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Histological analysis of thrombi for differential diagnosis of ischemic stroke subtypes

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Abstract

Background. *Despite a complex diagnostic evaluation, the cause of ischemic stroke (IS) remains unidentified in 23-40% of cases. The implementation of endovascular thrombectomy has created the opportunities for morphological analysis of thrombotic masses.*

Objective. *To compare the histological structure of thrombi in patients (pts) with different subtypes of acute IS.*

Material and methods*. For analysis, thrombotic masses were extracted from 107 pts with IS during aspiration thrombectomy. The relationships with clinical and procedural parameters were assessed.*

Results. *Fractions of erythrocytes, fibrin, detritus and leukocytes in the extracted thrombi were comparable in patients with different subtypes of IS. In pts with cardioembolic IS and IS of undetermined etiology, the plasma cell count in thrombi was statistically significantly higher than in pts with atherothrombotic IS (10 (6;13) vs. 6 (4;9) number of cells, p=0,020; 10 (5;18) vs. 6 (4;9) number of cells, p=0,035, respectively).*

Conclusions. *Quantitative examination of clot content may be used to distinguish between different IS subtypes. We suppose on the notion that the majority of IS of undetermined etiology was associated with cardioembolic source.*

Keywords: stroke, etiology, thrombectomy, clot, plasma cells

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AF, atrial fibrillation
BCS, blood coagulation system
BMI, body mass index
CI, confidence interval
CT, computed tomography
DBP, diastolic blood pressure
ECG, electrocardiography
EchoCG, echocardiography
HR, heart rate
IS, ischemic stroke
Me (Q_1;Q_3), median (lower and upper quartiles)
MRI, magnetic resonance imaging
mRS, Rankin scale
NIHSS, National Institutes of Health Stroke Scale
SBP, systolic blood pressure
TIA, transient ischemic attack
TOAST, Trial of Org 10172 in Acute Stroke Treatment Classification

Introduction

Routine diagnostic methods, despite their diversity, fail to establish the etiology of ischemic stroke (IS) in 23–40% of cases [1–2]. In clinical practice, IS of unknown etiology poses a range of major challenges, one of which is secondary stroke prevention. Recent studies have shown that after IS of unknown etiology, the risk of a recurrent acute cerebral event within the first year can reach 9.5% [3]. A complete explanation for the high rate of recurrent strokes is currently lacking, so, for improving the

patient care and stroke prevention, it is crucial to study in-detail the key characteristics of IS of the unknown etiology by using advanced diagnostic methods.

Endovascular thrombectomy has fundamentally changed approaches to treating patients with acute ischemic stroke [4, 5], and has also opened up a new line of research in stroke based on the study of the composition of the extracted thrombotic masses [6]. Studies have assessed the basic morphological components of thrombi, and attempts have been made to classify ischemic stroke subtypes based on this data; however, the results of these studies are contradictory [7–10].

The aim of our study was to compare the histological composition of thrombi in patients with different subtypes of ischemic stroke in relation to fibrin, erythrocytes, detritus, their proportions, leukocytes, lymphocytes, as well as granulocytes and plasma cells.

Material and methods

A prospective study included 107 patients with acute ischemic stroke subjected to a complete diagnostic examination and signed informed consent and who underwent endovascular thrombectomy using an aspiration catheter (Sofia [MicroVension, USA] or AXS Catalyst [Stryker Neurovascular, USA]) and stent retriever (Trevo [Stryker Neurovascular, USA] or Solitaire [Medtronic, USA]). In all cases, thrombus removal was performed by aspiration [11, 12] in accordance with current recommendations [13]. The effectiveness of the blood flow restoration was assessed using a modified version of the Treatment in Cerebral Ischemia (mTICI) score, for which score of 2b or 3 indicated successful reperfusion [4, 5, 13].

The final analysis included 90 patients whose thrombus samples were of sufficient quality for histological examination (Table 1).

Table 1. Clinical and demographic characteristics of ischemic stroke patients who underwent endovascular thrombectomy

Parameter	n=90
Age, years, Me (Q_1;Q_3)	75 (65;82)
Gender (m), n (%)	40 (44)
BMI, kg/m^2, Me (Q_1;Q_3)	26.3 (23.9;30.8)
Smoking, n (%)	9 (10)
Arterial hypertension, n (%)	8 4 (96)
Previous history of myocardial infarction, n (%)	16 (18)
History of stroke/TIA, n (%)	15 (17)
Diabetes melitus, n (%)	16 (18)
Atrial fibrillation, n (%)	51 (57)
Chronic heart failure, n (%)	14 (16)
Chronic kidney disease, n (%)	12 (14)
Active cancer, n (%)	12 (14)
Dyslipidemia, n (%)	88 (98)
HR, beats/min, Me (Q_1;Q_3)	83 (74;92)
SBP, mmHg, Me (Q_1;Q_3)	148 (136;174)
DBP, mm Hg, Me (Q_1;Q_3)	90 (80;105)
CHA_2DS_2VASc, points, Me (Q_1;Q_3)	3 (2;4)
NIHSS on admission, score, Me (Q_1;Q_3)	16 (11;21)
Thrombolytic therapy, n (%)	21 (24)
TOAST classification, n (%):	
- atherothrombotic	12 (13)
- cardioembolic	41 (46)
- other determined etiology	2 (2)
- undetermined etiology	35 (39)

Notes: BMI, body mass index; TIA, transient ischemic attack; HR, heart rate; SBP/DBP, systolic/diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment Classification

The risk of systemic thromboembolic complications was calculated in all patients before the onset of an acute cerebral event, regardless of the presence of atrial fibrillation (AF), using the CHA_2DS_2VASc scale (where C stands for heart failure/left ventricular dysfunction, H stands for arterial hypertension, A_2 means age over 75 years, D for diabetes mellitus, S_2 stands for stroke/TIA/systemic thromboembolism, V stands for vascular diseases, A means age 65–74 years old, Sc means sex category [female]) [13].

The etiology of IS was identified in accordance with the international classification of pathogenetic subtypes Trial of Org 10172 in Acute Stroke Treatment (TOAST) [14]; and it was determined based on all diagnostic and clinical data available for each patient, including laboratory test results, computed tomography (CT) of the brain, CT angiography and magnetic resonance imaging (MRI), transcranial and extracranial duplex sonography, standard 12-lead electrocardiography (ECG) and 48-hour ECG, echocardiography (EchoCG). A complete diagnostic work-up was defined as at least any cerebral imaging (CT or MRI) and extracranial vessels (angiography, CT angiography or duplex sonography), prolonged ECG monitoring, transthoracic and/or transesophageal EchoCG.

After two complete neurological examinations, the severity of IS was assessed using the National Institute of Health Stroke (NIHSS) Scale [15]. The modified Rankin scale (mRS) was used to assess functional outcomes within 30 days after discharge [16].

Histological examination. The extracted thrombotic masses were immediately fixed in 10% phosphate-buffered formalin and then sent for histopathological examination. In the pathology laboratory, the thrombotic mass material was distributed into cassettes, where it underwent histological processing, paraffin embedding, microtomy, and hematoxylin and eosin staining. Two to three sections, cut at different depths within the paraffin block, were placed on each slide. The finished slides were scanned in a histoscanner, and the resulting images were analyzed by a pathologist.

At the initial stages of the morphological study of thrombotic masses, histochemical staining according to Van Gieson was also performed, however, since no signs of organization were detected in any thrombus, it was decided to abandon this research method.

When assessing the histology of thrombotic masses, the ratio of fibrin to erythrocytes was calculated, thereby determining the nature of

the thrombus structure: erythrocyte-rich thrombus, fibrin thrombus, or mixed (Fig. 1).

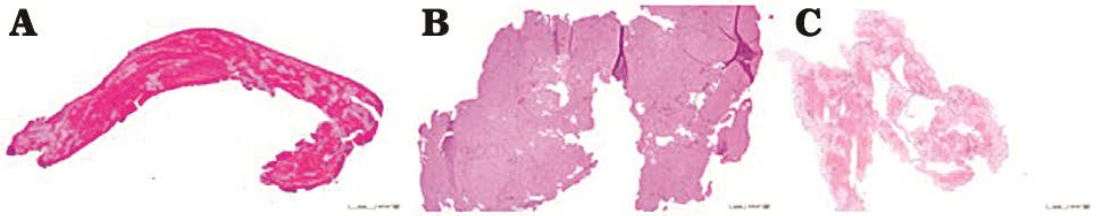

Fig. 1. Variants of thrombus structure: A) erythrocytic; B) fibrinous, C) mixed. Stained with hematoxylin and eosin (magnification x5)

In case of an erythrocyte-rich thrombus, the amount of erythrocytes was more than 60%, and fibrin was less than 40%. Fibrin thrombi, on the contrary, had more than 60% of fibrin fibers and less than 40% of red blood cells. Mixed thrombi were characterized by an approximately equal ratio of red blood cells to fibrin.

The average number of inflammatory cells in one high-power field of view was also assessed. These were primarily neutrophils, with occasional eosinophils and, less commonly, lymphocytes and plasma cells (Fig. 2). Necrotic debris was not included in the assessment.

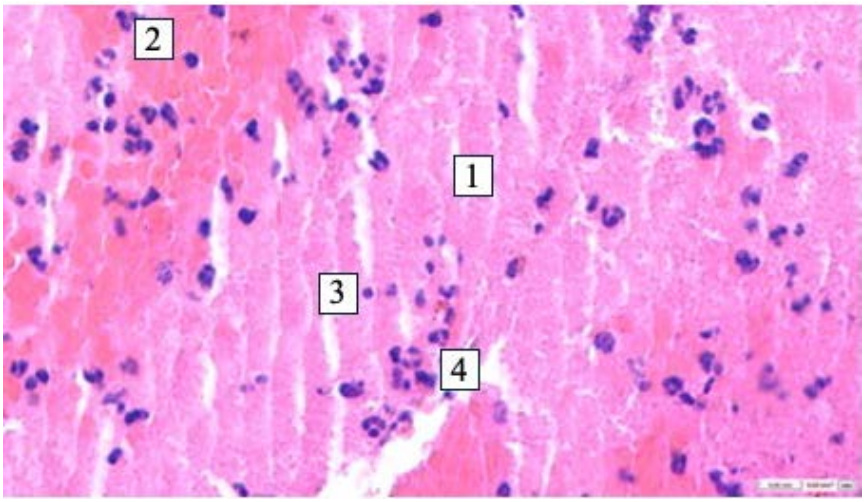

Fig. 2. Cellular content of thrombus: 1, fibrin; 2, erythrocyte; 3, lymphocyte; 4, cluster of neutrophilic granulocytes. Stained with hematoxylin and eosin (high power magnification x80)

The primary endpoint was defined as the difference in the histological composition of thrombi in patients with cardioembolic and atherothrombotic stroke subtypes.

Statistical processing of the study results. Statistical processing of the study data was performed using the SPSS Statistics version 26.0 software package. The median and the lower and upper quartiles (Me (Q_1;Q_3)) were used to describe quantitative data. Qualitative variables were described by absolute (n) and relative (%) values. When comparing quantitative characteristics in patient subgroups, the nonparametric Mann–Whitney test was used. Differences in qualitative characteristics were judged by the χ^2 and Fisher's exact test. To analyze the relationships between parameters, the Spearman rank correlation coefficient was calculated. To calculate the optimal threshold value for parameters, sensitivity, and specificity, the ROC curves (AUC) were analyzed. Differences were considered statistically significant at a significance level of $p<0.05$.

Results

Comparison of the histological composition of thrombi in patients with cardioembolic and atherothrombotic subtypes of stroke

According to the TOAST classification, "other determined etiology" of stroke in one patient (1%) was related to right internal carotid artery dissection; and in another patient (1%), it was related to polycythemia vera. The latter of these two patients was excluded from further analysis, and the first patient, due to a similar mechanism of thrombus formation, was combined with patients having the atherothrombotic stroke subtype.

Patients with cardioembolic stroke were 12 years older than patients with atherothrombotic stroke ($p<0.001$), the former were

characterized by a statistically significantly lower proportion of males (37% versus 77%, respectively, p=0.024) (Table 2).

Table 2. Clinical and demographic characteristics and surgical intervention parameters in patients with cardioembolic and atherothrombotic stroke subtypes

Parameter	Stroke		p
	Cardioembolic (n=41)	Atherothrombotic (n=13)	
Age, years, Me (Q_1;Q_3)	77 (73;85)	65 (58;72)	<0.001
Gender (m), n (%)	15 (37)	10 (77)	0.023
CHA_2DS_2VASc, score, Me (Q_1;Q_3)	4 (3;5)	2 (2;5)	0.024
NIHSS at admission, points, Me (Q_1;Q_3)	19 (12;21)	13 (11;22)	0.419
Thrombolytic therapy, n (%)	8 (19)	4 (31)	0.453
Time to reperfusion, min, Me (Q_1;Q_3)	225 (191;330)	205 (155;266)	0.168
Duration of operation, min, Me (Q_1;Q_3)	45 (30;61)	53 (39;71)	0.213
Thromboaspiration passages, n, Me (Q_1;Q_3)	2 (1;2)	2 (1;2)	0.913
Reperfusion mTICI, n (%): – 2b gr. – 3 gr.	 1 (2) 40 (98)	 3 (23) 10 (77)	0.062

AF was documented in 40 patients (98%) with cardioembolic stroke and only in 1 patient (8%) in the group atherothrombotic stroke (p<0.001, statistically significant). Despite the fact that the CHA2DS2VASc score was statistically significantly higher in patients with cardioembolic stroke, the severity of the acute cerebral event according to the NIHSS scale was comparable in the groups (p=0.419).

Interventional parameters, including the time from symptom onset to surgery, surgery duration, the number of thrombotic aspirations, and

the degree of perfusion restoration according to the mTICI scale, were comparable in two groups.

In any cases, no signs of thrombus organization were detected. The percentage content of fibrin, red blood cells, and debris to thrombus composition, as well as the thrombus type identified based on the above characteristics, did not show statistically significant differences between the groups with cardioembolic or atherothrombotic stroke subtypes (Table 3).

Table 3. Comparison of thrombi histological characteristics in patients with cardioembolic and atherothrombotic stroke subtypes

Parameter	Stroke		p
	Cardioembolic (n=41)	Atherothrombotic (n=13)	
Fibrin, %, Me (Q_1;Q_3)	30 (18;48)	40 (20;65)	0.428
Erythrocytes, %, Me (Q_1;Q_3)	60 (45;72)	5 0 (25;75)	0.465
Detritus, %, Me (Q_1;Q_3)	5 (5;10)	5 (5;10)	0.730
Thrombus type, n (%): - erythrocytic - fibrinous - mixed	 22 (54) 7 (17) 12 (29)	 5 (38) 4 (31) 4 (31)	0.504
Leukocytes, n (%): – 1–100 cells* – 101–200 cells* – >200 cells*	 12 (29) 22 (54) 7 (17)	 8 (61) 4 (31) 1 (8)	0.109
Neutrophils, number of cells*, Me (Q_1;Q_3)	94 (68;120)	60 (22;152)	0.250
Eosinophils, number of cells*, Me (Q_1;Q_3)	3 (2;6)	3 (1;9)	0.983
Macrophages, number of cells*, Me (Q_1;Q_3)	1 (0;3)	1 (0;1)	0.403
Lymphocytes, number of cells*, Me (Q_1;Q_3)	29 (18;50)	15 (6;55)	0.100
Plasma cells, number of cells*, Me (Q_1;Q_3)	10 (6;13)	6 (4;9)	0.020

*Note: * high power increase (x80)*

Patients in both groups were comparable in terms of white blood cell count and types. The only statistically significant difference identified was a higher plasma cell count in thrombi in patients with cardioembolic stroke than in patients with atherothrombotic stroke (10 (6;13) vs. 6 (4;9), p=0.020).

In order to differentiate cardioembolic and atherothrombotic strokes, when constructing ROC curves, a threshold value of plasma cells of at least 7 was obtained (AUC 0.716 (95% confidence interval (CI) [0.555–0.876]), p=0.020, sensitivity 70.7%, specificity 30.8%) (Fig. 3).

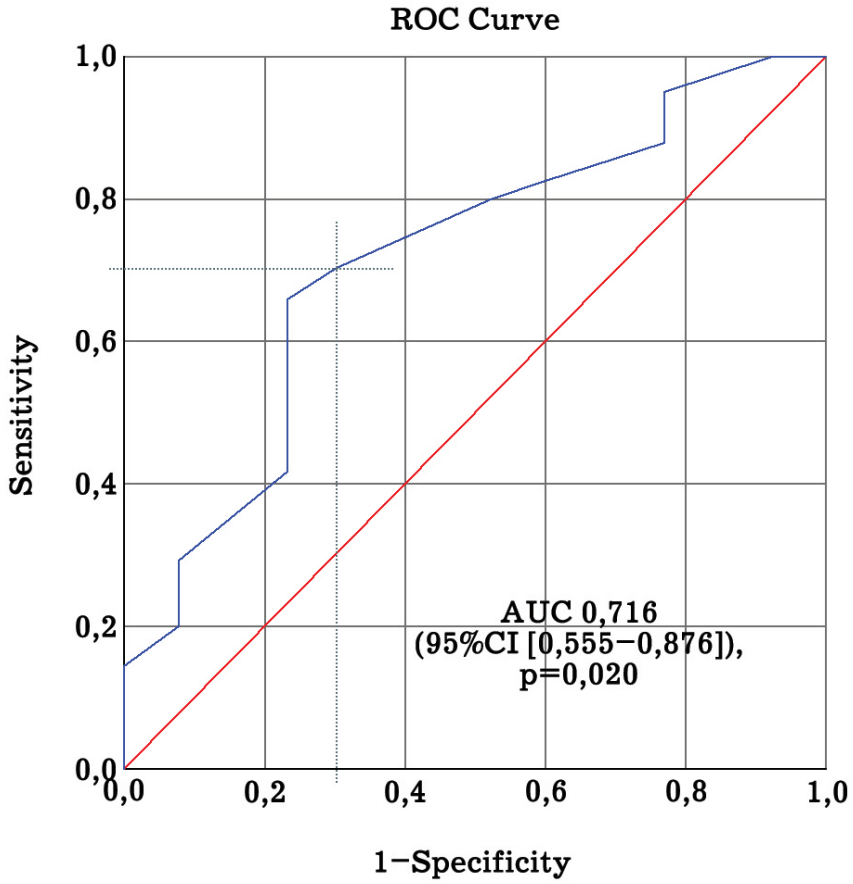

Fig. 3. ROC curve of the threshold value of plasma cells in thrombi of ischemic stroke patients for differentiating cardioembolic and atherothrombotic stroke subtypes

Comparison of the histological composition of thrombi in patients with unspecified and atherothrombotic subtypes of stroke

As can be seen from Table 4, the number of men among patients with unspecified stroke subtype was statistically significantly lower than among individuals with atherothrombotic stroke (40% versus 77%, p=0.049).

Table 4. Clinical and demographic characteristics and surgical intervention parameters in patients with unspecified and atherothrombotic stroke subtypes

Parameter	Stroke		p
	Unspecified etiology (n=35)	Athero-thrombotic (n=13)	
Age, years, Me (Q_1;Q_3)	72 (58;81)	65 (58;72)	0.140
Gender (m), n (%)	14 (40)	10 (77)	0.049
CHA_2DS_2VASc, score, Me (Q_1;Q_3)	3 (2;4)	2 (2;5)	0.369
NIHSS on admission, score Me (Q_1;Q_3)	15 (7;19)	13 (11;22)	0.659
Thrombolytic therapy, n (%)	9 (26)	4 (31)	0.728
Time to reperfusion, min, Me (Q_1;Q_3)	240 (176;501)	205 (155;266)	0.146
Surgery duration, min, Me (Q_1;Q_3)	69 (39;99)	53 (39;71)	0.338
Thromboaspiration passages, n, Me (Q_1;Q_3)	2 (1;2)	2 (1;2)	0.669
mTICI, n (%): - 2b gr. - 3 gr.	 0 35 (100)	 3 (23) 10 (77)	0.098

No statistically significant differences were found for other clinical and interventional parameters. The composition of thrombotic masses was also comparable between the groups, with the exception of a higher

plasma cell count in patients with unspecified stroke than in patients with atherothrombotic stroke (Table 5).

Table 5. Comparison of histological characteristics of thrombi in patients with unspecified and atherothrombotic stroke subtypes

Parameter	Stroke		p
	Unspecified etiology (n=35)	Athero-thrombotic (n=13)	
Fibrin, %, Me (Q_1;Q_3)	45 (20;64)	40 (20;65)	0.802
Erythrocytes, %, Me (Q_1;Q_3)	48 (30;70)	50 (25;75)	0.782
Detritus, %, Me (Q_1;Q_3)	5 (5;10)	5 (5;10)	0.751
Thrombus type, n (%): - erythrocytic - fibrinous - mixed	 14 (40) 10 (29) 11 (31)	 5 (38) 4 (31) 4 (31)	0.915
Leukocytes, n (%): – 1–100 cells* – 101–200 cells* – >200 cells*	 9 (26) 16 (46) 10 (28)	 8 (61) 4 (31) 1 (8)	0.0 57
Neutrophils, number of cells*, Me (Q_1;Q_3)	91 (56;128)	60 (22;152)	0.317
Eosinophils, number of cells*, Me (Q_1;Q_3)	3 (1;7)	3 (1;9)	0.788
Macrophages, number of cells*, Me (Q_1;Q_3)	2 (0;4)	1 (0;1)	0.136
Lymphocytes, number of cells*, Me (Q_1;Q_3)	35 (17;60)	15 (6;55)	0.116
Plasma cells, number of cells*, Me (Q_1;Q_3)	10 (5;18)	6 (4;9)	0.035

*Notes: * high power increase (x80)*

In patients with cardioembolic and unspecified stroke subtypes, plasma cell counts were comparable (p=0.715), as were other thrombus characteristics.

Taking into account the differences established during the analysis, a comparison of the number of plasma cells in the thrombus was made in patients with stroke (n = 90) depending on the median age and gender, which did not reveal statistically significant differences: age under 75 years *versus* age equal and over 75 years was 9 (6;12) versus 9 (5;12) patients, respectively (p=0.983); men *versus* women were 9 (6;12) versus 9 (5;13), respectively (p=0.756).

Correlation analysis revealed no relationship between thrombolytic therapy and thrombus components. A correlation was established between the number of plasma cells in thrombi and the number of thromboextraction passages (r=0.287; p=0.056), active cancer (r= –0.239, p=0.027), SBP (r=0.301, p=0.045), and DBP (r=0.339, p=0.023).

Discussion

Cardioembolic, atherothrombotic, and lacunar strokes are the most common subtypes of acute ischemic stroke [17]. Unlike lacunar stroke, which can be diagnosed at the bedside, the differentiation between cardioembolic and atherothrombotic strokes in patients based on clinical presentation and instrumental examination results is very difficult, as there is no “gold standard” to determine the cause in each case.

The implementation of endovascular thrombectomy techniques has increased the proportion of patients with a favorable outcome after major ischemic strokes caused by occlusion of a large cerebral artery, usually due to embolism. [4, 5]. The most common source of such occlusive thromboembolism is the internal carotid artery, left atrial appendage, or left ventricle. However, in a significant proportion of patients, despite a wide range of examinations, it is not possible to determine the pathogenetic subtype of the acute cerebral event, and it is regarded as unspecified or embolic stroke of unknown origin. This creates uncertainty

regarding the choice of optimal secondary prevention tactics, since an undifferentiated approach to treating patients with strokes of unknown etiology with indirect oral anticoagulants has not shown benefit in randomized clinical trials [18–20].

One of diagnostic approaches to solving this problem has been the histological examination of thrombotic emboli obtained as a result of thrombectomy [6–9]. Since experience in this area is limited, the optimal methodology for studying thromboembolic material still remains unknown [10, 21].

A number of studies have examined the relationship between the histological composition and origin of extracted thrombi [6–9]. Most studies focused primarily on the quantitative assessment of red blood cells and fibrin and showed conflicting results. While some studies showed that thrombi in patients with cardioembolic stroke had a higher number of red blood cells and a lower amount of fibrin compared to thrombi in patients with atherothrombotic stroke [9, 22, 23] , other studies reported opposite data [24, 25] or found no relationship at all [26, 27].

Data on leukocytes also remain conflicting. Various researchers have indicated a lack of association between leukocyte levels and stroke etiology [8, 9, 26, 27], while others emphasize higher leukocyte levels in patients with cardioembolic stroke [7, 8].

S. Duffy et al. showed that the composition of thrombotic masses extracted during the first two passages of thrombectomy contains significantly more erythrocytes and less fibrin compared to thrombi obtained in subsequent attempts, which indicated that erythrocyte-rich thrombi are easier to remove than fibrin-rich thrombi [26]. In another work, T. Boeckh-Behrens et al. demonstrated that a higher number of leukocytes in the thrombus is associated with a higher number of passages for thromboextraction [7]. We noted a tendency for the number

of plasma cells to increase with increasing passages of thromboextraction. (r=0.287; p=0.056).

In our work, in most cases, thromboaspiration was performed in two passes in most cases, restoring adequate perfusion in all patients with mTICI grades 2b – 3 in occluded cerebral arteries. Due to the lack of organization signs, all removed thrombi were considered fresh and contained more red blood cells than fibrin. However, these differences were statistically insignificant, as was the case with thrombus typing (erythrocyte/fibrin/mixed).

Thus, based on the content of erythrocytes, fibrin, detritus, leukocytes in thrombi, we were unable to identify a specific IS subtype, which, on the one hand, was consistent with the data reported by a number of authors [8, 9, 26, 27], and on the other hand, the absence of differences in the mentioned thrombus components may be determined by different methods of staining and quantitative assessment of the material, as well as the above-described features of the endovacular thromboextraction procedure.

Thrombolytic drugs can influence the histological composition of the thrombus through the blood coagulation system (BCS), however, our study did not reveal a relationship between thrombolytic therapy and the cellular components of thrombi.

Being the main target of antiplatelet therapy, platelets are actively involved in thrombus formation. Two studies found that thrombi in cardioembolic stroke contain a higher number of platelets compared to thrombi in atherothrombotic stroke [25, 28], while other authors wrote the opposite [29]. Various studies have not found a relationship between the etiology of stroke and the level of platelets in thrombi [9, 27].

A few studies have examined the relationship between the number of granulocytes, monocytes/macrophages, T- and B-lymphocytes in

thrombotic masses and the etiology of stroke, but the general conclusions currently remain fragmentary and preliminary [8, 27, 30, 31]. For example, in the study by P. B. Sporns et al., where the clusters of differentiation co-receptors CD3, CD20 and CD68/KiM1P were analyzed using immunohistochemical methods, no statistically significant differences were found in the content of T- and B-lymphocytes in thrombotic masses between those in patients with cardioembolic store (n=77) and non-cardioembolic (n=46) ones; however, there were more macrophages (CD68/KiM1P) in thrombi in the former (3.0 (0.5;18.0) versus 1.0 (0.5;5.0), respectively, p=0.061) [8]. In another study, the percentage of macrophages in thrombi was statistically significantly higher in individuals with cardioembolic stroke (0.9% (0.1–3.3%)) than in those with atherothrombotic (0.3% (0.1–3.8%), p=0.021) or unspecified (0.4% (0.0–5.2%), p=0.037) stroke subtypes [32].

The relationship between circulating blood plasma cells, inflammation, and the immune system is well known [33]. Monocytes are an important source of tissue factor, which initiates the extrinsic circulating blood plasma cell pathway [34]. Their bidirectional interaction with platelets and endothelium enhances fibrin formation during thrombosis [35]. During thrombus formation, platelets enhance lymphocyte adhesion [36, 37]. The correlations we found between the number of plasma cells in thrombi and SBP and DBP are possibly mediated through endothelial function and increased shear stress.

The results of our study have confirmed that histological assessment can be successfully used to differentiate cardioembolic and atherothrombotic pathogenesis of thrombus formation in patients with ischemic stroke. We demonstrated for the first time that the plasma cell content in the extracted thrombi is statistically significantly higher in patients with cardioembolic than atherothrombotic stroke. The performed

ROC analysis established the optimal threshold number of plasma cells in the extracted thrombus, being at least 7, which determined the etiological affiliation of patients with the cardioembolic subtype of ischemic stroke with a sensitivity of 70.7% and a specificity of 30.8%. The area under the ROC curve of 0.716 (95% CI [0.533–0.867], p=0.020) indicated the diagnostic significance of the model.

The median plasma cell content in thrombotic masses was statistically significantly higher in individuals with unspecified stroke subtype than in patients with atherothrombotic stroke (p=0.035) and the same in comparison with patients with cardioembolic stroke (p=0.715). One of the possible causes of an unspecified source of thromboembolism in ischemic stroke may be active malignant tumors [38], which were observed in 12 patients (14%) in our study. In this regard, it is interesting that patients with active cancer are characterized by a lower number of plasma cells in the thrombus, as indicated by the inverse correlation "cancer-to-plasma cells" (r=-0.239, p=0.027). Transthoracic, and in case of suspicion, transesophageal echocardiography did not reveal a patent foramen ovale in any patient.

All of the above allows us to say that the source of thromboembolism in the cerebral artery in patients with unspecified etiology of stroke in most cases is probably the left chambers of the heart, rather than atherosclerotic plaques of the carotid arteries, which is consistent with the results of studies with hematoxylin and eosin staining of thrombi [7, 8]. Our conclusion coincides with the findings of other authors that the frequency of AF detection in patients with unspecified etiology of stroke increases significantly with a combination of prolonged ECG registration methods [39].

The limitations of the study include: first, the relatively small number of patients in the atherothrombotic ischemic stroke group;

second, we did not perform immunohistochemistry, which would ensure a more precise cell typing. Therefore, the question remains as to whether the cells we detected in the thrombi by microscopy are plasma cells or plasmacytoid lymphocytes. However, this does not reduce the diagnostic value of the finding. Third, the use of intravenous thrombolytic agents could have altered the samples. Fragmented material during extraction may not always correspond to the intact thrombus structure. The formation of some thrombi during intra-arterial catheter manipulations also cannot be ruled out; however, thromboembolic complications during cerebral angiography are rare, occurring in 1–2% of cases. A strength of our study is the analysis based on complete diagnostic information on patients, including the cellular composition of the thrombi.

Conclusions

1. Fresh thrombi removed by endovascular thromboextraction in different subtypes of acute ischemic stroke have similar histological characteristics, with the exception of the plasma cell content, which was statistically significantly higher in patients with cardioembolic stroke than atherothrombotic stroke (10 (6;13) versus 6 (4;9) cells, respectively, p=0.020).

2. The resulting model with a plasma cell threshold of at least 7 cells and an area under the ROC curve of 0.716 (95% CI [0.555–0.876], p=0.020) allows differentiation between cardioembolic and atherothrombotic strokes with a sensitivity of 70.7% and a specificity of 30.8%.

3. A statistically significant difference in the median number of plasma cells in aspirated thrombi between the stroke of unspecified etiology and atherothrombotic stroke (10 (5;18) versus 6 (4;9) cells, respectively, p=0.035) indicates the cardioembolic origin of most strokes of unspecified etiology.

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