenal cortex under a high magnification microscope, it turned out that the blood vessels of the interstitial tissue were sharply dilated, full of blood, and there was perivascular hemorrhage around some of them (Fig. 3). It has been determined that in some areas of interstitial connective tissue, around blood vessels, lymphoid cells form clusters. Due to vacuolar and fatty degeneration, the cytoplasm of adrenocorticocytes swells and enlarges, as a result of which the bundle arrangement is disrupted, the cells appear in separate bundles, as a result, the nuclei come closer to each other, and false multinucleated cells appear.

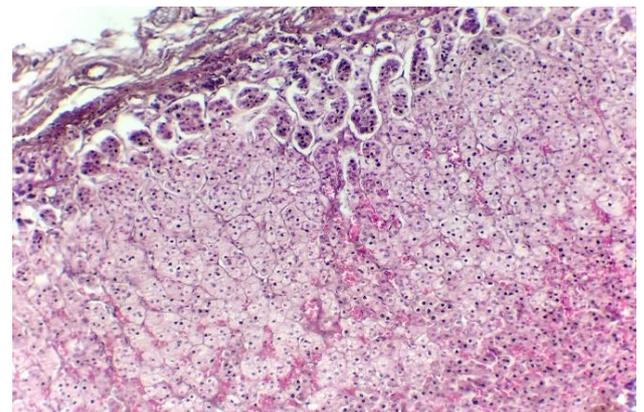


Figure 2. A, 51-year-old man who died of COVID-19, adrenal cortex, severe plethora, hemorrhage, edema of zona glomerulosa, severe vacuolar dystrophy of columnar cells. H-E(10x10)

Due to the impact of COVID-19 infection, the discirculatory process that began in the arteries and arterioles of the outer layer of the adrenal gland spreads to the glandular tissue, the capillaries in the interstitial tissue of the columnar region expand and fill with blood, blood vessels rupture at the border of its reticular layer, massive blood flows into the interstitial tissue and parenchyma of the gland. It is determined that it was poured out. It is noted that the spilled blood completely occupied the interstitial tissue, caused inflammation, disorganization of parenchymal cells, some cells were destroyed and necrotic. It was established

that the remaining parenchymal cells are located in separate bundles and regenerative cells appeared among them.

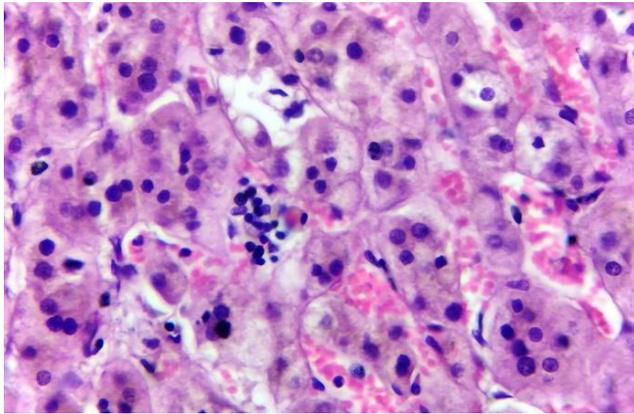


Figure 3. A, 51-year-old man who died of COVID-19, the cortex of the adrenal gland, the vessels are full, diapedesis hemorrhages, the cytoplasm of parenchymatous cells are swollen and enlarged. H-E(10x40)

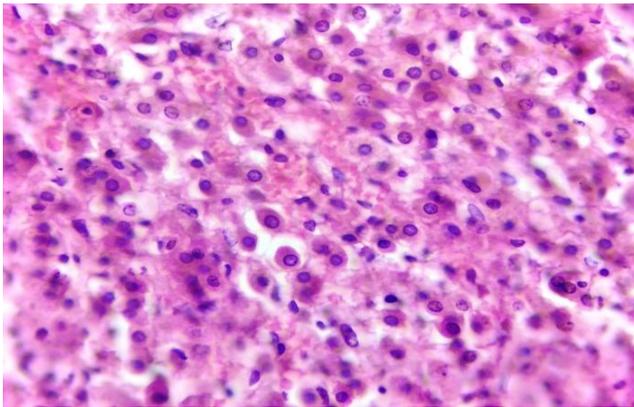


Figure 4. B, 55-year-old man who died of COVID-19, showed adrenal cortical, columnar area microinfarct foci and interstitial tissue proliferation. H-E(10x40)

4. Discussion

It has been established that blood cells poured into the columnar region of the adrenal gland disintegrate, are absorbed by macrophages and other connective tissue cells and turn into hemoglobinogenic pigments, as a result of which histiocytic cells and connective tissue macrophages multiply in the interstitial tissue, and an infiltrate appears. It is observed that the parenchymal cells of the columnar region of the gland have lost their columnar arrangement and are located chaotically, most of the cells have undergone necrosis and necrobiosis, and foci of necrosis have appeared in the form of microinfarcts (Fig. 4). Among the parenchymal cells, the presence of regenerating and restoring cells was determined. These cells are relatively small in size, the cytoplasm is thin and eosinophilic, the nucleus is round and relatively large.

In the columnar region of the adrenal cortex, necrosis of both parenchymal and stromal cells and foci of infarction in areas affected by ischemia are observed. In such foci, nuclei under the influence of hematoxylin-eosin are absent, the

cytoplasm of cells and interstitial tissue are palely stained with eosin, which indicates the occurrence of necrosis, i.e., infarct foci (Fig. 5). It has been established that the parenchyma of the gland around the infarction has lost its columnar structure, adrenocorticoyte cells are located chaotically and these cells are separated from each other, due to self-regeneration their sizes are reduced, the cytoplasm is concentrated and painted in a dark color by eosin, and the nucleus is hypertrophied and hyperchromic. The fact that a lymphoid infiltrate appeared in the center of the infarction, as well as the presence of macrophages and pigments in this infiltrate, indicates that these histiocytic cells phagocytose and clear necrotic tissue fragments.

During this period, as a result of severe discirculation and edema in the deep layers of the columnar region of the adrenal cortex, parenchymal cells undergo deep vacuolar degeneration and colliquative necrosis. At the same time, the interstitial space of the gland tissue was greatly swollen, and uncolored discharge appeared in the form of cavities. It has been established that the parenchymal cells of the gland are compressed under the influence of swelling, collapse and do not swell, the cytoplasm of the cells is filled with small and large vacuoles, some of them have undergone colliquative necrosis.

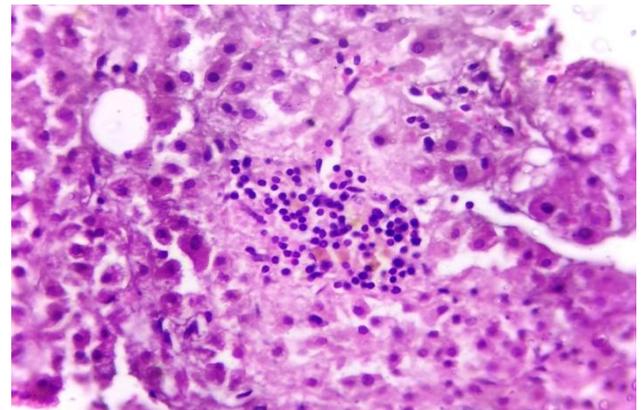


Figure 5. Z, 45-year-old woman who died of COVID-19, had an infarct in the columnar area of the adrenal cortex and lymphoid infiltrate. H-E(10x40)

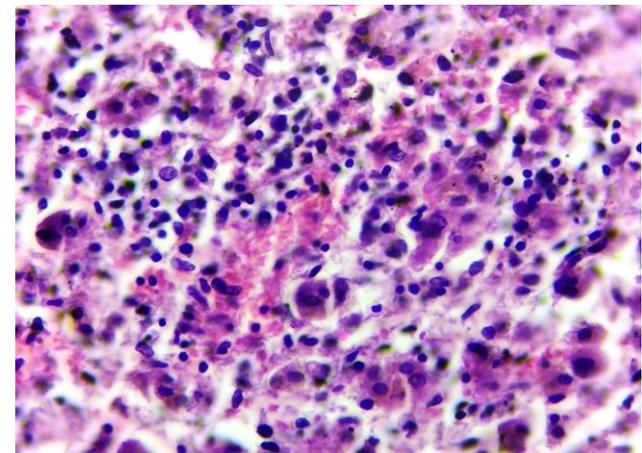


Figure 6. Y, 61-year-old man who died of COVID-19, macrophages, histiocytic, and lymphoid cell infiltration in a focus of necrosis in the columnar area of the adrenal cortex, H-E(10x40)

Necrobiosis of parenchymal cells and foci of necrosis developed in the adrenal tissue under the influence of COVID-19 infection and is caused by various mechanisms due to the activation of lymphohistiocytic cells in the interstitial tissue and the acceleration of the process of reparative regeneration diffusely with macrophage and other histiocytic cells, as well as diffusely with infiltration by lymphoid cells (Fig. 6). Hemoglobinogenic pigments are observed during phagocytosis of macrophages during the breakdown of erythrocytes in necrotic foci. In the affected areas of the gland parenchyma, macrophages and other histiocytic cells destroy the necrotic mass. As a result, it is determined that the focus of necrosis is completely and diffusely infiltrated by macrophages, histiocytic cells and lymphocytes. It has been established that the parenchymal cells preserved in this infiltrate undergo regeneration and have a different morphological appearance: some of them are hypertrophied and enlarged, and others are atrophied and wrinkled.

5. Conclusions

When infected with COVID-19, severe discirculation, edema, hemorrhage and inflammatory infiltrate are observed in the interstitial tissue and blood vessels of the columnar region of the adrenal cortex.

In those patients who died from COVID-19, severe interstitial edema and destruction developed in the outer membrane and capsular zones of the adrenal cortex, and in the columnar zone, the cytoplasm of parenchymal cells grew and swelled due to vacuolar and fatty degeneration.

It has been established that necrobiosis, necrosis and infarction foci occur in the columnar region of the adrenal cortex due to various mechanisms, including discirculation, dystrophy, hypoxia and ischemia.

Foci of necrosis and infarction undergo reparative regeneration over time and are morphologically infiltrated by macrophages, other histiocytic cells and lymphocytes.

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