MAYO CLINIC

CONCISE REVIEW

Ischemic Stroke in Patients With Malignancy

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CME Activity

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1. Describe the epidemiology of malignancy-related ischemic stroke.
2. Describe potential mechanisms of stroke in patients with cancer.
3. Discuss approach to diagnosis and management of ischemic stroke related to malignancy.

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Abstract

Approximately one-quarter to one-third of patients with ischemic stroke have an embolic stroke of undetermined source (ESUS). An estimated 5% to 10% of patients with ESUS have an active cancer diagnosis. Presence of cancer potentially increases the risk of acute ischemic stroke through various mechanisms such as cancer-related hypercoagulability, intracranial tumors leading to an arterial compression, or intracardiac tumors leading to cardioembolism. Certain cancer therapeutics can also contribute to risk of ischemic stroke. Multiple vascular lesions involving bilateral anterior and posterior circulations, high plasma D-dimer levels, and elevated inflammatory markers might suggest cancer-related ischemic stroke. Patients with ischemic stroke related to malignancy are also at higher risk of stroke recurrence, early neurologic deterioration, and mortality. Cancer screening in acute ischemic stroke patients can be considered when no other etiology for stroke can be established and clinical history such as tobacco use, unexplained constitutional symptoms such as fever or night sweats, or unexplained weight loss suggests an underlying malignancy. Selection of antithrombotics for secondary stroke prevention remains controversial as clinical trial data for use of antiplatelet therapy vs anticoagulation in ESUS and cancer patients is limited. Future clinical trials should specifically focus on patients with ischemic stroke related to malignancy are needed to guide appropriate therapeutic agent selection.

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Stroke is a leading cause of death and long-term disability in the United States. Seven hundred ninety-five thousand cases of stroke are reported annually, 87% of which are ischemic.[1] Hyperacute management of ischemic stroke involves thrombolytic administration and mechanical thrombectomy to restore cerebrovascular blood flow in a timely fashion.[2] After initial stabilization, accurate identification of ischemic stroke etiology allows initiation of appropriate secondary prevention measures such as aggressive vascular risk factor modification, administration of antiplatelet therapy or anticoagulation, and/or endovascular or surgical interventions.

Despite these measures, recurrent stroke is common, with 185,000 cases reported annually in individuals who previously experienced a cerebrovascular event.[1] This is in part due to difficulty in identifying stroke mechanism in a significant proportion of cases. An estimated 16% to 40% of patients with ischemic stroke do not have a clearly identified etiology with the event designated as an embolic stroke of undetermined source (ESUS).[3] Optimal management of patients with ESUS is unclear. Two large-scale clinical trials, RE-SPECT-ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) and NAVIGATE-ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source), showed no benefit from use of dabigatran or rivaroxaban compared with aspirin for preventing recurrent ischemic stroke in this patient population.[4,5]

An estimated 5% to 10% of patients with ESUS have an active cancer diagnosis.[6] Ischemic stroke can precede diagnosis of cancer with malignancy discovered during workup for stroke etiology.[7] In a review of American cancer registry data, ischemic stroke risk was increased 59% in the year before cancer diagnosis.[7] In a subgroup analysis of NAVIGATE-ESUS, across all age groups, 1.7% of patients with ESUS had a new cancer diagnosis after 11 months of follow-up.[8] Among US adults older than 65 years of age, overall cancer incidence was 2% per year in 2019.[9] Thus, ischemic stroke preceding diagnosis of systemic malignancy is likely to be frequently encountered in clinical practice.

Ischemic stroke can also occur following cancer diagnosis.[10] Among cancer patients, rate of fatal stroke has been reported as 21.64 per 100,000 person years, estimated at two times the risk in the general population.[10] Studies variably associate lung, colorectal, pancreatic, breast, and prostate cancer with particularly increased ischemic stroke risk.[6,11] In one study investigating patients with cancer who experienced a stroke, cumulative incidence was highest for lung cancer at 5.1%, followed by pancreatic cancer at 3.4%, and colorectal cancer at 3.3% for stroke within 3 months of cancer diagnosis.[12] With a predicted rate of 4950 new cancer cases diagnosed per day in the United States and improved cancer survival rates, concurrent diagnosis of ischemic stroke and cancer is likely to increase.[13] Management of these patients requires complex multidisciplinary input.

PATHOPHYSIOLOGY

Several mechanisms can contribute to development of ischemic stroke in patients with cancer (Figure 1). Cancer-related hypercoagulability leads to both venous thromboembolism and arterial embolic events.[6] An estimated 4% to 20% of cancer patients experience a venous thromboembolism during their illness.[14] In the setting of a right-to-left cardiac shunt, a deep venous thrombosis or pulmonary embolism can result in an embolic stroke.[15] Intracranial tumors such as primary central nervous system neoplasms or brain metastases can directly compress cerebral blood vessels resulting in large vessel ischemia such as middle cerebral artery stroke.[16] Intracardiac tumors such as atrial myxomas can cause cerebral embolism.[17] Infective endocarditis related to immunosuppression from cancer treatment or presence of a central line is another source of embolism.[16] Hematologic malignancies such as multiple myeloma can be

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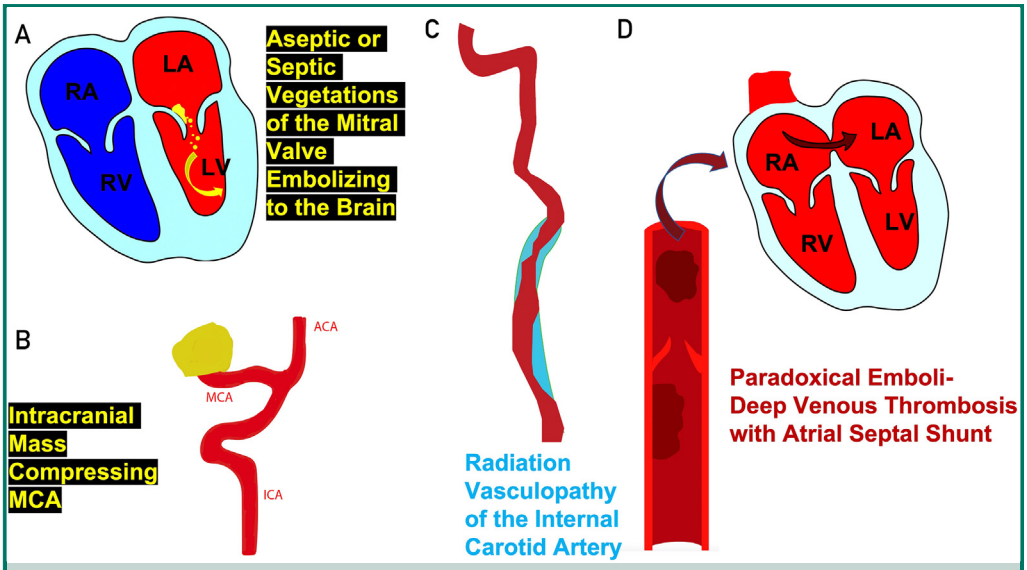

FIGURE. Ischemic stroke mechanisms in cancer. A, Septic or aseptic vegetations on the mitral valve embolizing to the brain through the aorta. B, Intracranial mass compressing over the middle cerebral artery (MCA) and causing an occlusion. C, Radiation vasculopathy causing multifocal stenoses of the internal carotid artery (ICA). D, Deep venous thrombosis causing paradoxical embolism in the setting of the atrial septal shunt.ACA = anterior cerebral artery; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

associated with small vessel stroke due to hyperviscosity syndrome.[11]

Cancer treatment can also contribute to risk of ischemic stroke.[10,11] Radiation therapy administered for head and neck tumors as well as intracranial tumors can result in large vessel vasculopathy, intracranial vessel stenosis, and development of cavernous malformations, contributing to both ischemic and hemorrhagic stroke risk.[18] Prior intracranial radiation therapy is also associated with a rare and typically reversible condition called Stroke-like Migraine Attacks after Radiation Therapy (SMART) syndrome.[19] SMART syndrome should be considered in the differential diagnosis for patients presenting with sudden-onset neurologic deficits in the setting of prior intracranial radiation therapy.

Antiangiogenic chemotherapeutic agents such as bevacizumab and thalidomide are associated with an increased risk of arterial ischemia.[20,21] Increased risk of stroke has also been suggested with antiestrogen agents such as selective estrogen receptor modulator tamoxifen.[22]

However, in many cases, the precise mechanism of ischemic stroke is unclear and the event is described as ESUS.[6,11,13] The pathophysiology of cancer-related ESUS is incompletely understood. Emerging data suggest patients with malignancy represent a distinct subgroup among individuals with ESUS.[6,23] In a multi-institution study, mRNA expression profiles from cancer patients who had ischemic stroke were compared with cancer-only and stroke-only controls.[23] Increased activation of inflammatory, transcription regulation, and hypoxia response pathways were noted among patients who had cancer-associated ischemic stroke.[23] This differential gene expression likely contributes to development of cancer-related hypercoagulability in general and ESUS in particular.[6] Hypercoagulability is mediated by multiple factors including inflammatory cytokines and fibrinolysis inhibitors released by tumor cells, increased platelet aggregation and coagulation factors, increased endothelial adhesiveness, and circulating tumor and platelet extracellular vesicles.[6]

How hypercoagulable pathways lead to development of ischemic stroke is less clear. One possible explanation is nonbacterial thrombotic endocarditis.[6] In an autopsy series, nonbacterial thrombotic endocarditis was identified as the most frequent mechanism of symptomatic stroke in cancer patients.[24] In another study, cerebral microemboli were frequently detected in cancer patients with ESUS undergoing transcranial Doppler ultrasound.[25]

Bihemispheric, anterior, and posterior circulation distribution of infarcts frequently identified among cancer patients with stroke of unclear etiology also supports possibility of a central source of embolism such as nonbacterial thrombotic endocarditis.[6]

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with ischemic stroke related to malignancy can present with sudden-onset focal neurologic deficit or diffuse encephalopathy.[6,11] Differential diagnosis in cancer patients with focal neurologic deficits or confusion includes intracerebral hemorrhage, parenchymal or leptomeningeal metastasis, seizure, and toxic metabolic encephalopathy. Initial evaluation should include a noncontrast computed tomography (CT) scan to rapidly assess for intracerebral hemorrhage. Magnetic resonance imaging with and without contrast is often required to confirm diagnosis of ischemic stroke and to assess for other etiologies such as brain metastasis.[6,11]

Other than history of tobacco use, patients with cancer-associated ischemic stroke may lack traditional stroke risk factors such as hypertension or hyperlipidemia.[6,26] Multiple vascular lesions involving bilateral anterior and posterior circulations, high plasma D-dimer levels, and elevated inflammatory markers are frequent findings in cancer patients with ischemic stroke.[6,26] Patients with ischemic stroke related to malignancy are also at higher risk of stroke recurrence, early neurologic deterioration, and mortality.[27]

Once diagnosis of ischemic stroke is made, workup should be undertaken to establish the mechanism. Computed tomography or magnetic resonance angiogram of the head and neck can assess for vessel stenosis and arterial dissection. Cardiac monitoring can identify atrial fibrillation or other potentially contributory arrythmia. Transthoracic echocardiogram can identify cardiac vegetations or presence of a cardiac mass or thrombus. However, nonbacterial thrombotic endocarditis may not be recognized with transthoracic echocardiography, requiring a transesophageal echocardiogram for detection of cardiac vegetations. Similarly, transcranial Doppler study should be considered for microemboli detection.[6] In patients with a right-to-left shunt, assessment for deep venous thrombosis should be undertaken to detect paradoxical embolism.[16]

In patients presenting with ESUS and no prior cancer diagnosis, the role of screening for malignancy is less certain.[6] Assessment can be considered in select cases where no other etiology for stroke can be established and clinical history such as tobacco use, unexplained constitutional symptoms such as fever or night sweats, or unexplained weight loss suggests an underlying malignancy.[6,16] Although there is no consensus regarding the amount of weight loss that should trigger concern for underlying malignancy, a cutoff of 5% loss over 6 to 12 months has been suggested.[28] Completion of routine cancer screening should be ensured and general exam including a breast or testicular exam should be considered.[16] However, routine use of whole-body CT imaging to assess for occult malignancy in the setting of cryptogenic stroke is not supported by current level of evidence. A similar approach to assess for underlying malignancy with a CT of the abdomen and pelvis following unexplained venous thromboembolism was not found to be beneficial.[29]

MANAGEMENT

Acute Management

All patients with acute ischemic stroke should be evaluated for thrombolytic therapy and thrombectomy, which can improve neurologic deficits and stroke-related patient outcomes. A known cancer diagnosis does

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not represent a contraindication to administration of thrombolytics in absence of a parenchymal mass lesion or intracerebral hemorrhage. However, patients with malignancy undergoing chemotherapy associated with hematologic toxicity should be assessed for thrombocytopenia before thrombolytic administration. If the platelet count is less than 100,000 per cubic millimeter, thrombolytic administration is contraindicated. All patients should be considered for care in a stroke unit staffed by nursing, allied health, and medical team members specialized in stroke care.

Stroke Prevention

After initial stabilization, all stroke patients should be evaluated for risk factor modification and secondary prevention efforts directed at addressing stroke mechanism such as use of anticoagulation for atrial fibrillation, consideration of patent foramen ovale closure in patients with ischemic stroke and venous thromboembolism, and carotid endarterectomy or stenting in patients with symptomatic carotid stenosis. Hypertension, hyperlipidemia, and hyperglycemia should be managed in all patients.

In patients with head and neck cancer treated with radiation therapy, extracranial carotid stenosis can develop. When degree of carotid stenosis is moderate to severe and causing ischemic events, similar to other carotid pathologies, carotid stenosis related to radiation vasculopathy can be managed with carotid revascularization including carotid angioplasty and stenting and less preferably carotid endarterectomy (due to long-term effects of radiation in the soft tissue in the neck).[30] Similarly, radiation therapy for primary brain tumors can lead to development of intracranial stenosis and associated stroke. Depending upon the degree of stenosis and symptomatic status of the vessel, single or dual antiplatelet therapy is typically used for management of radiation related intracranial stenosis, but large-scale prospective investigation is needed.[30]

All cancer patients with ischemic stroke should also be evaluated for antiplatelet therapy and anticoagulation. In two broad studies for patients with ESUS, there was no benefit from use of oral anticoagulants dabigatran or rivaroxaban compared with aspirin for recurrent stroke prevention.[4,5] However, these trials did not specifically study patients with known malignancy.[4,5]

Clinical trial data for use of antiplatelet therapy vs anticoagulation in cancer patients with ESUS is limited. In a pilot randomized trial, use of enoxaparin was compared with aspirin in patients with malignancy, but enrollment was limited due to injection aversion, and 60% of patients in the enoxaparin arm crossed over to aspirin due to injection discomfort.[31] In the OASIS-Cancer (Optimal Anticoagulation Strategy in Stroke Related to Cancer) study, D-dimer levels were evaluated in patients with stroke and active cancer.[32] Successful correction of hypercoagulability as measured by reduction in D-dimer was associated with improved 1-year survival, suggesting potential benefit from use of anticoagulation in this patient population.[32] On the other hand, in a retrospective analysis of cancer patients with stroke, no difference in risk of recurrent stroke was noted between use of antiplatelet therapy and anticoagulation.[27] Selection should be individualized and take into consideration factors such as comorbidities and bleeding risk. Treatment of malignancy following stroke also requires multidisciplinary input with balancing of rehabilitation efforts and cancer therapeutics.[16]

SUMMARY AND FUTURE DIRECTIONS

Ischemic stroke represents a common complication of cancer with variable mechanisms. Cancer-related stroke is associated with high risk of neurologic deterioration and mortality as well as a high rate of recurrence. Although factors such as direct vascular compression from intraparenchymal mass lesions, vasculopathy related to radiation therapy, and administration of antiangiogenic chemotherapeutics contribute to stroke risk, the majority of cancer-related stroke cases are cryptogenic and descried as ESUS. Nonbacterial thromboembolic endocarditis can be identified with transesophageal echocardiography in cancer patients, representing a possible source of embolism. Routine use of

screening for malignancy in patients with ESUS requires further validation.

Acute management of malignancy-associated stroke is similar to the general population with thrombolytic administration and thrombectomy considered in all cases. Secondary prevention of ESUS related to malignancy is complex with limited clinical trial evidence to guide antiplatelet therapy and anticoagulation selection. Rather than broadly studying patients with ESUS, future studies focused on patients with ischemic stroke related to malignancy are needed to guide appropriate therapeutic agent selection.

POTENTIAL COMPETING INTERESTS

Dr Sener has received funding through Yale - Mayo Clinic U19 grant for his research in glioma involving PARP inhibitors and proton radiation, unrelated to this submission.

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