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B-LYMPHOPLASMACYTIC LYMPHOMA WITH WALDENSTRÖM'S MACROGLOBULINEMIA VARIANT

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A hematological malignant disease of human lymphoid tissue in the form of a rare Waldenström disease with a long asymptomatic course and short-term clinical course usually ends fatally for an elderly patient. Clinical verification of the disease is based on a monoclonal IgM diagnosis and bone marrow biopsy results. The purpose of the study was to deepen knowledge of the clinical course and pathomorphological diagnosis of lymphoid organ tumors of B-cell origin, specifically Waldenström macroglobulinemia, a variant of non-Hodgkin lymphoma. The research methods were a review of the professional scientific literature on the pathology of B-cell lymphomas and a retrospective clinical and anatomical analysis of a fatal case of Waldenström's disease in an elderly patient with a short clinical course and concomitant diseases of a compensated nature in the form of general vascular atherosclerosis and hypertension. As a result of the literature analysis, data were obtained on the molecular basis of the mechanism of formation of tumors of the immune system of B-lymphocyte origin, which are associated with the MYD88 gene with the L265P mutation; CXCR4 with oncogenic properties and changes in certain "signaling proteins" CD79B, MYD88 and others. They transmit an activating signal to cell proliferation genes through receptors on their surface, which are activated upon interaction with specific antigens, interleukins from macrophages, T-lymphocyte helpers, chemokines from bone marrow stromal cells, and lymph nodes. The mutual potentiating effect stimulates proliferation and uncontrolled activity of the tumor clone of lymphocytes. As a result of the analysis of the autopsy protocol and clinical and anatomical epicrisis of the case from the clinic, the course of Waldenström macroglobulinemia disease was clarified, and the possibilities of additional methods of verification of this pathology were explored.

Key words: B-lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, pathomorphology.

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В-ЛІМФОПЛАЗМОЦИТАРНА ЛІМФОМА З ВАРІАНТОМ МАКРОГЛОБУЛІНЕМІЇ ВАЛЬДЕНСТРЕМА

Гематологічне злоякісне захворювання лімфоїдної тканини людини у вигляді рідкісної хвороби Вальденстрема з тривалим малосимптомним перебігом і короткочасною клінікою закінчується, зазвичай, летально для пацієнта похилого віку. Клінічна верифікація хвороби базується на діагностиці моноклонального Ig M та даних біопсії кісткового мозку. Метою дослідження стало поглиблення знань з клінічного перебігу та патоморфологічної діагностики пухлини лімфоїдних органів В-клітинного походження, як варіанту неходжкінської лімфоми – макроглобулінемії Вальденстрема. Методами дослідження став огляд фахової наукової літератури з патології В-клітинних лімфом та ретроспективний клініко-анатомічний аналіз летального випадку від хвороби Вальденстрема пацієнта похилого віку з коротким клінічним перебігом та супутніми хворобами компенсованого характеру у вигляді загального атеросклерозу судин та гіпертонічної хвороби. Результатом проведеного аналізу літератури отримані дані про молекулярні основи механізму становлення пухлини імунної системи В-лімфоцитарного походження, що повязані із геном MYD88 з мутацією L265P; CXCR4 з онкогенними властивостями та змінами певних «сигнальних протеїнів» CD79B, MYD88 та інших, які передають активуючий сигнал на гени проліферації клітин з рецепторів на її поверхні, що активуються при взаємодії із специфічним антигеном, інтерлейкінами макрофагів, Т-лімфоцитів хелперів, хемокіном стромальних клітин кісткового мозку, лімфатичних вузлів. Взаємопотенціюючий ефект стимулює проліферацію, неконтрольовану активність пухлинного клону лімфоцитів. В результаті аналізу протоколу розтину та клініко-анатомічного епікризу випадку із клініки, перебігу хвороби макроглобулінемії Вальденстрема стало з'ясування можливостей додаткових методів верифікації даної патології.

Ключові слова: В-лімфоплазмоцитарна лімфома, макроглобулінемія Вальденстрема, патоморфологія.

The study is a fragment of the research project "Regularities of morphogenesis of organs, tissues and vascular-neuroforms in normal, pathological and under the influence of external factors", state registration No. 0118U004457.

Waldenström macroglobulinemia (WM) is a rare lymphoproliferative disorder belonging to the group of asymptomatic B-lymphoplasmacytic lymphomas of non-Hodgkin origin. Epidemiologically, its frequency is about three cases per million per year (USA), and only one case of the disease has been described in Ukraine [8, 10]. WM is more common in men than women, with a mean age of 63 years [7]. Waldenström macroglobulinemia is characterized by bone marrow infiltration by lymphoplasmacytic cells and hyperproduction of monoclonal immunoglobulin M (IgM) [3, 7]. The clinical manifestations of the disease are variable, ranging from asymptomatic to severe complications, including hyperviscosity syndrome (increased blood viscosity), autoimmune manifestations, and involvement of various organs and tissues [1]. The above complicates the diagnosis of WM and requires a comprehensive approach, including morphological, immunohistochemical, and molecular genetic studies [4]. Recently, significant advancements have been made in understanding the molecular mechanisms underlying the pathogenesis of Waldenström macroglobulinemia. One of the significant achievements in this issue was the discovery of a monoallelic local mutation in the primary myeloid differentiation response gene (MYD88), characterized by the substitution of

the amino acid leucine (L) for proline (P) at position 265 (MYD88L265P). The latter is detected in more than 90 % of patients with WM [2]. This mutation is key in the activation of a cellular transcription factor, nuclear factor Kappa B (NF-kB), and dependent signaling pathways, which determines the resistance and proliferative capacity of tumor cells. Of additional importance is the mutation of the CXCR4 gene, which encodes the chemokine receptor protein, affecting the spread of tumor cells and their sensitivity to therapy [6]. The molecular genetic features of tumor cells of B-lymphocyte origin provide the basis for the invention of targeted therapies aimed at blocking key signaling pathways. Pathomorphological diagnosis of WM remains crucial in confirming the disease. Histological examination of the bone marrow reveals infiltration of lymphoplasmacytic cells, among which signs of plasmatic differentiation of B lymphocytes may be present. Immunohistochemical analysis can detect the expression of CD19, CD20, CD22, and other B-cell markers. And the detection of monoclonal IgM in the blood serum confirms the diagnosis [6, 9]. Today, it is relevant to utilize flow cytometric analysis and next-generation sequencing of the cellular genome, which enables the most reliable establishment of the cell's molecular profile [4].

This article reviews the current pathomorphological aspects of Waldenström macroglobulinemia with an emphasis on morphological changes in the organs of the immune system (bone marrow, lymph nodes, spleen) and other internal human organs detected during autopsy. Special attention is paid to the features of lymphoplasmacytic infiltration, the degree of maturity of immune cells, and their immunohistochemical characteristics. An essential aspect of the retrospective analysis is the relationship between pathomorphological changes and the molecular genetic features of the disease, which include MYD88L265P and CXCR4 mutations, as well as their impact on NF-κB signaling pathways (RELA [p65]-p50 and RELA–p52) and the pathogenesis of this disease. A retrospective analysis of a fatal case of Waldenström macroglobulinemia with a detailed analysis of pathomorphological changes in the human body allows us to deepen our understanding of the mechanisms of disease progression and its complications.

Thus, the pathogenesis of rare proliferative B-lymphocyte disease is based on the following:

1. Waldenström macroglobulinemia is a rare variant of non-Hodgkin's lymphoplasmacytic lymphoma characterized by the presence of IgM monoclonal proteins in the blood serum, with a malignant course.

2. Main genetic mutations: MYD88 L265P leading to activation of the transcription factor – NF-kB (also has an anti-apoptotic effect), which enhances the signal from B-lymphocyte receptors: TLRs, IL-1, IL-2 on the way to the cell nucleus, activating the transcription of target genes of cell proliferation and maturation (respectively: RELA [p65]-p50 and RELB-p52). A less common mutation in CXCR4**,** which encodes a chemokine receptor protein, causes proliferative activity and maintenance of stem-like properties of B-lymphocytes.

3. Patients live to an advanced age, suffering from anemia, increased blood viscosity, and polyneuropathy associated with demyelination of nerve fibers.

4. Diagnosis is based on the detection of a lymphoplasmacytic infiltrate in the trephine biopsy material, as well as AS-PCR and digital PCR.

5. Proliferation of genetically modified clonal B-lymphocytes in the organs of the immune system.

The purpose of the study was to conduct a retrospective analysis of a fatal case of Waldenström macroglobulinemia in an elderly patient, aiming to clarify the pathogenesis of Waldenström macroglobulinemia and its pathomorphological diagnostic features.

Materials and methods. Examination microscopy of histological sections of internal organ preparations, 5 μm thick, after applying the histological method –staining with hematoxylin and eosin.

Autopsy report of a patient who died from intoxication in Waldenström's disease; clinical data on the development of the disease from the epicrisis of the protocol, microslides of the patient's fatal case.

Results of the study and their discussion. Patient B., 62 years old. Upon referral from the Regional Hematology Department, he was admitted for planned treatment with a diagnosis of B-cell non-Hodgkin's lymphoplasmacytic lymphoma (Waldenström macroglobulinemia), immunosecreting IgM-kappa, stage IV B (Ann Arbor) with bone marrow involvement, in the terminal stage.

From the anamnesis: the diagnosis was established in January 2024 according to the hemogram (leukocytosis 11.78 $x10^9$\l, lymphocytosis 50 %, blast cells 2 %, anemia er. – 2.74$x10^9$/l, Hb 82 g/l; myelogram (lymphocytosis 22 %, plasmacytosis 3.5 %, monocytosis 5.5 % and data of PGZ+IGH No. 24 CN000316 dated 01/05/2024; according to immunofixation and electrophoresis of protein fractions of blood serum and urine (01/25/24): monoclonal paraprotein of the IgM-Kappa class was detected in blood serum (Kappa < 24.19 mg/l) and BJ-protein of the Kappa class in urine in the Y-zone of the electrophoresis. Examination of the patient allowed clinicians to establish the presence of a neoplastic process in the bone marrow of lymphocytic genesis, accompanied by anemia. The monoclonal paraprotein of the IgM-Kappa class is a defective constant region of the IgM light chain. In this case, the function of the latter is impaired,

which indicates its neoplastic origin. This paraprotein is synthesized by B lymphocytes that have not turned into plasma cells. Kappa class BJ protein in urine is a light chain of monoclonal Ig synthesized by tumor cells. Its amount in the urine was found to be elevated.

In January 2024, specific therapy was initiated. The course was interrupted due to the development of bilateral polysegmental pneumonia. In February and March 2024, 2 courses of chemotherapy conducted. In the last week, the patient's condition deteriorated significantly, and the patient was hospitalized in the hematology department for further specialized treatment.

In the department, the patient underwent a comprehensive laboratory and instrumental examination, was consulted by a cardiologist and a pulmonologist, and was repeatedly examined by a panel of doctors. The patient received specific replacement, antibacterial, and detoxification therapy. But, despite the treatment, the patient's condition progressively worsened.

On 04.05.24 at 15:50, the anesthesiologist on duty recorded signs of clinical death and immediately initiated ineffective resuscitation measures. On 04.05.24 at 16:20, the patient's biological death was confirmed.

Pathomorphology of autopsy data. An external examination of the deceased's body, according to the autopsy report, revealed that he was well-nourished. Paleness of the skin and mucous membranes, in our opinion, was a sign of anemia. Small subcutaneous hematomas were found on the skin of the trunk and extremities at the injection sites. Petechial hemorrhages were also present, indicating impaired blood rheology and increased vascular permeability at the microcirculatory level.

Retrospective internal abdominal examination was free of adhesions and contained traces of clear fluid. The peritoneum is smooth and shiny. The intestine is not distended. The diaphragm is pale gray, smooth, and shiny. The pleural cavities were free of adhesions, but contained 200 ml of clear fluid, and the parietal pleura appeared smooth and shiny.

Central nervous system: when the brain was removed, free fluid flowed out, and the sulci of the hemispheres were smoothed. The boundary between the gray and white matter of the brain is clear. The brain tissue is moderately full-blooded, moist and shiny. The lateral ventricles of the organ also contain a moderate amount of clear fluid, the ependyma is shiny, and the choroid plexus is cyanotic. The arteries of the brain are thin-walled, their lumen is free. Retrospective examination of a micropreparation of brain tissue revealed: perivascular and pericellular edema of its substance; intravascular platelet aggregation and thrombosis of thin-walled cerebral vessels. Thus, retrospectively, the deceased patient had cerebral circulatory disorders caused by the formation of blood clots in the vessels of the microcirculatory bed of the brain tissue, which was a consequence of its edema. Pathomorphological examination of other vital organs revealed the following (Fig. 1).

Respiratory organs: The trachea, main bronchi, and lobar bronchi had moderate to foamy contents. The visceral pleura is smooth, shiny with petechial hemorrhages. Lung tissue is of splenic density, gray-pink. A bloody, foamy fluid flowed profusely from the surface of the lung incision. The bronchial openings are not narrowed and contain a small amount of mucus. The pulmonary trunk, arteries, lobes, segments, and subsegments contained liquid blood. Retrospective examination of the lung microscopy of this fatal case revealed: pleurisy of the venous vessels of the organ; erythrocyte sludge and thrombi in the small branches of the pulmonary artery; edematous fluid in the lumen of individual alveoli and inflammatory cellular infiltrate, as well as atelectasis of the lung tissue; peribronchial and perivascular proliferation of connective tissue. Thus, pulmonary hemodynamics are also impaired, which is primarily observed in the terminal sections of the pulmonary artery, characterized by platelet aggregation and vascular thrombosis.

Retrospective analysis of the circulatory system revealed the following. Aortic intima with numerous atheromatous plaques. There is 50 ml of clear fluid in the pericardial cavity. The heart is enlarged due to the left chambers, and the subepicardial fat layer is insignificant. At autopsy, the thickness of the left ventricular wall was 1.7 cm, and the right ventricular wall was 0.3 cm. The parietal endocardium is smooth and shiny. The valves of the aortic, mitral, and tricuspid valves are thin, translucent, and have small whitish fibrous plaques. The cavities of the atria and ventricles contain loose blood clots. The myocardium is flabby, pale brown in color. Coronary arteries are not contoured, thin-walled, with individual atheromatous plaques that slightly narrow their lumen. The superior and inferior vena cava contain liquid blood. Microscopy of myocardial tissue revealed hypertrophy and fragmentation of cardiomyocytes, foci of myocytolysis, and small focal cardiosclerosis. Perivascular foci of connective tissue and lipocytes were also observed. Thus, the analysis of the condition of the heart and its vessels retrospectively revealed both compensatory myocardial hypertrophy of a concomitant disease of hypertension and the damaging toxic effects of a malignant tumor. The spleen is enlarged, the capsule is smooth. The pulp is somewhat compacted, grayish-cherry in color on the cut, and there is no scraping from the surface of the cut. Microscopy of spleen tissue: disruption of the follicle structure, diffuse round cell infiltration of small

lymphocytes and plasmacytic-like cells; hyalinosis with elastofibrosis of the central artery of the follicles. Retrospectively, an increased content of immature lymphoid cells and plasma cells was detected in the spleen tissue.

Peripheral lymph nodes**,** para-aortic, and pancreatic-duodenal were difficult to identify. The bifurcation and para-aortic nodes were up to 1.0 cm in size, without connections between them, elastic, homogeneous on section, and juicy, with a grayish appearance. Microscopically: follicular structure is disrupted; small focal hemorrhages; carbon pigment; focal infiltrates of small B-lymphocytes, plasmacytic-like cells. Retrospectively, the sternal bone marrow was abundant, juicy, semi-liquid, and gray-pink. Microscopically, in the sternum tissue, fatty bone marrow was replaced mainly by small lymphocytes, their plasmacyte-like variants, and individual plasmacytes. Thus, retrospectively, increased proliferative activity of lymphoid cells was observed in the bone marrow tissue, characterized by the replacement of adipose tissue with small lymphocytes and plasmacytic-like cells.

Examination of the liver revealed its dense-elastic structure. On the surface and at autopsy, the organ appeared smooth, pale, and brownish-yellow in color. The intrahepatic and extrahepatic bile ducts were patent and contained dark olive bile. Retrospective microscopic examination of the liver revealed extensive and medium-droplet fatty degeneration of hepatocytes; perinuclear grains of lipofuscin; a focus of round cell infiltration of small lymphocytes; preserved lobular structure; and excessive venous perfusion of the triad areas. Thus, the liver parenchyma underwent a damaging effect in the form of fatty degeneration due to an increase in the volume of venous blood delivered to the sinusoids due to the engorgement of the portal veins. The organ tissue was also affected by focal lymphoma cell infiltrate.

The kidneys, upon retrospective examination, had a fine-grained surface, pale parenchyma, and not clearly defined layers. The renal calyces and pelvis were not dilated and contained traces of clear fluid. The openings of the ureters are wide and free. Microscopy of kidney tissue revealed protein dystrophy and necrosis of the proximal tubular epithelium with its desquamation; venous congestion; pericellular edema of the mesangium epithelium of the renal corpuscles and its hypercellularity; erythrocytes, protein flakes in the lumen of the tubules (Fig. 2).

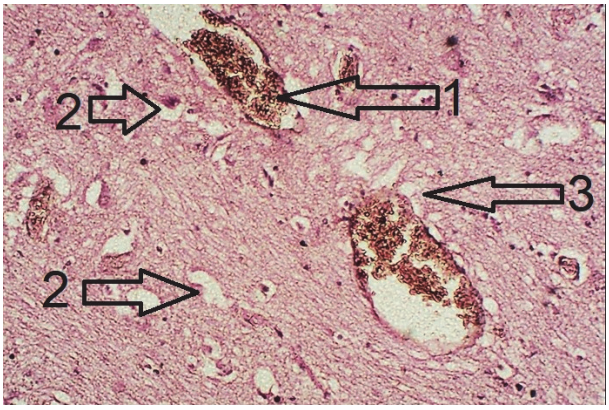

Fig. 1. Brain tissue of a patient with Waldenström macroglobulinopathy. Histological staining with hematoxylin and eosin. Magnification x400: 1 – thrombus in the terminal cerebral artery; 2 – pericellular edema of the brain substance; 3 – perivascular edema of the brain.

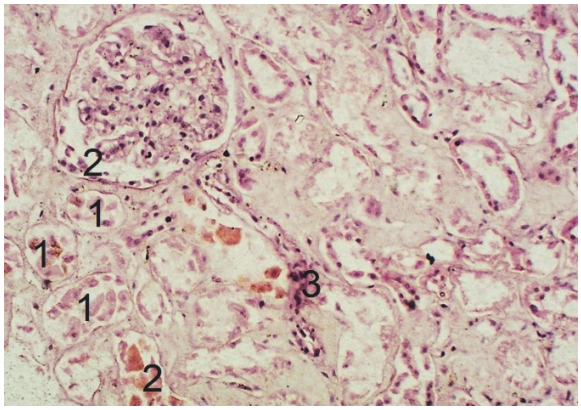

Fig. 2. Damage to the kidney tissue of a patient with Waldenström macroglobulinopathy. Histological staining with hematoxylin and eosin. Magnification x400: 1 – necrosis and desquamation of the renal tubular epithelium; 2 – protein plates in the cavity of the Shumlyansky-Bowman capsule; 3 – lympho-plasmacytic infiltrate.

The above-mentioned changes in renal tissue are due to the high content of the monoclonal paraprotein Ben-Jones (BJ) of the Kappa class in the urine. The amino acid chains, combining, created the IgM light chain constant region protein molecule. At the same time, its large amount affected the epithelium of the renal tubules, destroying its structures, which is known as necrotic nephrosis. Desquamation of the latter into the lumen of the tubules led to a disruption in the dynamics of urine excretion, resulting in a delay in its excretion and renal failure. Intoxication with metabolic products in the body potentiated the lethal outcome of this disease as a result of B-lymphocyte neoplasia.

According to the European Guidelines on Hematological Malignancies – the result of the fruitful work of the European Hematology Association (EHA) and the Society for Medical Oncology (ESMO), as well as the 11th International Workshop on Waldenström Macroglobulinemia (IWWM-11), Waldenström macroglobulinemia is defined as a rare disease related to non-Hodgkin lymphomas (accounting for 1–2 %). Clinical verification of the disease is based on histological detection of bone marrow infiltration by lymphoplasmacytic lymphoma cells, as well as the presence of a certain amount of monoclonal immunoglobulin M (IgM), confirmed by immunofixation. Whereas the presence of only monoclonal IgM

without histological verification is not considered Waldenström disease, as it can also occur in monoclonal gammopathy of undetermined origin (MGUS) and nodular lymphoplasmacytic lymphoma (NLL). The clonal nature of bone marrow lymphoplasmacytic cells should be confirmed by immunophenotypic studies (detection of CD19, CD20, CD22, and CD79a on the lymphocytic component, and CD38 on the plasmacytic component) [3–5, 9, 11].

The acquisition of oncogenic properties by the MYD88 gene of the same name as the signaling protein is caused by its monoallelic local mutation (93 % of patients with this disease, which leads to the replacement of the amino acid leucine (L) with proline (P) at position 265 (L265P) (MYD88 L265P) in this protein. However, it is nonspecific, as it is sometimes found in other forms of lymphoma (primary lymphoma of the testicle – 68 %, central nervous system – 38–86 %, etc.) and chronic lymphocytic leukemia. The mutation even serves as a differential diagnosis due to its absence in multiple myeloma [6]. Approximately 7 % of patients with this disease who lack a mutation in MYD88 have other gene defects that cause NF-κB activation and dysregulation of genes involved in DNA repair.

Also involved in the development of BM is the CD79B protein, which, as part of the BCR receptors of B lymphocytes, also participates in the activation of B-cell lymphogenesis. Under physiological conditions, its effect on proliferation genes is mediated by activation of the NF-κB pathway. A potentiating effect of BCR and MYD88L265P mutations in the development of this type of lymphoma has been observed [7].

Some of the AG-stimulated B-lymphocytes travel to the lymphatic organs (their marginal zone), transforming into extrafollicular B-lymphocytes with the characteristics: IgD (-), CD 23 (-), CD39 (+), and the ability to react with carbohydrate AGs (T-cell-dependent immune response), but produce only low-specific Ig.

Patients with Waldenström disease, mostly elderly individuals who are carriers of the CXCR4 gene mutation, have high levels of IgM in their blood plasma and associated hyperviscosity (due to the considerable molecular weight of IgM and its pentameric form). There is a more severe course of the disease. This gene mutation precedes the appearance of the first clinical symptoms of the disease and, without treatment, correlates with shorter survival [7].

The variability of disease symptoms is associated with the diverse effects of pathogenic factors on the human body. Thus, B-cell lympho-plasmacytic infiltration of the bone marrow causes the development of anemia. Cytopenia is associated with the development of fatigue in patients. Excess IgM, both in the patient's blood plasma and its deposits in tissues, and the aggression of IgM autoantibodies cause an increase in blood viscosity, which disrupts blood circulation and leads to the development of encephalopathy, headache, visual impairment, and nosebleeds. About 50 % of patients suffer from peripheral neuropathy, which is accompanied by impaired tactile sensitivity and motor activity of the extremities, with muscle atrophy and pain, paresthesia. Demyelination also causes polyneuropathy in the form of bilateral numbness of the feet [10].

In our opinion, the patient's kidney parenchyma suffered severe damage from the effects of the products of the synthetic activity of the clonal population of B-lymphocytes in the lymphoma. Pathohistologically, severe protein dystrophy of the epithelium of the proximal renal tubules and their membranes was identified, definitely caused by the action of the Ben-Jones (BJ) protein of the Kappa class. Due to its high concentration in the urine, the proteolytic failure of the nephrothelium, which affects the protein of immune complexes present in large quantities, leads to their intracellular accumulation, resulting in damage to the epithelium and basement membranes. Desquamation of the latter into the lumen of the renal tubules caused a mechanical delay in urine excretion, leading to intoxication of the patient's body with products of impaired protein metabolism.

Edematous changes and hypercellularity of the stromal component of glomerular corpuscles are caused by the destructive activity of the immune component of blood plasma, identified as a paraprotein of monoclonal nature of the Kappa class (IgM-Kappa). Alteration of the glomerular vascular wall by paraprotein BJ caused significant edema of the renal filter mesangium, contributing to the accumulation of exudate in its tissue, destructive changes, and a subsequent increase in the regenerative proliferative activity of mesangiocytes and the endothelium of the glomerular vascular loops. Of course, the above only contributed to the paraprotein reaching the lumen of the renal tubules and its destructive activity in them. Thrombosis led to pathological changes in human brain tissue caused by hemodynamic disorders. The latter is due, according to the reviewed literature, to an increased content of IgM in peripheral blood. The highest molecular weight among immunoglobulins, along with its pentameric molecular structure, increased blood viscosity, slowed the flow of its formed elements, particularly platelets, which underwent aggregation and led to tissue hypoxia. This resulted in blood clots forming in the cerebral vessels. In addition, hypertensive disease diagnosed during life and pathomorphologically (left ventricle of the heart 1.7 cm thick, arterio-

arteriosclerosis, glomerulosclerosis) and its damaging effect on the vascular wall contributed to the above-mentioned pathological process.

The liver has undergone damaging changes, characterized by medium- to fine-droplet fatty degeneration, which is caused by several factors. Firstly, as a result of the toxic effect of tumor paraprotein, which, due to its high concentration in plasma, infiltrates the organ parenchyma, as well as due to the detected portal hypertension (blood stasis in the hepatic vein), which caused an increase in the concentration of carbon dioxide in the sinusoids of the organ and contributed to hypoxic damage to hepatocytes. Round cell infiltrates of the organ parenchyma were also detected, consisting of small lymphocytes and plasmacytic-like cells, which is unequivocal evidence of the generalization of this B-cell lymphoma.

On the respiratory side, the lungs also suffered hemodynamic disorders. Thrombosis of small branches of the pulmonary artery was identified, caused by increased blood viscosity due to paraproteinemia. Remnants of protein exudate and fragments of cellular elements of the inflammatory infiltrate are detected in the alveoli - a consequence of an immunopathological condition. Sometimes edematous fluid is detected in the alveolar lumen, along with atelectasis of the lung tissue and emphysema.

One of the sites of generation of a clonal population of tumor cells, as well as B-lymphocytes, has been discovered in the bifurcated lymph node of the lung. Histological staining with hematoxylin and eosin at high magnification using a light microscope allowed us to examine the morphological characteristics of the infiltrate, which consisted of lymphocyte–type cells, small B-lymphocytes, activated B-lymphocyte variants, and plasma cells.

Finally, bone marrow removed from the sternum during the postmortem examination of the deceased's body had classic signs of this lymphoma. Macroscopically abundant, juicy, gray-pink. Histopathological examination revealed small lymphocytes, their plasmacyte-like variants, and plasma cells. Tumor proliferation cells from B-lymphocytes displaced the brain adipose tissue, which led to the subsequent entry of their tumor clone into the blood in large quantities, with the accumulation of the product of its synthetic activity. The proliferation of neoplastic tumor cells, caused by the genetic changes described in the literature review, suppresses the growth of other elements of hematopoiesis, such as erythrocytes, leading to the development of anemia in the patient. At the same time, platelet deficiency disrupts blood clotting, leading to a tendency to bleed. The latter was observed during a retrospective analysis of the autopsy report in the form of petechial hemorrhages in the serous membranes, which was emphasized in the reviewed scientific medical literature.

Conclusions

1. As a result of a review of the literature on a rare disease of the hematopoietic and lymphoid systems of the human body in the form of Waldenström macroglobulinemia, the pathogenesis of the disease was clarified, which consists of the following: a) genetic mutation MYD888 L265P and CXCR4; b) monoclonal proliferation of B lymphocytes; c) hyperproduction of monoclonal antibodies – IgM, d) formation of infiltrates in the bone marrow, liver, spleen, and lymph nodes.

2. A retrospective analysis of pathomorphological changes in a fatal case of an elderly male patient with Waldenström's disease revealed focal B-cell proliferations in the internal organs, including the bone marrow, lymph nodes, liver, and spleen. The cause of the patient's mortality was determined to be decompensated renal failure as a result of the damaging effect of BJ-protein of the Kappa class on the tubular epithelium. The high content of IgM in the blood, combined with its branched (pentamer) molecular structure, contributed to the disruption of hemomicrocirculation, leading to thrombus formation in the terminal branches of the pulmonary artery and the brain, and ultimately causing hypoxic organ damage. The patient's decreased immunity, due to the detected B-lymphoplasmacytic lymphoma, led to a prolonged episode of bacterial pneumonia resistant to treatment.

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EFFECTS OF AUTOLOGOUS PLASMINOGEN ON ANGIOSTATIN LEVELS AND MATRIX METALLOPROTEINASE ACTIVITY IN THE HEALING OF A CHRONIC VENOUS SKIN ULCER

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This clinical case report describes the application of autologous plasminogen to a chronic venous skin ulcer of six years' duration and its effects on wound healing, proteinase activity, and angiogenesis regulation in the affected tissue. Plasminogen was isolated from the patient's blood plasma and applied locally every two days for twenty days. Wound size was tracked through planimetric analysis, while levels of protein markers in skin biopsies were assessed using immunoblot analysis and zymography assay. By the twenty-fourth day, the ulcer area has reduced significantly, and this improvement was accompanied by a marked decline in both angiogenesis inhibitors and enzymes associated with tissue degradation. These findings suggest that the normalization of molecular processes induced by plasminogen plays a crucial role in restoring reparative functions in chronic wounds. This is the first report documenting the clinical benefits of autologous plasminogen in treating non-healing lower limb ulcers associated with venous insufficiency.

Key words: chronic wounds, venous insufficiency, plasminogen, angiostatins, matrix metalloproteinases.

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ВПЛИВ АУТОЛОГІЧНОГО ПЛАЗМІНОГЕНУ НА РІВЕНЬ АНГІОСТАТИНІВ ТА АКТИВНІСТЬ МАТРИКСНИХ МЕТАЛОПРОТЕЇНАЗ НА ЗАГОЄННЯ ХРОНІЧНОЇ ВЕНОЗНОЇ ВИРАЗКИ ШКІРИ

У представленому клінічному випадку описано застосування аутологічного плазміногену для лікування хронічної венозної виразки шкіри, що не загоювалася шість років, та його вплив на загоєння рани, активність протеаз і регуляцію ангіогенезу в пошкодженій тканині. Плазміноген було ізольовано з плазми крові пацієнта, білок застосовували місцево кожні два дні протягом двадцяти днів. Динаміка загоєння оцінювалася планіметрично, рівні маркерних протеїнів у біоптатах визначали методом імуноблотингу та зимографії. До двадцять четвертого дня площа виразки суттєво зменшилася, що супроводжувалося зниженням вмісту інгібіторів ангіогенезу та літичних ферментів, які сприяють деградації тканин. Отримані результати свідчать, що нормалізація молекулярних процесів під дією плазміногену є важливою передумовою відновлення репаративного потенціалу хронічних ран. Представлена робота є першим повідомленням про клінічну ефективність місцевого застосування аутологічного плазміногену для лікування трофічних виразок нижніх кінцівок на фоні венозної недостатності.

Ключові слова: хронічні рани, венозна недостатність, плазміноген, ангіостатини, матриксні металопротеїнази.

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Venous ulcers are the most common chronic lower limb ulcers, affecting 1 to 3 % of the population in industrially developed countries [9]. It has been proven that venous hypertension resulting from venous reflux (insufficiency) or occlusion is the primary mechanism of venous ulcer development. Ulcers develop as the result of a complex process that includes secondary hypertension (venous hypertension) and inflammation along the venous circulation pathway, in venous walls and valve leaflets, along with the inflammatory debris interstitial extravasation [7]. Factors, which contribute to the development of venous ulcers, include being 55 years of age or older, a history of venous insufficiency, pulmonary embolism,