Research Article
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Oncologic Diseases as a Risk Factor for Cryptogenic Stroke

G.R. Ramazanov[1], E.A. Kovaleva[1] ✉, N.A. Shamalov[2]

Educational Department
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department
3 Bolshaya Sukharevskaya Square, Moscow 129090, Russian Federation
[2] Federal Center of Brain and Neurotechnologies FMBA of Russia
1, bld. 10 Ostrovityanova St., Moscow 117513, Russian Federation

✉ **Contacts:** Ella A. Kovaleva, Candidate of Medical Sciences, Senior Lecturer of the Educational Department, Neurologist of the Neurological Department for Patients With Acute Cerebrovascular Accidents and Resuscitation and Intensive Care Unit of N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: kovalevaea@sklif.mos.ru

BACKGROUND Acute cerebrovascular accidents in general, and ischemic stroke (IS) in particular, are multifactorial diseases with extremely heterogeneous and numerous risk factors. Currently, despite the development of diagnostic technologies, in approximately 25% of patients with IS, it is not possible to establish the causes and mechanism of its development (the so-called cryptogenic stroke (CS)). As a result, the optimal antithrombotic therapy as a secondary prevention in this group of patients remains unclear. It was found that in 10–20% of patients with CS, a detailed examination reveals oncological disease (OD). It is highly likely that the prevalence of OD-related IS will increase. The US National Cancer Registry has shown a decrease in mortality in patients with the most common forms of OD (lung, breast and prostate cancer). Active OD is a proven risk factor for both IS and other thrombotic events. Nevertheless, about 50% of IS in patients with OD are classified as cryptogenic, which significantly exceeds this indicator in patients without OD. This is associated with the difficulties of intravital diagnosis of the pathogenetic mechanism of IS in patients with OD.

AIM OF STUDY Raising the awareness of neurologists about the causes, pathogenetic mechanisms of development and methods of diagnosing IS in patients with OD.

MATERIAL AND METHODS To achieve this goal, the results of scientific research on OD as a risk factor for CS were analyzed. The literature search was carried out in electronic search engines Scopus, eLibrary, PubMed by keywords: ischemic stroke, cryptogenic stroke, cancer, pathogenesis of ischemic stroke. Scientific articles published between 1856 and 2021 were selected for analysis, 45% of the analyzed papers on the topic of CS were published not earlier than 5 years ago.

CONCLUSION The cause of the development of ischemic stroke can be both the oncological process itself and the means and methods of treating it. Despite the fact that in 10–20% of patients with cryptogenic stroke OD is diagnosed, the question remains whether patients with cryptogenic ischemic stroke should be screened for latent oncological pathology, and if so, how full should the screening be. Typical radiological patterns of ischemic stroke in patients with OD are multiple foci of acute cerebral ischemia in different vascular areas, which may indicate a cardioembolic nature and, in particular, non-bacterial thrombotic endocarditis. Lifetime diagnosis of the causes of cryptogenic stroke in patients with OD is extremely difficult. Since nonbacterial thrombotic endocarditis is one of the leading causes of cryptogenic stroke in the setting of cancer, it is advisable to perform transesophageal echocardiography due to the low sensitivity of transthoracic echocardiography.

Keywords: ischemic stroke, cryptogenic stroke, oncologic disease, pathogenesis of ischemic stroke
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Affiliations

Ganipa R. Ramazanov	Candidate of Medical Sciences, Head of the Scientific Department of Emergency Neurology and Rehabilitation Treatment, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-6824-4114, ramazanovgr@sklif.mos.ru; 45%, search and analysis of literature data, generalization of results, writing a working version of a manuscript, formatting text material
Ella A. Kovaleva	Candidate of Medical Sciences, Senior Lecturer of the Educational Department, Neurologist of the Neurological Department for Patients With Acute Cerebrovascular Accidents, N.V. Sklifosovsky Research Institute for Emergency Medicine ; https://orcid.org/0000-0002-8490-1417, kovalevaea@sklif.mos.ru; 30%, search and analysis of literature data, writing a working version of a manuscript
Nikolay A. Shamalov	Dr. Med. Sci., Director of the Institute of Cerebrovascular Disorders and Stroke, Federal Center for Brain and Neurotechnology, Chief Freelance Neurologist of the Moscow Department of Health; https://orcid.org/0000-0001-6250-0762, shamalovn@gmail.com; 25%, generalization of results, editing of a manuscript

ASA - acetylsalicylic acid
IS - ischemic stroke
MI - myocardial infarction
CS - cryptogenic stroke
NBTE - nonbacterial thrombotic endocarditis
OD - oncological disease
ACVA - acute cerebrovascular accident
PFO - Patent Foramen Ovale
DVT - deep vein thrombosis
EchoCG - echocardiography
ESUS - Embolic Stroke of Undetermined Source: criteria for the diagnosis of cryptogenic stroke
TOAST - classification of pathogenetic subtypes of ischemic stroke

Acute cerebrovascular accidents (ACVA) in general and ischemic stroke (IS) in particular are multifactorial diseases with extremely heterogeneous and numerous risk factors. Currently, despite the development of diagnostic technologies, it is not possible to establish the causes and mechanism of IS development in approximately 25% of patients (the so-called cryptogenic stroke (CS)); and the optimal antithrombotic therapy as a secondary prevention in this group of patients remains unclear [1]. Since the concept of "cryptogenic stroke" is very general, in 2014 the so-called ESUS criteria (Embolic Stroke of Undetermined Source) were proposed [1]. Despite the fact that in most patients with CS who meet the ESUS criteria, the examination reveals cardioembolic factors of average risk according to the TOAST classification [1], this cohort of patients is far from homogeneous, and therefore unified approaches to antithrombotic therapy are hardly applicable. This is further confirmed by the results of two trials (NAVIGATE ESUS and RESPECT ESUS), the purpose of which was to study the safety and efficacy of oral anticoagulants (rivaroxaban and dabigatran) in comparison with acetylsalicylic acid (ASA) in patients meeting the ESUS criteria [3, 4]. The results of the trials showed that the rates of bleeding complications in the groups of patients treated with rivaroxaban and dabigatran are higher compared with ASA, and the efficacy in preventing recurrent IS and / or systemic embolism does not exceed those of ASA [3, 4]. Patients are currently being enrolled in the ARCADIA and ATTICUS trials to investigate the benefits of apixaban over ASA in patients with CS [5, 6].

In many respects, the course, functional and clinical outcomes of IS, and most importantly, secondary prevention of recurrent ACVA are due to the pathogenetic variant of the developed CS. Along with such causes of CS as patent foramen ovale (PFO), non-atherosclerotic vasculopathy and non-stenotic atherosclerosis, it is important to study the relationship between oncological diseases (OD) and the development of IS.

It was found that in 10–20% of patients with CS, a detailed examination reveals OD [7, 8]. Thromboembolic complications, including IS, are diagnosed in 7% of patients with OD in vivo and in 15% according to autopsy data [9]. In patients with an active oncological process, CS is much more often diagnosed compared with patients without it (47% versus 12%) [10]. According to P.C. Chen et al. (2011), the incidence of stroke in patients with cancer is 1.5 times higher than in the general population [11]. The incidence of repeated stroke in patients with CS on the background of OD ranges from 14 to 29%, which is 3 times higher than in CS patients without oncological process [12].

OD-related IS is highly likely to increase. The US National Program of Cancer Registries has shown a decrease in mortality in patients with the most common forms of OD (lung, breast and prostate cancer) [13]. Thus, the 2-year survival rate in men with non-small cell lung cancer increased from 26% in 2001 to 35% in 2014, which may be associated with the use of targeted approaches and immunotherapy in this cohort of patients, as well as decreased number of smokers [14].

Active OD is a proven risk factor for both IS and other thrombotic events [15, 16]. Nevertheless, about 50% of IS in patients with OD are classified as cryptogenic, which significantly exceeds that parameter in patients without cancer [17, 18]. This is due to the difficulties of intravital diagnosis of the pathogenetic mechanism of IS in patients with OD. The risk of stroke is highest during the first 6 months from the date of OD diagnosis, as well as in patients with distant metastases. It was also found that the risk of developing IS depends on the type of OD, and it is highest in patients with lung and pancreatic cancer, the risk of venous thromboembolic complications for those patients is maximal [17].

It should be noted that CS may be the first manifestation of cancer [19-21]. Thus, in their study B.B. Navi et al. (2019) found that the risk of developing IS exceeded 59% 12 months before the OD diagnosis [22]. It was also shown that the risk of arterial thromboembolic events in patients over 67 years of age begins to increase 150 days before the date of OD diagnosis verification and reaches its peak 30 days before that [22]. Studies have shown that 2-10% of patients with CS are diagnosed with OD within the next 12 months [23–25]. CS is associated with a decrease in survival of patients with active OD regardless of age and the presence of distant metastases [26]. Thus, the median survival in patients with CS and OD was 55 days versus 147 days in cancer patients with an established pathogenetic variant of IS [26].

Currently, several pathogenetic mechanisms of IS development in patients with oncological pathology have been identified [27]. These include direct cerebral embolism by tumor cells (solid tumors of the heart or lungs, as well as intravascular lymphoma), nonbacterial thrombotic endocarditis (NBTE), disseminated intravascular coagulation (thrombosis *in situ*), acceleration of atherosclerosis during chemotherapy, as well as coagulopathy which can be directly related to OD or a complication of OD treatment [27]. Paradoxical embolism should also be considered as one of the risk factors for IS in patients with oncological pathology, since one out of four patients with a malignant neoplasm has a PFO, and 1 out of 5 patients has deep vein thrombosis (DVT) of the lower limbs [28–30]. One of the causes of stroke in patients with OD is anthracycline-induced cardiac dysfunction which develops against the background of neoadjuvant chemotherapy of malignant neoplasms [31]. These pathogenetic mechanisms are difficult to diagnose in vivo, which, as a result, leads to an increase in the number of patients with CS [9]. This is confirmed by the statistical data on the prevalence of CS in patients with oncological pathology - 40-50% of patients with OD and IS are diagnosed with CS, which on average is 2.5 times higher than that in IS patients without OD [17, 32–34].

Possible mechanisms of CS in patients with OD can be divided into two groups - associated and not associated with hypercoagulability [12]. The first group includes cerebral intravascular coagulation, NBTE, and paradoxical embolism. CS mechanisms not related to hypercoagulability in patients with OD include atheroma of the aortic arch, non-stenotic atherosclerosis, atrial cardiopathy, anthracycline cardiomyopathy, vasculitis, as well as tumor embolism (solid tumors of the heart or lungs, as well as intravascular lymphoma) [12].

One of the dominant theories of thrombosis is Virchow's triad which can be best demonstrated by the example of patients with OD [35]. In patients with OD, there is a slowdown in the flow of blood (stasis) due to increased plasma viscosity and / or limitation of the patient's mobility [36, 37]. Hypercoagulation also takes place, which is manifested by increased activation and aggregation of platelets, increased concentration of P-selectin and beta-thromboglobulin, cancer procoagulant, fibrinogen and plasminogen activator inhibitor-1, von Willebrand factor, tissue factor and simultaneous reduction of tissue plasminogen activator. Endothelial damage or dysfunction in the form of higher levels of soluble E-selectin, soluble thrombomodulin, as well as angiogenesis in the form of altered release of growth factors and response to them are observed [38].

OD-related hypercoagulability syndrome is mediated by a number of factors. The concentration of blood coagulation factors, including thromboplastin, increases with OD. This is confirmed by the fact that in more than 10% of patients with OD venous thromboembolic events as well as elevated D-dimer levels, a nonspecific marker of hypercoagulation, are verified [33, 39]. Thus, in the study by C.J. Schwarzbach et al. (2012), the concentration of D-dimer in blood plasma was significantly higher in OD patients with CS than in OD patients with IS in the setting of traditional risk factors (8.39 μg / mL versus 3.91 μg / mL, $p < 0,05$). It was also found that in patients with IS and metastatic OD, the concentration of D-dimers in the blood is higher than in patients with IS and oncological process without metastatic lesions (8.1 μg / mL versus 2.8 μg / mL, $p < 0.01$). The incidence of venous thrombotic complications (DVT and pulmonary embolism) was significantly higher in patients with cryptogenic IS and OD than in patients with OD and IS against the background of traditional risk factors (15% versus 1%, $p < 0.01$) [33].

Another factor leading to hypercoagulability is an increase in the number of extracellular vesicles produced by cancer cells. OASIS-CANCER study revealed that in OD patients with CS, the concentration of extracellular vesicles is significantly higher than in OD patients with stroke against the background of traditional risk factors - with OD or with IS alone. The concentration of extracellular vesicles in the blood correlated with the concentration of D-dimers [40]. It was found that in patients with lung cancer the concentration of extracellular vesicles circulating in the blood, as well as manifestations of coagulopathy are most pronounced in adenocarcinoma [41]. Also, in patients with OD there is an increase in the formation of neutrophil extracellular traps which are part of the innate immune response contributing to the activation of

platelets and blood coagulation factors [42]. It was shown that in OD patients with IS, the concentration of neutrophil extracellular traps as well as the associated activities of the thrombin-antithrombin and P-selectin complex, which in turn are markers of platelet activity, are increased [42]. Another confirmation of an increase in platelet aggregation activity in OD patients with IS is the results of histopathological examination of the composition of intracranial thrombi extracted by endovascular retrieval [43]. It was shown that in patients with IS and OD, thrombocytes prevailed in the thrombus, and erythrocytes constitute a smaller part (platelets - 43.2%, erythrocytes - 3.4%), while in patients with IS without OD erythrocytes predominated in the thrombus composition (platelets - 14.1%, erythrocytes - 40.7%) [43]. Another feature of OD is endothelial damage and increased platelet adhesion. This is confirmed by a decrease in endothelial thrombomodulin with a simultaneous increase in the concentration of soluble thrombomodulin [38]. With OD, the concentration of von Willebrand factor increases, which leads to increased platelet adhesion to endothelial cells [38]. The MOST-CANCER study found an increase in the concentration of three markers of endothelial dysfunction in patients with IS associated with OD (thrombomodulin, intercellular adhesion molecule 1, endothelial adhesion molecule-1) [29]. Cancer-mediated hypercoagulation may be associated with the expression of fibrinolysis inhibitors and inflammatory cytokines by tumor cells, as well as with the activation of the internal blood coagulation pathway [44].

Further evidence that IS in patients with OD is a special form of stroke are the results of the study by B.B. Navi et al. (2019), where more than 400 differences in gene expression were found in patients with OD and IS, in contrast to patients with IS alone [45]. A specific feature of IS patients on the background of OD was the activation of genes that regulate autophagy signaling, immune response and inflammation, base excision repair, phagosome formation, and signaling of the triggering receptor expressed on myeloid cells [45].

Multiple foci of acute cerebral ischemia located in different vascular regions of the brain are a characteristic radiological pattern that allows one to suspect OD in a patient with CS. Thus, in a study by Gon Yasufumi et al. (2016), such changes were significantly more often detected in patients with IS on the background of OD compared with IS patients without OD (71% versus 16%, $p < 0.001$) [10]. It was also shown that in OD patients with CS, compared with OD patients with an established cause of stroke, multiple foci of acute cerebral ischemia located in different vascular basins are significantly more often detected (71% versus 40%, $p < 0.001$, respectively), despite the fact that patients with CS were younger, and their body mass index, concentration of platelets, hemoglobin and lymphocytes in the peripheral blood were lower [10].

The development of IS can be associated not only with the presence of OD, but also with the ongoing therapy for it. This is confirmed by the fact that the prevalence of chemotherapy and / or radiation therapy is higher in patients with CS than in patients with OD and IS with an established pathogenetic variant (40% versus 9%, $p < 0.001$) [10]. According to M. Volkova et al. (2012), the incidence of anthracycline cardiomyopathy after neoadjuvant chemotherapy varies from 1 to 5% [31]. Despite the fact that according to Gon Yasufumi et al. (2016) in patients with CS associated with OD, the severity of atherosclerosis and other traditional IS risk factors was significantly less than in patients with CS without oncopathology, it should be borne in mind that both OD itself and its treatment can accelerate the progression of atherosclerosis and the formation of intracardiac thrombi [10].

Despite the fact that upon admission to the hospital, the severity of neurological deficit in OD patients with IS does not significantly differ from that in patients with IS without an oncological process, the functional and clinical outcomes of the disease in OD patients with stroke are significantly worse; in addition, these patients are characterized by a longer average stay in the intensive care unit [39].

NBTE is characterized by the deposition of fibrin and platelets on the cusps of previously intact heart valves in the absence of infection in the systemic circulation. In a study by Y. Joonsang et al. (2020) the detection rate of NBTE in patients with IS associated with oncopathology was 8.2% [46]. However, in an autopsy study by F. Graus et al. (1985) the incidence of NBTE verification in patients with IS was 2 times higher and amounted to 16.4%, which indicates the difficulty of intravital diagnosis of this condition [9]. It is highly likely that the prevalence of NBTE in patients with IS and OD is even higher. This conclusion can be made based on the results of the study by J.M. Seok et al. (2010), in which, using transcranial Doppler sonography, bilateral microembolic signals were recorded in 57.9% of patients with IS on the background of OD [47]. In case of stroke development, mortality of patients with OD and NBTE can reach 80% [46]. Since transthoracic echocardiography (EchoCG), as a rule, does not allow verifying the diagnosis of NBTE, it is necessary to perform transesophageal EchoCG [48]. Since the first description of sterile vegetations on the

cardiac valve leaflets by R. Zeigler in 1888, NBTE has been described in patients with systemic lupus erythematosus, antiphospholipid syndrome and OD, which must be taken into account when identifying this pathology [49]. The detection of vegetations on the valve apparatus in patients with OD and IS does not in any way exclude the infectious nature of these changes, especially since the treatment of OD predisposes to their development. Moreover, patients with oncological pathology often receive immunosuppressive therapy and wear venous catheters, therefore, are at risk of developing infective endocarditis [50]. A.A. Milta et al. (2016) described a clinical case of a patient with non-small cell lung cancer who experienced complete regression of NBTE and developed IS on the background of targeted therapy with erlotinib and anticoagulant therapy with enoxaparin [51]. However, the optimal antithrombotic therapy for the prevention of recurrent cerebrovascular events in these patients is currently unclear.

Insulin resistance, diabetes mellitus, smoking, obesity, arterial hypertension, hypertriglyceridemia induce inflammation which is the unifying mechanism of cardiovascular diseases and cancer [52–57]. Moreover, radiation therapy, which is part of the OD treatment regimens, accelerates atherosclerosis of the coronary and brachiocephalic arteries, which can cause the development of IS [58]. In combination with pro-inflammatory effects, radiation therapy for several months can destabilize existing atherosclerotic plaques which may become a source of acute cerebral ischemia [59]. In addition to arteries, radiation therapy can injure myocardium and pericardium, and immunotherapy can cause myocarditis and vasculitis and thus lead to IS [60].

Considering the significant role of proinflammatory cytokines in the formation of the inflammatory response of the vascular wall and, as a consequence, cerebrovascular and cardiovascular events, targeted therapy is of particular interest [57] Thus, in the CANTOS study, monoclonal antibody targeted at interleukin-1 beta (canakinumab) was used to reduce the risk of fatal and non-fatal IS and myocardial infarction (MI) in patients after MI with high C-reactive protein levels [61]. It was found that the use of canakinumab at a dose of 150 mg every 3 months leads to a significant reduction in the risk of recurrent cardiovascular events, irrespective of cholesterol levels [61]. The results of this study may serve as a starting point for the search for new therapeutic strategies for the prevention of cerebrovascular and cardiovascular events in patients with IS associated with OD.

In addition to the fact that OD is an independent risk factor for IS, malignant neoplasms increase the risk of atrial fibrillation, which must be taken into account during the treatment of patients with IS on the background of OD [50]. At present, the question of the choice of optimal antithrombotic therapy as a secondary prophylaxis in OD patients with IS remains unclear. In a study by J.M. Seok et al. (2010) in patients with stroke on the background of OD, the use of anticoagulants was accompanied by D-dimer levels decrease [47]. The survival rate of patients with IS and OD in the OASIS-CANCER study was significantly better in the case of lower D-dimer values during anticoagulant therapy [62]. Currently, two studies have shown the safety and efficacy of factor Xa inhibitors (edoxaban and apixaban) in preventing venous thromboembolic events in patients with cancer [63, 64]. However, there are no similar studies involving cancer patients with IS. Since blood clots retrieved endovascularly from large cerebral arteries in patients with OD are 47% platelets, antiplatelet drugs can be effective in preventing recurrent cerebrovascular events in this group of patients [43]. At present, the ENCHASE study is ongoing, which purpose is to compare the efficacy and safety of oral administration of edoxaban with injectable enoxaparin in patients with CS on the background of oncopathology [65].

CONCLUSION

Thus, the cause of ischemic stroke development can be both the oncological process itself and the means and methods of its treatment. Despite the fact that 10–20% of patients with cryptogenic stroke are diagnosed with oncological diseases, the question remains open whether patients with cryptogenic ischemic stroke should undergo screening for latent oncological pathology and, if so, to what extent [7, 8]. For example, whole-body CT screening for "latent oncology" in patients with venous thromboembolic syndrome gave a result only in 4.5% of cases, which did not statistically significantly exceed the diagnostic value of a standard examination with an indicator of 3.2% ($p = 0.2$) [66]. Typical radiological patterns of ischemic stroke in patients with cancer are multiple foci of acute cerebral ischemia in different vascular basins, which may indicate a cardioembolic nature and, in particular, non-bacterial thrombotic endocarditis. Intravital diagnosis of the causes of cryptogenic stroke in patients with cancer is extremely difficult. Since nonbacterial

thrombotic endocarditis is one of the leading causes of cryptogenic stroke in the setting of cancer, it is advisable to perform transesophageal echocardiography due to the low sensitivity of transthoracic echocardiography. The above reasons create the prerequisites for an urgent need for research in the direction of finding optimal means of secondary prevention of ischemic stroke and other thrombotic events in patients with cancer.

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