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The state of vascular smooth muscle cells and their association with immune responses in atherosclerosis on the metabolic syndrome background

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Abstract:
Background: *Metabolic syndrome (MS) plays an important role in the atherosclerotic process associated with the risk factors clustering that may increase the risk of atherogenic lesion. There is a link between the metabolic syndrome components and atherosclerosis (AS) progression, which is the leading cause of death by cardiovascular disease and cerebrovascular diseases.*
In atherosclerosis there predominates a pro-inflammatory immune response controlled by T-helpers, but there is also an anti-inflammatory response mediated mainly by regulatory T-cells (T-suppressors). T-cells help B-cells to change antibody class to produce high-affinity antibodies. Humoral immunity is mediated by B-cells, which secrete antigen-specific antibodies. Subsequent studies have shown that smooth muscle cell (SMC) phenotype change leads to less differentiated forms, including macrophage-like cells, and this change directly contributes to atherosclerosis. In addition, smooth muscle cell proliferation may be useful throughout atherogenesis, although macrophage-like cells derived from smooth muscle cells may contribute to inflammation. Our goal was to examine the role and consequences of phenotype change, smooth muscle cell proliferation and migration balance in atherosclerosis, and whether smooth muscle cells are critical for atherogenesis in metabolic abnormalities.
Materials and Methods: *we studied 50 cases of death with cerebral atherosclerosis on the metabolic syndrome background, 50 cases of death with cerebral atherosclerosis without metabolic syndrome manifestation and 50 cases of death by causes not related to MS and AS (comparison group). We studied arteries of two structural and functional levels: main – carotid arteries and extracerebral – cerebral floor arteries. Histological specimens of vessels were stained with hematoxylin-eosin, Masson's Trichrome, Van Gizon's picrofuxin and Weigert's resorcinol-fuchsin. Immunohistochemical study was performed using the following markers: CD4 (CD4 Ab-8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68/Macrophage Marker Ab-4), Actin Smooth Muscle Ab-1 (Clone 1A4); Desmin (Muscle Cell Marker Ab-1 Clone D33); Vimentin Ab-2.*
Results: *under atherosclerotic lesions of cerebral arteries with metabolic syndrome manifestations, there is a significantly higher desmin expression in SMC of the arterial wall media if to compare with other groups under study. Intensive activation of smooth muscle cell proliferation in vessels intima, myocytes migration from the media and increase in their number depends on fibroblast and endothelial factors. Upon immunohistochemical reaction with vimentin we noted connective tissue components presence as well as expressed artery wall fibrosis. Vimentin expression showed that vascular wall fibrosis increases as and when the underlying disease, i.e. MS, progresses.*
We also identified synthesis of connective-tissue matrix components, i.e. collagen and elastin, which subsequently led to intima thickening and fibrous plaque formation. We noted the monocytes adhesion on arteries luminal surface, presence of a large number of monocytes under the endothelium and more mature macrophages in the intima depth, which indicates these cells penetration from the blood into arterial wall.
Conclusion: *change in the arteries intima SMC phenotype is accompanied by increased proliferation and collagen synthesis, and modified SMC with their high proliferation activity and synthesis of connective tissue matrix components is responsible for the fibrous plaques skeleton formation.*
Key Word: *metabolic syndrome, atherosclerosis, lymphocytes, macrophages, smooth muscle cells, CD4 (CD4 Ab-8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68 / Macrophage Marker Ab-4), Actin Smooth Muscle Ab-1 (Clone 1A4); Desmin (Muscle Cell Marker Ab-1 Clone D33); Vimentin Ab-2.*

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I. Introduction

For more than 30 years metabolic syndrome (MS) has been in the spotlight as a model for a better understanding of the cardiovascular disease etiology, namely metabolic abnormalities. It is considered that the

metabolic syndrome in terms of pathogenetic development is quite complex, but reversible condition. Its uniqueness lies in the fact that you can reduce its manifestations by affecting one of the components.[1,2,3,4,5] The main morphological substrate of arterial lesions in metabolic syndrome is atherosclerosis (AS), the morphogenesis of which is insufficiently studied at present.[6,7,8,9]

In recent years, the AS origin and development are considered from the standpoint of smooth muscle cells (SMC) monoclonal proliferation and immune inflammation, where high priority is assigned to immune-competent cells.[10,11] In a series of experimental studies it was found that vascular wall SMC can change their phenotype from contractile to synthetic with the rearrangement of cells ultrastructural components, in which expression of proteins like vimentin, actin and desmin changes. However, there is considerable ambiguity as to which cells in atherosclerotic lesions originate from smooth muscle cells and which from macrophages, mainly due to the lack of rigorous, definitive studies on origin traceability.[12,13]

Monocytes adhesion on the arteries luminal surface, presence of a large number of these cells under the endothelium and more mature macrophages in the intima depths indicates these cells penetration from the blood into arterial wall.[14] Local infiltration by macrophages in the atherosclerotic lesions loci is often combined with T-lymphocytes accumulation, which indicates the inflammatory nature of the process.[15] In follow-on studies it was noted that in vascular atherosclerotic plaques there found smooth muscle cells that actively express II class-antigens of the main histocompatibility complex. These activation proteins are peculiar to T-lymphocytes and macrophages and are involved in the receptor transmission of immune information, which indicates the SMC ability to participate in immune responses in AS.[16,17]

Goal of research was to determine vascular wall smooth muscle cells ability to change the phenotype and their participation in immune responses in atherosclerosis on the metabolic syndrome background.

II. Material And Methods

To meet the goal set in the work we conducted a set of clinical and morphological studies. The specimens were sampled at the premises of the centralised Pathological Anatomical Department of the MPI Regional Clinical Hospital in Ivano-Frankivsk. Histological and histochemical examinations were performed at the premises of the histological laboratory of the centralised Pathological Department of the MPI Regional Clinical Hospital in Ivano-Frankivsk and at the premises of the histological laboratory of the Department of Pathological Anatomy of Ivano-Frankivsk National Medical University. Immunohistochemical studies were performed in the pathomorphological laboratory of the diagnostic and consulting centre "CSD Health care", Kyiv. The study was conducted in the period of 2018-2020 (3 years).

Study Design: Prospective open label observational study

Study Location The specimens were sampled at the premises of the centralised Pathological Anatomical Department of the MPI Regional Clinical Hospital in Ivano-Frankivsk. Histological and histochemical examinations were performed at the premises of the histological laboratory at the premises of the centralised Pathological Anatomical Department of the MPI Regional Clinical Hospital in Ivano-Frankivsk and at the premises of the histological laboratory of the Department of Pathological Anatomy of Ivano-Frankivsk National Medical University. Immunohistochemical studies were performed in the pathomorphological laboratory of the diagnostic and consulting centre "CSD Health care", Kyiv.

Study Duration: The study was conducted in the period of 2018-2020 (3 years).

Sample size: 150 cases.

Sample size calculation We studied 50 cases of cerebrovascular atherosclerosis deaths on the metabolic syndrome background, 50 cases of cerebrovascular atherosclerosis deaths without metabolic syndrome and 50 cases of deaths by causes not related to MS and AS (comparison group).

Subjects & selection method: We studied arteries of two structural and functional levels: main – carotid arteries and extracerebral – cerebral floor arteries, wherein 2-3 segments with lipid and fibrous plaques were sampled, while in the comparison group – unchanged areas.

Procedure methodology Histological specimen of vessels were stained with hematoxylin-eosin, Mason's Trichrome, Van Gizon's picrofuxin, Weigert's resorcinol-fuchsin; and also we performed immunohistochemical examination using markers CD4 (CD4 Ab-8), CD8 (SP-16), CD20 (CD20 Ab-1), CD68 (CD68/Macrophage Marker Ab-4), Actin Smooth Muscle Ab-1 (Clone 1A4); Desmin (Muscle Cell Marker Ab-1 Clone D33); Vimentin Ab-2 (Clone V9).

The specimens were fixed in a 10% neutral buffered formalin solution, tissues processing was performed according to established procedure. For immunohistochemical reactions, sections of 4-5 μm thick were mounted on Super Frost Plus adhesive slides (Menzel), dewaxed, hydrated and treated with 3% hydrogen peroxide solution to block endogenous peroxidase. The Ultra Detection System kit (Thermo Scientific) was used as the second antibody. To separate nonspecific structures sections were additionally stained with Mayer's hematoxylin.

Results of immunohistochemical reactions of CD4 markers (CD4 Ab-8) – T-helpers marker, CB8 (SP 16) – T-suppressors marker, CD20 (CD20 Ab-1) – B-lymphocytes marker and CD68 (CD68/Macrophage Marker Ab-4) were evaluated by counting cells with a positive staining in 10 randomly selected microscope's fields of view at a magnification of 400. In addition, we evaluated the degree of staining intensity: 0 – no staining, 1 (+) – weak light brown staining, 2 (++) – moderate brown staining, 3 (+++) – expressed dark brown staining.

Actin Smooth Muscle Ab-1 (Clone 1A4), Desmin (Muscle Cell Marker) Ab-1 (Clone D33), Vimentin Ab-2 (Clone V9) were used to determine mesenchymal cells and their derivatives – endothelial cells, smooth myocytes, fibroblasts and pericytes, which were estimated as the specific volume of immunopositive cells per unit area. The immunohistochemical reaction results were evaluated by the semi-quantitative method in points from 0 to 6 according to established procedure with consideration of the stained cells [66]. 0 points were rated in the absence of staining, 1 point – up to 10%, 2 points – up to 20%, 3 points – up to 30%, 4 points – up to 40%, 5 points – up to 50%, 6 points – more than 50% stained cell. In addition the degree of staining intensity was evaluated: 0 – no staining, 1 (+) – weak light brown staining, 2 (++) – moderate brown staining, 3 (+++) – expressed dark brown staining.

Micro slides histological examination and photography was performed on an AxioScop 40 microscope (Zeiss). Morphometric studies data underwent statistical processing using a personal computer through the standard Microsoft Excel program, the results were processed by variation statistics method and considered reliable at $p < 0.05$.

III. Result

Manifestations in the form of lipid spots, fibrous plaques, calcification, stenosis and obliteration were observed in the groups under study. The decrease in vascular lumen was caused mainly by muscular-elastic or muscular-fibro-elastic hyperplasia of intima.

The most evident changes are observed in the areas of blood vessels functional load – arteries bifurcation. We noted predominance of stenotic and obliterating variants of main vascular lesions with the intima hyperplasia with diffuse focal lymphocytic-macrophage infiltration (Fig. 1).

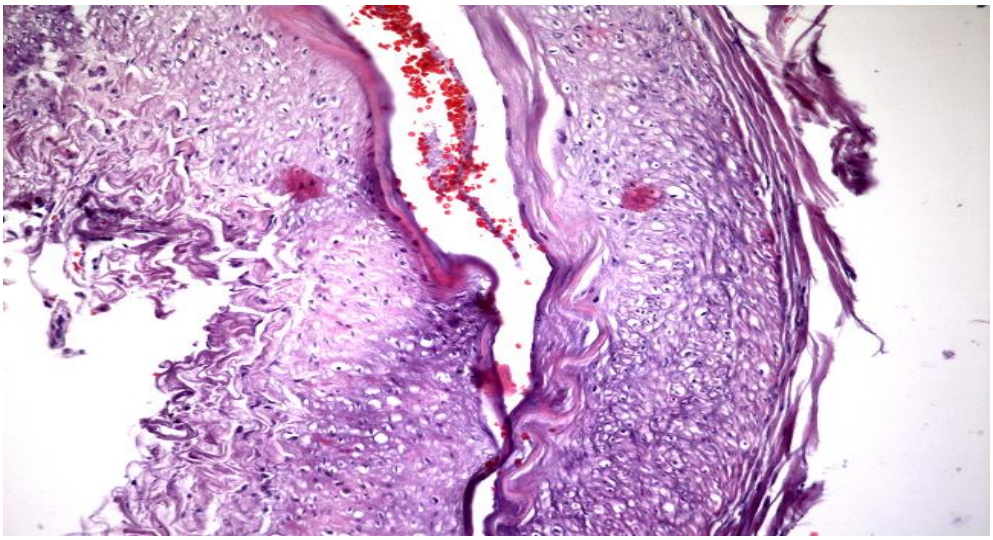

Fig.1 Significant artery wall thickening with lumen narrowing. Staining: hematoxylin-eosin. ^{x} 200.
Sourse: Author

Macrophages with lipid inclusions, so-called xanthoma cells, with foamy cytoplasm and round nucleus were observed in the areas of intima proliferation (Fig. 2).

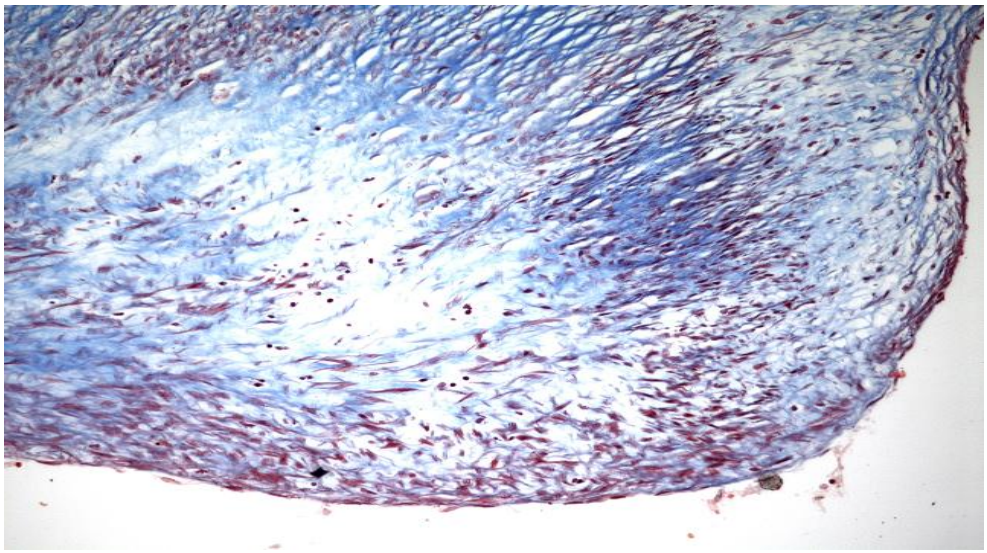

Fig. 2. Xanthoma cells with foamy cytoplasm. Masson's Trichrome staining x 200.
Sourse: Author

Most arteries wall thickening was associated with connective tissue fibres proliferation, mainly collagen ones (Fig. 3). Collagen fibres proliferation led to artery intima thickening, which caused a significant narrowing of their lumen. In many cases we observed the presence of homogeneous eosinophilic masses with a distinct boundary with unchanged tissue, macrophage reaction and fibroblast proliferation.

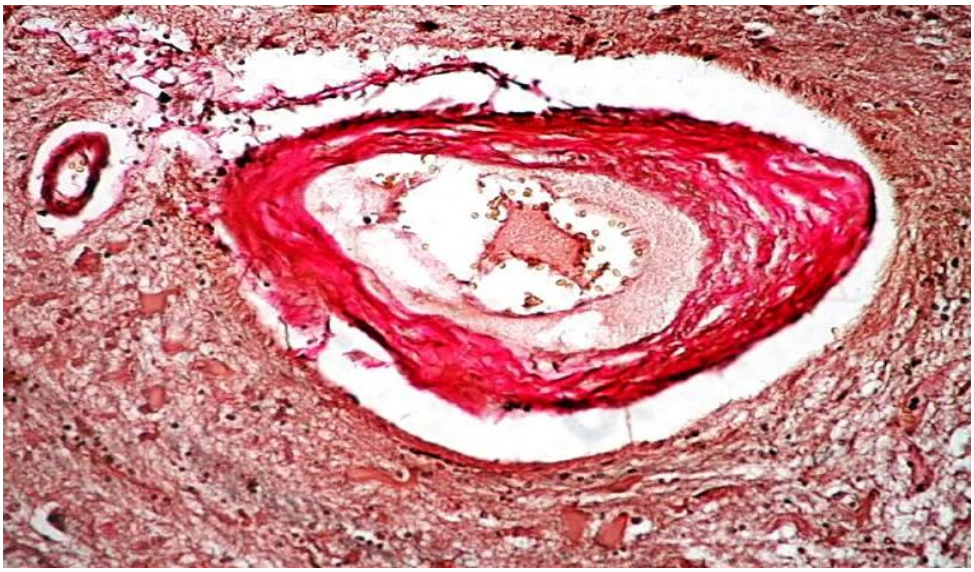

Fig. 3 – Artery wall thickening wall due to collagen fibres proliferation. Staining: Van Gizon' picrofuxin, Weigert's resorcinol fuchsin x200.
Sourse: Author

Atherosclerotic lesions development was characterised by smooth muscle cells migration into the intima and their proliferation. In all atherosclerotic plaques we noted fibrosis areas, which encapsulated the lipid focus, and consisted mainly of collagen fibres, among which elastic fibres and a large number of fibroblasts were found.
Atherosclerotic plaques protruded into vascular lumen, creating an obstacle to blood flow (Fig. 4).

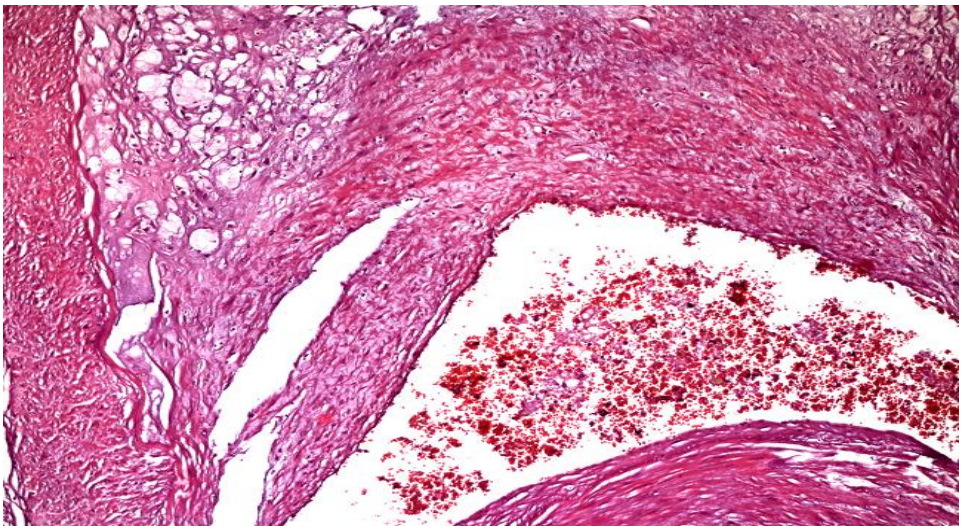

Fig. 4 - Atherosclerotic plaque in the artery wall. Staining: hematoxylin-eosin $^{x}400$.
Sourse: Author

Smooth muscle cells that migrated to the intima from the media were transformed into secretory cells and intensively produced connective tissue proteins – elastin and collagen. Subsequently, fibrous tissue was formed, which encapsulated the lipid focus. Smooth muscle cells that migrated to the intima from the artery media became metabolically active despite the scavenger receptors absence, they intensively absorb modified lipoproteins, i.e. they also formed foam cells.

Immunomorphological analysis of the arteries walls showed that, except for endothelium, all the intima and media cells react with antibodies to vimentin (Fig. 5). At immunohistochemical reaction with vimentin the connective tissue components presence as well as the expressed artery wall fibrosis was noted. Fibrous plaques assume different sizes and shapes, from small segmental to circular, and sometimes multiple, which led to vessel sclerosis in large areas.

In the study of vimentin in the wall of atherosclerotic affected arteries in the group with MS, its expression constituted 59.6 ± 4.8% ($p > 0.05$) against total area; in the group without MS manifestations – 54.8 ± 3.7% ($p > 0.05$). In the comparison group, vimentin expression constituted 52.2 ± 6.4 ($p > 0.05$).

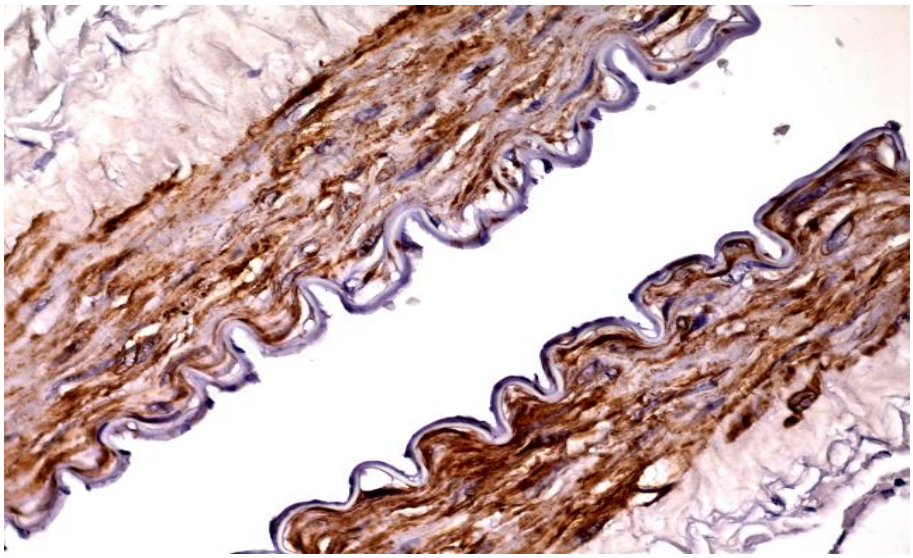

Fig. 5 - Intense expression of Vimentin Ab-2 marker in the artery wall. Staining: immunohistochemical technique with primary antibodies Vimentin Ab-2 positive cells. ^{x} 200
Sourse: Author

In many cases we observed formation of vessel wall longitudinal folds, which protruded into the vessel lumen and narrowed it by half; herewith we noted changes in the muscular layer: the muscular layer was distinctly thickened with dissection and high vimentin expression. There was a distinct tortuosity of the inner elastic membrane.

Vimentin expression showed that vascular wall fibrosis increases as and when the underlying disease, i.e. MS, progresses.

Also, all media and intima cells reacted with antibodies to alpha-actin. Alpha-actin expression in the group with MS constituted 62.8 ± 7.6% ($p > 0.05$) and in the group without MS manifestations – 58.5 ± 4.7% ($p > 0.05$) (Fig. 6). In the comparison group, the expression constituted 55.7 ± 5.2% ($p > 0.05$).

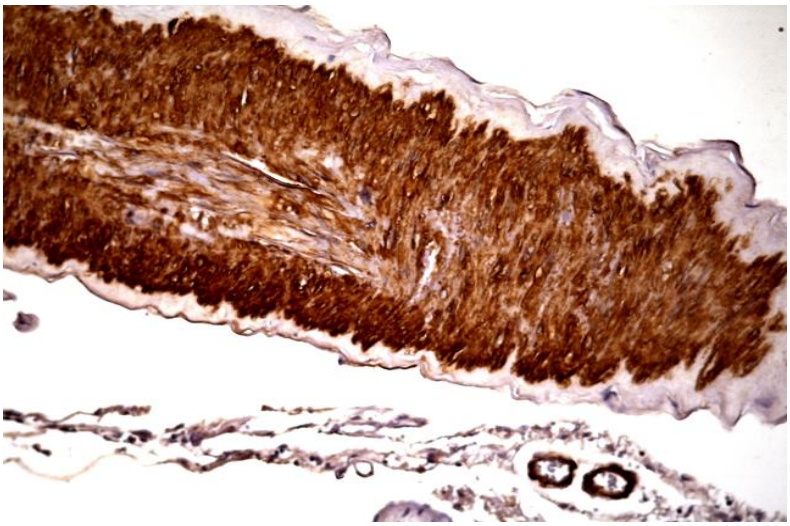

Fig. 6 - Intense expression of Actin Smooth Muscle Ab-1 marker in the artery wall with metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of Actin Smooth Muscle Ab-1 positive cells. ˣ 200.

Sourse: Author

Changes in the inner elastic membrane were manifested in its dissection, sometimes to its complete disappearance, which probably led to lipids penetration into the media, as well as in fibres separation and increased tortuosity.

In many cases desmin expression was of diffuse nature with a distinct boundary line with the surrounding tissues. We noted smooth muscle cells proliferation and connective tissue fibers hyperproduction; this explains the cause for the intima thickening with the subsequent fibrous plaque formation. Desmin expression was not found in the intima cells, but was detected only in part of the media SMC (Fig. 7).

Quantitatively, in the group of patients MS with manifestations the desmin expression constituted 14.6 ± 3.4% ($p > 0.05$) against the total area; in the group without MS manifestations, the expression of the desmin marker constituted 12.8 ± 4.7% ($p > 0.05$).

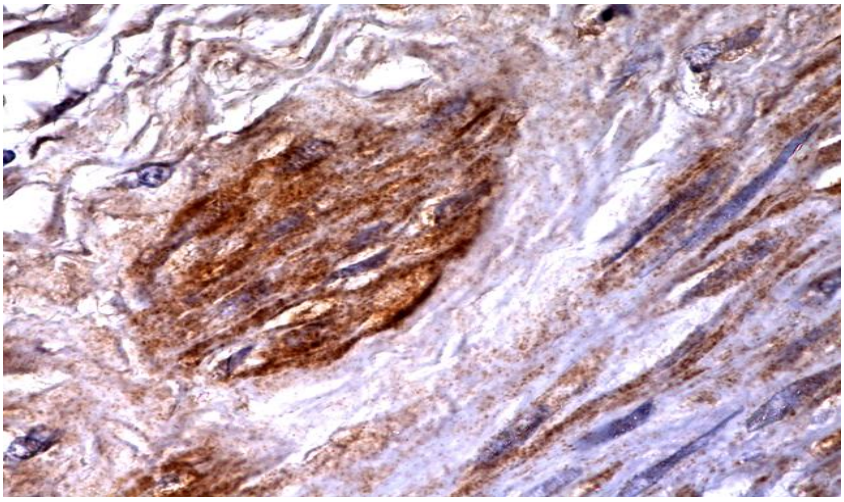

Fig. 7 - Intense expression of the Desmin marker in the artery wall of a patient with metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of Desmin positive cells. ˣ 400.

Sourse: Author

In areas of atherosclerotic lesions, we noted a significant number of CD68-positive cells with marker expression in the cytoplasm (Fig. 8), which constituted 16.68 ± 1.82 ($p > 0.05$) in the group with MS manifestations, in the group without MS manifestations – 14.56 ± 1.28 ($p > 0.05$). In the control group, the number of CD68 positive cells with marker expression in the cytoplasm constituted 7.34 ± 1.73 ($p > 0.05$).

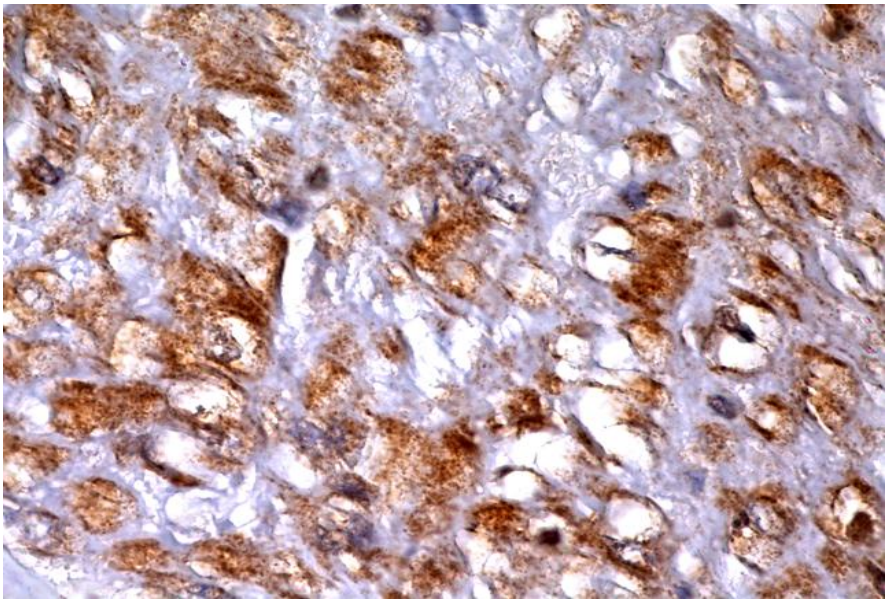

Fig. 8. - Intense expression of the CD68 marker in the artery wall of a patient with metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of CD68 positive cells. x 400
Sourse: Author

We observed blood monocytes accumulation in the damaged layer of endothelium and subendothelial space, with their subsequent transformation into macrophages and lipids capture the cytoplasm acquired a foamy appearance, i.e. foam cells were formed.

Local infiltration by macrophages in the atherosclerotic lesions loci was often combined with the accumulation of T-lymphocytes, which indicates the inflammatory nature of the process.

T-lymphocytes helpers (CD4, membrane expression) in the areas of atherosclerotic lesions constituted 11.18 ± 1.76 ($p > 0.05$) in the group with MS manifestations and 10.32 ± 1.24 ($p > 0.05$) in the group without MS manifestations (Fig. 9). T-lymphocyte suppressors (CD8, membrane expression) constituted 8.56 ± 1.16 ($p > 0.05$) and 9.12 ± 1.64 ($p > 0.05$), respectively (Fig. 10).

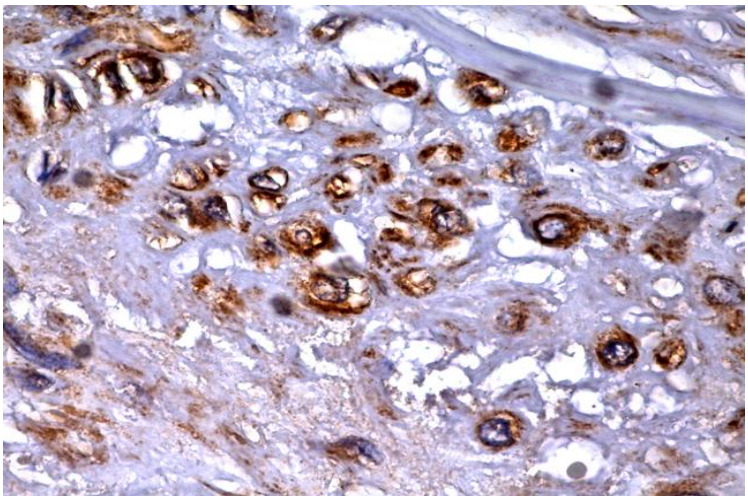

Fig.9 - Intense CD4 marker expression in the artery wall of the patient without metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of CD4 positive cells. x400
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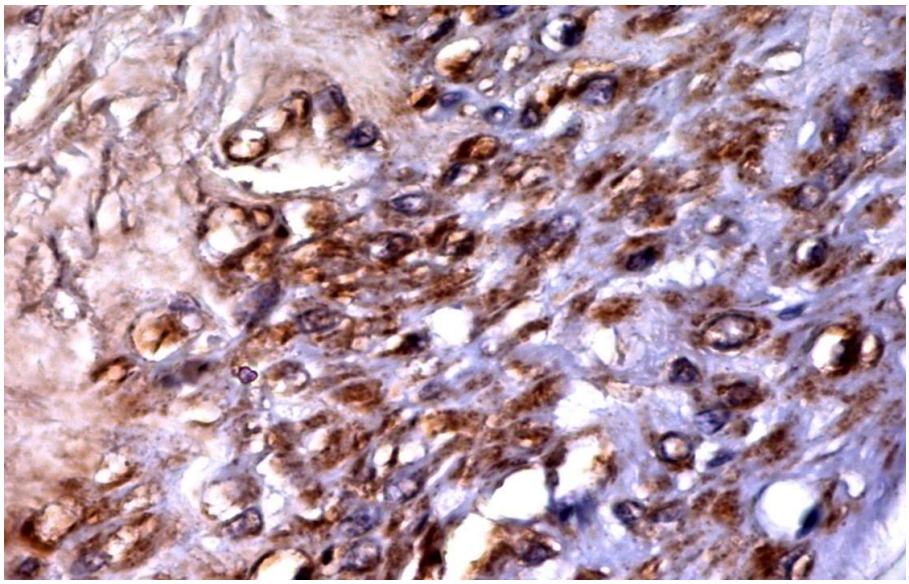

Fig. 10 - Intense expression of the CD8 marker in the artery wall of a patient with manifestations of metabolic syndrome. Staining: immunohistochemical technique with primary antibodies of CD8 positive cells. x 400.
Sourse: Author

B-lymphocytes (expression – layer, cytoplasm) were under-represented – 5.34 ± 0.86 ($p > 0.05$) in the atherosclerotic lesions locus with MS manifestations and 6.04 ± 1.14 ($p > 0.05$) in the group without MS manifestations (Fig. 11). In atherosclerotic lesions loci of the arteries without MS manifestations there was a tendency to increase the number of positively stained cells. Single or small groups of cells with suppressor functions were present among the endothelial cells of the microcirculatory tract.

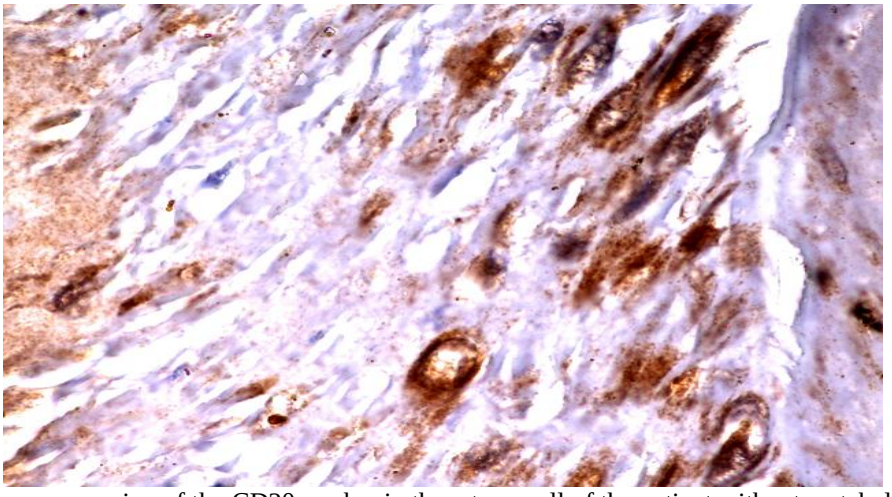

Fig. 11 - Intense expression of the CD20 marker in the artery wall of the patient without metabolic syndrome manifestations. Staining: immunohistochemical technique with primary antibodies of CD20 positive cells x 400.
Sourse: Author

The immune response in atherosclerotic lesions was represented by cellular and humoral arms of response, i.e. cellular arm was ensured by T-helpers and cytotoxic T-lymphocytes, whereas humoral arm – by B-lymphocytes that produce immunoglobulins.

IV. Discussion

To determine vascular smooth muscle cells condition and their participation in immune responses in atherosclerosis on the metabolic syndrome background, we studied cerebral vessels structural features in the dead with cerebral atherosclerosis.

Vascular smooth muscle cells play a significant role in AS development. Electron-microscopic examination of humans and test animals atherosclerotic plaques revealed that in addition to typical SMC, which cytoplasm is filled with microfilaments and the endoplasmic reticulum is localised in the perinuclear space,

there are also cells containing well-developed endoplasmic reticulum and Goldgi apparatus with a small amount of microfilaments. Such cells have been identified as modified or secretory SMC.[12,13]

In subsequent series of experimental studies, it was found that vascular wall SMC can change their phenotype from contractile to synthetic with the cells ultrastructural components rearrangement, in which the expression of a number of proteins changes.[13] Proteins, which expression changes under the SMC phenotype rearrangement, are actin, desmin and vimentin. Upon studies of SMC modulation markers it has been discovered that desmin-containing SMC appear in atherosclerotic plaques of the human aorta.[11,12,14]

Immunomorphological analysis of the arteries walls showed that, excluding the endothelium, all intima and media cells react with antibodies to vimentin and alpha-actin. Changes in the inner elastic membrane were manifested in dissection, sometimes until its complete disappearance, as well as in fibres separation and increased tortuosity. Alpha-actin expression in the group with MS constituted $62.8 \pm 7.6\%$ ($p > 0.05$) and in the group without MS manifestations – $58.5 \pm 4.7\%$ ($p > 0.05$). In the comparison group the expression constituted $55.7 \pm 5.2\%$ ($p > 0.05$). In some areas, we observed complete lysis of the inner elastic membrane, which led to the penetration of lipids into the media. Therefore, the inner elastic membrane edge acquired a scalloped appearance from the intima side.

Vimentin attaches to the nucleus of endoplasmic reticulum and mitochondria and plays a significant role in organelles attachment and their attachment maintaining in the cytoplasm. It is vimentin that ensures cells strength and their resistance to mechanical stress.[12,13] Upon vimentin study in the group with MS its expression in the wall of atherosclerotic affected arteries constituted $59.6 \pm 4.8\%$ ($p > 0.05$) against total area; in the group without MS manifestations – $54.8 \pm 3.7\%$ ($p > 0.05$). In the comparison group vimentin expression constituted 52.2 ± 6.4 ($p > 0.05$). We noted the presence of connective tissue components, as well as expressed artery wall fibrosis. Vimentin expression showed that vascular wall fibrosis increases as and when the underlying disease, i.e. MS, progresses.

Desmin expression was not found in the intima cells, and was detected only some media SMC. Therefore, it can be assumed that the appearance of cells that react with antibodies to desmin is a consequence of the SMC phenotype modulation accompanied by increased cell proliferation and synthesis of connective tissue matrix components, which can lead to the fibrous plaque formation.

Some authors perceive the fact of desmin-positive SMC detection in the visually unchanged aortic intima of young people as the beginning of fibrous plaque formation. Upon primary culture model study, the data obtained indicate that SMC phenotype change of human aortic intima is accompanied by increased collagen proliferation and synthesis. It is deemed that modified SMC with their high proliferation activity and synthesis of connective tissue matrix components are responsible for cell mass and fibrous skeletal plaques formation.[11,13,14]

In many cases desmin expression was diffuse in nature, with a distinct boundary line with the surrounding tissues. Quantitatively, in the group of patients with MS manifestations desmin expression constitutes $14.6 \pm 3.4\%$ ($p > 0.05$) against the total area; in the group without MS manifestations expression of the desmin marker constituted $12.8 \pm 4.7\%$ ($p > 0.05$). Smooth muscle cells proliferation and connective tissue fibers hyperproduction were noted; this explains the reason of the intima thickening with the subsequent fibrous plaque formation.

These data on desmin conform to other authors' studies, who found that desmin expression varies with age: in children desmin is found in all artery cells, in adolescents – only in some, and in adults desmin is never present in the intima cells, but only focally in media SMC, i.e. with age media SMC lose their ability to express desmin.[11,13,14]

The initial component of autoimmune reactions occurring in the vascular wall in atherosclerosis is modified low-density lipoproteins (LDL) formation under the influence of various factors.[14,15,17] Modified LDL activate hematogenous origin cells – monocytes, macrophages, lymphocytes that migrate into the arteries intima, and vascular wall cells – endothelial cells, stellate and smooth muscle cells, which cause reactions keeping the inflammatory focus in the wall.[12,16]

The study shows that 50% of foam cells in human coronary artery advanced disease express smooth muscle α-actin.[11] However, most of these cells also expressed the CD68 macrophage marker, and thus their origin is unclear, especially given that myeloid origin cells can be induced to express smooth muscle α-actin.[12,16]

We noted blood monocytes accumulation in the damaged layer of endothelium and subendothelial space, with their subsequent transformation into macrophages and lipid uptake; the cytoplasm acquired a foamy appearance, i.e. foam cells were formed. In atherosclerotic lesions loci, a significant number of CD68-positive cells with marker expression in the cytoplasm was observed, which in the group with MS manifestations constituted 16.68 ± 1.82 ($p > 0.05$) and in the group without MS manifestations – 14.56 ± 1.28 ($p > 0.05$). In the comparison group, the number of CD68 positive cells with marker expression in the cytoplasm constituted 7.34 ± 1.73 ($p > 0.05$).

The immune response in atherosclerotic lesions was represented by cellular and humoral response arms, i.e. the cellular response was ensured by T-helpers and cytotoxic T-lymphocytes and the humoral response – by B-lymphocytes, which produce immunoglobulins. T-lymphocytes helpers (CD4, membrane expression) in atherosclerotic lesions formation loci constituted 11.18 ± 1.76 ($p > 0.05$) in the group with MS manifestations and 10.32 ± 1.24 ($p > 0.05$) in the group without MS manifestations (Fig. 9). T-lymphocyte suppressors (CD8, membrane expression) constituted 8.56 ± 1.16 ($p > 0.05$) and 9.12 ± 1.64 ($p > 0.05$) respectively. B-lymphocytes (expression – layer, cytoplasm) were present in smaller numbers – 5.34 ± 0.86 ($p > 0.05$) in the atherosclerotic lesions locus with manifestations of MS and 6.04 ± 1.14 ($p > 0.05$) in the group without MS manifestations.

These data can be used in the development atherosclerosis treatment methods as a structural basis for the damage cerebral arteries in MS by developing new approaches to treatment based on the regulation of arterial wall cells kinetics.

V. Conclusion

There are SMC subpopulations in the arteries wall, which are characterised by desmin, so SMC are able to change their phenotype from contractile to synthetic, and this change in the SMC phenotype is one of the key moments in the atherosclerosis pathogenesis.

In atherosclerotic lesions of the cerebral arteries in MS a significant role in the morphogenesis the vascular wall changes with atherosclerotic plaques formation is played by immunocompetent cells – macrophages and lymphocytes, as evidenced by their accumulation in atherosclerotic lesion loci.

Due to the lipids accumulation macrophages in the vascular wall are transformed into foam cells, and lymphocytes potentiate the further atheromatous plaque formation as a result of the cellular and humoral immune response. Thus, the data obtained indicate that change in the arteries intima SMC phenotype is accompanied by increased proliferation and collagen synthesis, and modified SMC with their high proliferation activity and connective tissue matrix components synthesis are responsible for the formation of fibrous plaque. Smooth muscle cells that migrated to the intima from the arteries media became metabolically active, absorbing modified lipoproteins, and changed to foam cells.

There is no probable difference in vascular wall infiltration by immunocompetent cells in their number and nature depending on the MS manifestations, what indicates that vascular changes morphogenesis is determined namely by the underlying disease.

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