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HANTAVIRUS INFECTION -
PATHOLOGICAL FINDINGS*

HANTAVIRUSNE INFEKCIJE –
PATOLOŠKI NALAZ*

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Abstract

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Ključne reči

hantavirus, patološki nalaz, biopsija

The causes of human hantavirus infection belong to the family Bunyaviridae. The form and severity of the disease depend mainly on serotype of the particular virus. The following two diseases caused by hantaviruses have been most frequently described: hemorrhagic fever with renal syndrome (HFRS), and hantavirus pulmonary syndrome (HPS). Numerous studies using autopsied materials from the patients who died HFRS have been made. The most prominent pathohistological finding in the initial stage of the disease is a dilatation of blood vessels in the corticomedullary zone, while renal interstitial haemorrhage is detectable in in the later stadium. In addition, a frequent finding is the presence of hyaline granules in epithelial cells of tubules changed by degeneration and various degree of necrosis which includes the tubular basal membrane too. Glomerular changes are minimal and usually present as unequal thickenings of the glomerular basal membrane and capsule. A frequent common finding of all the researchers during autopsy in the acute stage of the disease was the hemorrhage in hypophysis, kidneys and in the myocardial wall. The main materials for pathomorphological investigations are tissue specimens taken by needle biopsy, most frequently from kidneys, rarely from liver. During autopsy the specimens were taken from all the tissues where macroscopic pathological changes were observed. Immunological techniques and methods of molecular genetics enabled identification of hantaviruses. Immunofluorescence, immunohistochemistry, in situ hybridization and PCR have been applied in diagnosing these diseases. These techniques enable the detection of specific viral antigens from blood and tissue. Since the first registered case of HFRS in the former Yugoslavia in 1952, sporadic cases have been constantly present and occasionally major or minor epidemics with mortality rate from 1- 16%. The analyzed tissue of the patients who died of HFRS from the territory of ex-Yugoslavia shows that, most frequently, serotype Belgrade hantavirus was present as an infectious agent. The tissue damages of the of kidneys and lungs infected by Belgrade hantavirus are more intensive than in those infected by the types Seoul, Puumala and others, and less prominent than in those infected by the type Sin Nombre (American serovariant).

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Numerous studies using autopsied materials from the patients who died from hemorrhagic fever with renal syndrome (HFRS) have been made. During Korean war in

1951, 37% patients suffernig from HFRS died in the stage of shock (from 2–10 days after the onset of the illness), 47% in the oliguric stage (from 7–17 days), and 18% in the end-stage renal failure (from 10–30 days after the onset). In the early stage, the most common cause of death was the shock, while in the later stage, the death occurred during the uremic syndrome¹.

Noticeable pathological findings in the supportive connective tissue of different organs in the patients with HFRS have been described by numerous authors. The most prominent pathohistological finding in the initial stage of the disease was first described by Steer in 1966. It was described as a dilatation of blood vessels in the corticomedullary zone, with a renal interstitial haemorrhage, present in the later stadium of the disease. Focal atypical ischemic necrosis were observed in the outer part of kidney (cortex). In addition, a frequent finding is the presence of hyaline granules in epithelial cells of tubules changed by degeneration and various degree of necrosis which includes the tubular basal membrane too. Glomerular changes are minimal and usually present as unequal thickenings of the glomerular basal membrane and capsule. Multiple authors point out that, in addition to dilatation of blood vessels, juxtamedullary zone and medulla, there is hemorrhage with extravasation of cellular blood elements into interstitial tissue^{2, 3, 4, 5}.

A frequent common finding of all the researchers during autopsy in the acute stage of the disease is hemorrhage in hypophysis, kidneys and in the wall of myocardium without atriums. Also, hemorrhages of various extent have been found in brain, lungs and gastrointestinal tract. Large edema was present in retroperitoneal tissue, mesenterium and mediastinum in the patient who died during the shock. The most frequent conclusion in explaining etiopathogenesis of HFRS is a blood vessels lesion with plasma extravasation and occurrence of hemorrhage^{6, 7, 8}.

One of the first works with published pathological findings in autopsy of the patients who died in Europe was written by Oldberk in 1941. The work shows only the finding on the kidney tissue which was edematous with adhering kidney capsule separable with difficulty, while no hemorrhages were visible. Laparotomy was done on several patients who had had abdominal symptoms. Orustein and Soderhjelm published in 1965 that in three patients subjected to laparotomy turbid liquid was found in the abdominal cavity with enlarged lymphatic glands. In one case, the appendix was edematous with petechiae on serosa. Kuhlback and al. performed four percutaneous renal biopsies in 1964. The pathohistological finding during the acute stadium was characterized by hemorrhage of medulla, changes in the wall of arteriolas and glomerulas, damages to tubula and interstitial edema. These lesions were not found five months later^{9, 10}.

Since 1952 when HFRS was registered for the first time in former Yugoslavia, sporadic cases have been constantly present and occasionally major or minor epidemics with mortality rate from 1- 16%. The first epidemic of HFRS in ex-Yugoslavia was described in a military camp on Fruska gora in 1961, when 46 soldiers got ill with one lethal outcome. During the epidemic in 1986, the diseased with HFRS were recorded in all six republics and two autonomous provinces of ex-Yugoslavia. Out of 161 serologically verified, 11 patients died (6%). A great epidemic with 226 diseased was registered in 1989 and 1995 again, with central location in Bosnia and Herzegovina. The number of 3000 diseased in 1995 was the result of war situation. In these epidemics lethality ranged from 1-16%, depending on the serotype of hantavirus. Lethal outcomes were recorded in the patients infected with Hantaan associated viruses (Hantaan and Belgrade serotype), while there were no fatal cases in those infected with Puumala serotype (European serovariant)^{11, 12, 13, 14, 15, 16}.

Methods of pathological investigation

The main materials for pathomorphological investigations were tissue specimens taken from the diseased by needle biopsy, most frequently from kidneys, rarely from liver. During autopsy the specimens were taken from all the organs and tissues, where macroscopic pathological changes were observed. The tissue was fixed in 10% formalin, moulded into paraffin moulds and then cut by microtome into sections 2–4 microns thick. For light microscopic analysis, the following pathohistological methods were most often used: hematoxylin – eosine, PAS, Giemsa, Trichrom Masson, Silver Methanamin per Jones, proofing of iron in tissue per Perls. For immunofluorescent (IF) analysis, the frozen tissue was cut on cryotome at -200 C. For direct IF, the samples were treated with IgA, IgG, IgM, IgE, albumin and fibrinogen. For immunohistochemical analysis, in addition to the same immunoglobulins, were used numerous tissue markers mainly as estimated by the researching pathologist. The most frequently used are common leukocyte antigen, CD3, CD4, CD8, CD15, NK-cell marker CD16, CD20, CD43, CD45, as well as wide range of antikeratin markers. Usage of synthetized hantavirus nucleo-capside protein, with reverse transcriptase (RT-PCR), intended for detection of RNK virus in blood and tissue is very helpful in making diagnosis and epidemiological research. Detection of RNK hantavirus is also for detection in formalin-fixed and in paraffin-moulded tissue by applying RT-PCR. Immunohistochemical investigation of formalin-fixed tissue, with specific mono - and polyclone antibodies can be used for detection of hantavirus antigens and represents a sensitive method for confirmation of hantavirus infection. Immunohistochemistry is used when the samples of serum and frozen tissue are not available. Immunoelectronic microscopy makes it possible to observe virus particles in the cell by indirect methods, using the serum with marked granules of gold. For electronic microscopy, the analyzed tissue after fixation in glutaraldehyde was moulded into eponic moulds and cut on ultramicrotome. The obtained semi-thin sections dyed in metulen blue were used for morphological analysis which precedes the electronic microscopy (EM).

Taking into consideration all these methods for making a reliable pathohistological diagnosis, the most recent investigations have made it possible to identify the illness more surely and to obtain significant elements in studying pathogenesis of this disease. Application of immunological and molecular techniques enabled identification of microorganisms. Immunofluorescence, immunohistochemistry, in situ hybridization and polymerase chain reaction have been applied in diagnosing these diseases. These techniques allow for antigen and nuclein acid sequences, specific for agent of infectious disease to be detected from formalin-fixed and paraffin embedded tissue. In this way, tissue reaction with the extent of lesion can be detected too, which is very important in observing the course of the disease and prognosis. In comparison with classical methods of tissue treatment, of special importance is reduction of risk from infection for the employees in pathohistological laboratories, in addition to their high sensitivity. Application of these techniques was achieved in cooperation with Sherif R. Zaki from the Center for Control and Prevention of Infectious Diseases, Atlanta USA (CDC), the leading institution in studying pathogenesis

of these diseases in the world. The cooperation made it possible to study hantavirus infection and infection of Crimean–Congo hemorrhagic fever (CCHF) on autopsied material. The rich experience of the experts in CDC has as ebola, Rift Valley HG and others^{17, 18}.

Macroscopic and microscopic pathological findings

Virus hemorrhagic fevers (VHF) have a rather similar pathological and immunopathological findings. In most cases microvascular lesions are present, which is an important morphological finding in hemorrhagic shock.

Cell infiltration by macrophages and other cells of mononuclear phagocyte system has a prominent role in pathogenesis of VHF, with secretion of physiological active substances, including cytokine and other inflammatory mediators. However, many elements of pathogenesis of VHF are unknown as well as how big are the differences in significant anatomic lesions in lethal cases, which is constantly being investigated in numerous studies. Possibility of hemorrhage is very risky for biopsy, so the investigations are mostly made on autopsy findings. The common pathological finding in autopsies includes widely spread petechial hemorrhages and ecchymosis of mucous membranes and internal organs, as seen in a female patient who died in a health institution in Belgrade where CCHF was confirmed by the molecular – biological, PCR, method and the autopsy was done at the Military Medical Academy. In some VHF, hemorrhages can be minimal or absent. Very frequent are necroses of organs, either massive or of focal ischemic nature, and the most common are in liver and lymphatic nodes.

In kidneys is tubular necrosis present, as a consequence of shock or direct cytopathogenic virus attack. Necrosis of lymphatic glands with cell depletion can be replaced by pathological changes of lymphatic tissue, particularly during hantavirus infections. Erythrophagocytosis is most frequently to be found in spleen, lymphatic nodes and liver. A fewer number of patients have microvascular thromboses which are in the form of disseminated intravascular coagulopathy, sometimes significant in differentiating pathogenesis of VHF. The common pathological findings on lungs are hemorrhage and interstitial pneumonitis.

Hanta virus pulmonary syndrome (HPS) includes large bilateral pleural effusions, marked edema of lungs, slightly to moderately expressed endothelial pneumonitis, immunoblasts and atypical lymphocytes in peripheral blood. Extensive infection of endothelial cells of lungs microvasculature is present too.

The causes of human hantavirus infection belong to the family Bunyaviridae. The form and severity of the disease depend mainly on serotype of the particular virus. Up to now, the following two diseases caused by hanta viruses have been most frequently described: hemorrhagic fever with renal syndrome (HFRS), with predominantly kidneys affected, and hemorrhagic fever with pulmonary syndrome (HPS), lungs predominantly affected. In acute stage of the disease, more outstanding and most frequently described pathological changes of HFRS are dilatation and congestion of blood vessels of small diameter on the corticomedullary zone in the tissue of kidney with surrounding interstitial

hemorrhage which occur in the late stage of the disease, with focal necrosis in the cortex more rarely present.

Hyaline material is present along with degenerative and necrotic changes which encompass tubular basal membrane too (TBM). On glomeruli pathological lesions are minimized with mild changes of glomerular basal membrane (GBM) and capillaries.

In other organs pathological lesions are rare, with degenerative changes present only in the liver. In fatal cases the most striking are hemorrhages of hypophysis, endocrine glands and right atrium of the heart. More infrequently, they can be also found in the brain, lungs and gastrointestinal tract. Edema of retroperitoneum, mesenterium, mediastinum has been found in the autopsied tissue of the patients who died after the shock. All these pathological changes in HFRS indicate that they occurred due to the lesion on blood vessels with extravasation of plasma and cell elements of blood which gives the morphological picture of hemorrhage.

The analyzed tissue of the patients who died of HFRS from the territory of ex-Yugoslavia shows that, most frequently, hantavirus serotype Belgrade was present as an infectious agent. This serotype was isolated from the material taken from the patients with severe findings and lethal outcome. As for the antigen, it is closer to the Far East serovariant of Hantaan virus, isolated in Korea than to the European serovariant Puumala virus, isolated in Scandinavian countries. The pathological damages of the tissue of kidneys and lungs infected by Belgrade hanta virus are more intensive than in those infected by the types Seoul, Puumala and others, and less prominent than in those infected by the type Sin Nombre (American serovariant) with high degree of mortality and morbidity. In the analysis of the tissue of kidneys, the most frequent finding on glomeruli is hypercellularity of varying extent, depending on virus serotype and time duration of the infection. Increased number of cells is inequally present from glomerul to glomerul, and the most proliferating are endothelial and mesangial cells. The volume of glomeruli does not increase only because of hypercellularity, but also due to hypertrophy of cells, their composition, particularly of epithelial cells in whose cytoplasm, more often than in other cells, can be found antigens of hantavirus infection thanks to immunohistological and immunohistochemical methods.

The changes of glomerular basal membrane are not outstanding, and the most frequently present are segmented thinnings or thickenings with preserved layers or perimesangial thickenings which are mildly expressed but accompanied by an increase of mesangial matrix of the same extent. Winding or rupturing of GBM are rarely present, glomerular subcapsular space (spacium Bowman) is most frequently free, and within it there are also individual glomerular – capsular synaehia, segmented adhesion and, infrequently, fibrocellular – crescentic. Bowman capsule is often of unequal thickness, rarely with herniation too, while epithelial parietal cells are hypertrophic, particularly on urinary end of glomerul. The tubules, both proximal and distal, are dilated to a less extent in cortical part than in juxtamedullary part of the tissue where the lumen is most frequently filled with cell elements of blood. Dilatation of collective channels with morphological elements of congestion is a frequent finding with pericanalicular edema and hemorrhages, especially in the tissue of kidneys of the

patients in early stage of the disease. Degenerations, necrosis and desquamation of epithelial cells of tubules, collective channels with presence of hyaline contents in the lumen, too, is a frequent finding, as well as the presence of hemosiderin pigment. Atrophy of tubules is most frequently found in cortical part of the tissue when the disease has a longer course and is accompanied by peritubular fibrosis. Interstitial edema is found in all parts of the tissue of kidney, both in cortical part and in the medulla with hyperemia and vascular congestion, particularly outstanding in the initial stage of the disease in the medulla and with prominent hemorrhage. Hemorrhages in cortical part are minimized and rarely seen. In biopsy findings in the later stage of the disease, presence of hemosiderin pigment is frequent in interstitium. Composition of cell infiltrate is poorly expressed in all stages of the disease; in the beginning it corresponds to acute cell reaction with edema and hemorrhage while in the later stage of the disease it corresponds to chronic cell reaction with proliferation of morphological elements of connective tissue. The tissue analyzed in the later stage of the disease was dominated by ripe connective tissue with collagen fibres of focal expression and mostly in juxtamedullary part of the tissue which is accompanied by tubular atrophy as well. Changes on blood vessels represent a very important element in making diagnosis which has been particularly emphasized in all the studies published in the recent years. Inequally demonstrated vasculitis is present, primarily in kidneys and lungs, but in other organs and tissues too, depending upon the type causing the hantavirus infection. Particularly outstanding are changes on blood vessels of the smallest diameter and changes on endothelial cells, both in immunocytological and in ultrastructural finding. In the early stage of the disease, in addition to congestion in lumen, there are agglutinations of cell elements of blood present, rarely initial thrombosis too. In the later stages of the disease morphological elements of internal and medium layer of the wall proliferate, so that the lumen gets narrowed and finally gives in to connective tissue and leads to sclerosis. Pathological lesions on the lungs tissue found in autopsies in the region of the Balkans are the most prominent in those infected by hanta virus of serotype Belgrade and Hantaan^{19, 20}.

Hantavirus hemorrhagic fevers and Balkan endemic nephropathy, which were confirmed in Serbia have similar pathologic and immunopathologic findings in late stage of illness. In mostly of lethal cases for both of hemorrhagic fevers, microvascular lesions are present as important morphologic characteristics. Similar lesions, some clinical characteristics, ecology as well as epidemiology data are present in patients suffering from Balkan endemic nephropathy. Observed similarities in pathohistologic findings of renal lesions in patients affected with hantavirus hemorrhagic fever and Balkan endemic nephropathy together with the fact that both diseases are present in same geographic area indicate the importance of further multidisciplinary studies concerning this topic²¹.

The lung tissue of those who died from HPS is distinctly edematous, mass double greater than normal, with large bilateral pleural effusions which are also strikingly demonstrated on pericard and peritoneum in addition to retroperitoneal edema. Histologically, there is alveolar and septal edema present, with fibrosated alveolar hyaline membranes. These membranes resemble a fine network of fibrines which is different from products of cell decay. Alveolar pneumocytes are of well preserved appearance. The cell mononuclear interstitial infiltrate is mildly to moderately expressed, mostly with cells of immunoblast appearance, while neutrophils are rarely present. In other organs pathological changes are expressed to a lesser degree. In liver, pathohistological finding was expressed to a minimum, with focal microvesicular steatosis, proliferation of the cells of reticuloendothelial system, Kupffer cells and individual immunoblasts in portal space^{22, 23, 24}. Most often, the spleen was of enlarged mass, in approximately one third of the autopsied the mass was over 200 grams. Histologically, in addition to congestion, there was inequally expressed number of immunoblasts in red pulp and periarterially in white pulp. The mucous membrane of gastrointestinal tract, more frequently in stomach than in other parts showed mildly to moderately expressed hemorrhages in about one quarter of the autopsied patients. The lymphatic glands were most often of the normal size, with slightly outstanding edema, while immunoblasts were numerous, particularly in pericortical region. In immunochemical analysis, the most frequent finding was a mixture of T-cell lymphocyte lineage. This finding coincides with the results obtained in analysis of biopsy and autopsy materials of the patients infected with type Belgrade hanta virus, however, it has to be noted that the pathological lesions are identical but with a minor degree of pathological damage than in HPS.

Apstrakt

Uzročnici humane hantavirusne infekcije pripadaju porodici Bunyaviridae. Oblik i težina bolesti zavise uglavnom od serotipa izolovanog virusa. Najčešće su opisivana dva oboljenja uzrokovana hanta virusima: hemoragijska groznica sa bubrežnim sindromom (HFRS) i hemoragijska groznica sa pulmonalnim sindromom (HPS). Do sada su uradene brojne studije autopsijskog materijala osoba koje su umrle od HFRS. Najuočljiviji patohistološki nalaz u početnoj fazi bolesti je dilatacija krvnih sudova u kortikomedularnoj zoni, dok se u kasnijem stadijumu uočava prisustvo intersticijalne hemoragije. Pored toga, čest nalaz je i prisustvo hijalinih granula u epitelnim ćelijama tubula izmenjenih degeneracijom i različitim stepenom nekroze, koji zahvata i bazalnu membranu tubula. Promene na glomerulima su minimalne i manifestuju se kao nejednaka zadebljanja glomerularne bazalne membrane i kapsule glomerula. Čest autopsijski nalaz kod ovih pacijenata u akutnoj fazi bolesti je hemoragija u hipofizi, bubrežima i u zidu srčanog mišića. U cilju dijagnostike tkivni isečci obolelih uzimani su iglenom biopsijom, najčešće iz tkiva bubrega, i predstavljali su glavni materijal za patohistološka ispitivanja. Tokom autopsije, uzimani su isečci iz svih tkiva u kojima su uočene makroskopske patološke promene. Primenom imunoloških tehnika i metoda molekularne genetike omogućena je identifikacija uzročnika. Imunofluorescenca, imunohistohemija, hibridizacija in situ i PCR su najčešće primenjivane metode u dijagnostici ovih oboljenja. Upotreba ovih tehnika omogućava identifikaciju specifičnih virusnih antigena u krvi i različitim tkivima. Od 1952. godine, kada je prvi put registrovana HFRS u tadašnjoj Jugoslaviji, na ovim prostorima su stalno prisutni sporadični slučajevi, kao i povremene manje ili veće epidemije sa mortalitetom od 1-16%. U analiziranom tkivu obolelih i umrlih od HFRS sa teritorije bivše Jugoslavije, najčešće je bio prisutan serotip Belgrade hantavirusa kao infektivni agens. Patološka oštećenja tkiva bubrega i pluća inficiranih Belgrade hantavirusom intenzivnija su u odnosu na inficirane sojevima Seul, Puumala i dr., a manjeg su obima nego kod osoba inficiranih sojem Sin Nombre (američka serovarijanta).

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