Cancer-Associated Arterial Thrombosis: An Updated Investigation of Cancer-Associated Ischemic Stroke

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Abstract

The recognition of cancer-associated ischemic stroke is increasing, shedding light on the previously overlooked problem of cancer-associated ESUS and its impact on late-stage cancer diagnoses. There is growing acknowledgment of the hypercoagulable state in cancer patients with ischemic stroke, with the risk of stroke significantly rising in the year preceding a cancer diagnosis, reaching its peak just before diagnosis. Several cancer types, with lung cancer being the most prevalent, are linked to cancer-associated ischemic stroke. The complex pathophysiology of this condition involves malignancy-related intravascular hypercoagulability, characterized by non-bacterial thrombotic endocarditis (NBTE) and paradoxical embolization as key mechanisms. The diagnostic work-up for stroke patients with cancer should include a standard etiological assessment, supplemented by an occult cancer detection protocol that encompasses various blood tests (especially D-dimer), imaging techniques, and Thoraco-Abdominal-Pelvic Computed Tomography (CT). Ongoing research explores the potential addition of FDG PET/CT to conventional cancer screening. Furthermore, a recent study investigating cancer-associated strokes introduced a machine learning-based prediction model utilizing immunohistochemically stained thrombi obtained during thrombectomy.

Keywords: Cancer-associated thrombosis, Cancer-associated ischemic stroke, Embolic stroke of undetermined source, D-dimer, FDG PET/CT (J Thai Stroke Soc. 2024;23(2): 23-29)

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โรคหลอดเลือดสมองตีบหรืออุดตันที่สัมพันธ์กับโรคมะเร็ง: แนวทางการตรวจวินิจฉัยเพิ่มเติมเพื่อการวินิจฉัยโรค

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**แพทย์ประจำบ้านต่อยอด อนุสาขาประสาทวิทยา โรคหลอดเลือดสมองและการตรวจหลอดเลือดสมองด้วยคลื่นเสียงความถี่สูง ศูนย์ความเป็นเลิศทางการแพทย์ด้านโรคหลอดเลือดสมองแบบครบวงจร สาขาประสาทวิทยา รพ.จุฬาลงกรณ์ สภากาชาดไทย กรุงเทพมหานคร 10330 ประเทศไทย*

บทคัดย่อ

ปัจจุบันพบผู้ป่วยโรคสมองขาดเลือดที่ตรวจไม่พบสาเหตุถึงแม้ว่าจะได้รับการตรวจวินิจฉัยอย่างครบถ้วนแล้ว (cryptogenic stroke) ประมาณร้อยละ 25 ของผู้ป่วยโรคสมองขาดเลือดทั้งหมด โดยพบเป็นสาเหตุจากโรคมะเร็งประมาณร้อยละ 5–10 ด้วยความรู้ที่ก้าวหน้าขึ้นในปัจจุบันทำให้โรคหลอดเลือดสมองตีบหรืออุดตันที่สัมพันธ์กับโรคมะเร็งได้รับการวินิจฉัยมากขึ้น จากเดิมซึ่งมักจะได้รับการวินิจฉัยว่าเป็นโรคหลอดเลือดสมองตีบหรืออุดตันประเภทไม่ทราบสาเหตุ การวินิจฉัยที่คลาดเคลื่อนดังกล่าว ส่งผลเสียให้ผู้ป่วยไม่ได้รับการรักษาที่ถูกต้อง และการวินิจฉัยต้นเหตุของโรค กล่าวคือ การสืบค้นโรคมะเร็งนั้นล่าช้าออกไป การเข้าใจถึงกลไกการเกิดโรคและแนวทางการสืบค้นเพื่อให้ได้มาซึ่งการวินิจฉัยโรคจึงมีความสำคัญ อันจะนำไปสู่การรักษาและการป้องกันการเกิดโรคซ้ำในระยะยาว การตรวจหาสาเหตุ ได้แก่ การตรวจเคมีในเลือด D-dimer, fibrinogen, hs-CRP ได้เข้ามามีบทบาทในการบ่งชี้สาเหตุของโรคหลอดเลือดสมองตีบหรืออุดตันที่สัมพันธ์กับโรคมะเร็ง โดยเฉพาะในผู้ป่วยที่สาเหตุของการเกิดโรคหลอดเลือดสมองขาดเลือดยังไม่ชัดเจน การตรวจภาพถ่ายทางรังสีสมองด้วยคลื่นแม่เหล็กไฟฟ้าซึ่งมีลักษณะหลายรอยโรคในหลายขอบเขตของหลอดเลือดแดง (multiple lesions within multiple arterial territories) ช่วยให้พิจารณาถึงสาเหตุจากโรคมะเร็งมากขึ้น รวมไปถึงการสืบค้นหามะเร็งต้นเหตุของโรคหลอดเลือดสมองตีบหรืออุดตันด้วยการตรวจเพทซีที เพื่อตรวจดูการทำงานของอวัยวะภายในร่างกายในระดับโมเลกุล (FDG PET/CT) และการใช้เทคโนโลยีสมัยใหม่ การเรียนรู้ของเครื่อง เพื่อใช้ในการจำแนกกลุ่มผู้ป่วยระหว่าง ผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันที่สัมพันธ์กับโรคมะเร็งและผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันที่ไม่สัมพันธ์กับโรคมะเร็งซึ่งอยู่ในระหว่างการพัฒนานั้นย่อมนำไปสู่การวินิจฉัยโรคและการรักษาป้องกันที่ถูกต้องตามมา บทความนี้จะช่วยให้เกิดแนวทางการสืบค้นโรคที่นำไปสู่การวินิจฉัยโรคได้ดียิ่งขึ้น

คำสำคัญ: โรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลันที่สัมพันธ์กับโรคมะเร็ง, โรคหลอดเลือดสมองอุดตันจากลิ่มเลือดที่ไม่ทราบสาเหตุ, ภาวะการแข็งตัวของเลือดผิดปกติ, ค่า D-dimer, การตรวจเพทซีทีด้วยสารเภสัชรังสี (J Thai Stroke Soc. 2024;23(2): 23–29)

Introduction

The hypercoagulable state of cancer patients increases the risk for stroke, and the association between stroke and occult malignancy, particularly among older adults, is becoming more widely recognized. The risk of experiencing an ischemic stroke exhibits an approximate 60% increase in the year preceding a cancer diagnosis, reaching its peak in the month just prior to the diagnosis. Moreover, among patients diagnosed with Embolic Stroke of Undetermined Source (ESUS), it is noteworthy that 2-10% receive a cancer diagnosis within the year following the stroke event[1, 2].

Multiple forms of cancer have been reported to be associated with cancer-associated ischemic stroke, which includes lung, gastric, colorectal, gynecological, hepatic, renal, and prostate cancers, as well as lymphoma. Among these, lung cancer emerges as the most frequently linked to cancer-associated ischemic stroke[3, 4, 5]. Enhancing awareness of this issue and fostering a proactive approach to investigating cancer-associated strokes could prove advantageous for preventing recurrent strokes and ultimately improving cancer outcomes.

Pathophysiology of Cancer-associated arterial thrombosis; ischemic stroke

The pathophysiology of cancer-associated ischemic stroke is complex and involves various factors[6]. The primary mechanism is believed to originate from ***intravascular hypercoagulability associated with malignancy.*** Active cancer and chemotherapy can intensify thrombin generation, leading to strokes associated with coagulopathy. Additionally, elevated levels of circulating cytokines in cancer patients, such as tumor necrosis factor and interleukin-1, can cause damage to vascular endothelial cells and heart valves, contributing to the development of ***non-bacterial thrombotic endocarditis (NBTE)-related vegetations.*** Graus et al., in a comprehensive autopsy study conducted at the Memorial Sloan Kettering Center, identified NBTE-related vegetation as a prominent mechanism of cancer-associated ischemic stroke[7, 8]. Another hypercoagulability-related mechanism that can result in embolic strokes in cancer patients is ***paradoxical embolization.*** Approximately 20% of cancer patients experience venous thromboembolism during their lifetime, and around 25% of the population has a patent foramen ovale (PFO).

Other non-hypercoagulability mechanisms that can lead to Embolic Stroke of Undetermined Source (ESUS) in cancer patients include:

- Aortic atheroma and non stenosing large artery atherosclerosis due to vascular risk factors or prior thoracic/head/neck radiation.
- Atrial disease stemming from atriopathy.
- Cardiomyopathy, particularly in patients who have undergone chemotherapy with anthracyclines and trastuzumab or thoracic radiation.
- Infective endocarditis associated with indwelling venous catheters, sepsis, or recent invasive procedures.
- Tumor embolism originating from centrally located lung tumors, thoracic surgery, or subsequent metastasis at the site of the stroke.
- Vasculitis triggered by post-immunotherapy treatment, fungal or varicella infection, or intravascular lymphoma.

Update in investigation in Cancer-associated ischemic stroke

a.) Patients with no known history of malignancy; diagnosed with Embolic Stroke of Undetermined Source (ESUS)

History clues

Historical factors that offer valuable support in the identification of cancer-associated ESUS include a patient's smoking history, unexplained and substantial weight loss, and a history of venous thromboembolism.

Imaging clues

The number of territories involved in cerebral imaging also provides a valid indicator for predicting hidden systemic malignancies in patients with cryptogenic stroke. The presence of the "three-territory sign" is proposed as a specific imaging marker for cancer -associated ischemic stroke. The "three-territory sign" is described as the presence of cerebral infarctions occurring in three distinct cerebral vascular territories, encompassing both anterior and posterior circulation. While this pattern is the most compelling magnetic resonance imaging (MRI) feature of cancer-associated ischemic infarctions, characteristic radiographic diffusion -weighted imaging (DWI) findings for cancer-associated infarctions are frequently observed. These findings typically involve non-enhancing, non-ring clusters, or singular areas with restricted diffusion, measuring between 0.5-2 cm in size, often displaying a peripheral distribution or involving large vascular territories, albeit less commonly in a watershed distribution. Additionally, there is typically an absence of diffuse cortical ribbon or deep gray matter involvement.

The suggested investigative protocol advocates for a proactive strategy in examining cancer -associated strokes, a supplementary component to standard stroke guidelines as following:

- ***Blood Tests:*** Elevated D-dimer (≥ 3 mg/L), fibrinogen level (>600 mg/dL), hs-CRP (>20 mg/L), WBC (>9,600/µl), and platelet count (>400,000/µl), along with decreased Hb level (<117 g/l for women, <134 g/l for men), provide supportive evidence for cancer-associated arterial thrombosis[9, 10, 11].

D-dimer, a degradation product of fibrin polymer, serves as a valuable diagnostic marker of hypercoagulability, which is frequently elevated in cases of cancer-associated strokes but not in strokes resulting from atrial fibrillation. The serum D-dimer level is significantly associated with mortality, prognostic outcomes, and the likelihood of recurring systemic thromboembolism among patients. However, it is essential to consider that numerous variables are associated with a positive D-dimer result.

In a comprehensive study conducted by Kabrhel et al., it was found that 44% of patients in the study cohort (1,903 out of 4,346 patients suspected of having pulmonary embolism regardless of cancer history) tested positive for D-dimers. Noteworthy predictors of D-dimer positivity included factors such as gender, advancing age, racial differences (with higher incidence in the black population compared to the white population), cocaine use, immobility due to general, limb, or neurologic conditions, hemoptysis, hemodialysis, the presence of active malignancy, rheumatoid arthritis, lupus, sickle cell disease, prior venous thromboembolism (without treatment), pregnancy and postpartum states, as well as a history of surgeries. The influence of these factors on the diagnostic utility of the D-dimer test should be thoughtfully considered before its clinical utilization[12, 13].

- ***Transcranial Doppler (TCD):*** TCD can be employed to identify an increment in microembolic signals. A prospective study from Korea revealed that TCD provided evidence for cerebral microemboli in 58% of patients with both cancer and ESUS. These microemboli were associated with high D-dimer levels and adenocarcinoma histology and were often observed bilaterally, indicating a central embolic source[14].
- ***Transthoracic Echocardiogram (TTE)/ Transesophageal Echocardiogram (TEE):*** When evaluating patients with suspected cancer-associated ischemic stroke, a thorough assessment for potential cardiogenic sources is imperative. Firstly, as noted by Kwon et al.15, patients presenting with bihemispheric infarctions of unknown origin often have concealed cancer. Additionally, Schwarzbach et al.16 have proposed that, once other causes of embolic stroke have been ruled out, the presence of scattered DWI lesions in multiple vascular territories strongly suggests a cancer -related etiology. It's essential to consider differential diagnoses for other common cardioembolic sources, always keeping in mind the possibility of cancer-associated ischemic stroke. Secondly, it is crucial to perform a transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) to identify marantic endocarditis, as it represents one of the most significant pathogenic factors in cancer-associated ischemic stroke. This two-step approach, TTE following by TEE, ensures a comprehensive evaluation of cardiac sources in the context of cancer-associated stroke.
- ***Thoraco-Abdominal-Pelvic Computed Tomography or Positron Emission Tomography:*** For the initial assessment of patient with no known history of malignancy, it is advisable to consider thoraco-abdominal -pelvic computed tomography (CT) or positron emission tomography (PET) scans. These imaging modalities are of particular importance as they can detect cancers that commonly underlie such stroke events. Specifically, they are effective in identifying malignancies in the lung, pancreas, genitourinary organs (prostate, ovarian, renal), gastrointestinal tract (colorectal and gastric), or breast. These types of cancer rank as the most prevalent, both in known cases and especially those that remain undiagnosed, among patients with cancer-associated stroke. This initial imaging step is essential for the identification of potential primary tumors and serves as a crucial component of the diagnostic and treatment strategy[17]. The ongoing INCOGNITO pilot trial, conducted by the Ottawa Hospital Research Institute, is a prospective randomized study aimed at evaluating the feasibility of an occult cancer screening strategy that involves FDG PET/CT in addition to standard cancer screening, as compared to the conventional cancer screening alone. This prospective study holds promise as it aims to confirm whether the enhanced screening approach can effectively increase the detection of occult cancers in patients with cryptogenic stroke.

In the latest extensive retrospective cohort study conducted by Seystahl et al. in 2023, findings suggest that a combination of white blood cell count (WBC), platelets, d-dimers, and the presence of multiple ischemic lesions without cardioembolic stroke etiology can effectively predict cancer diagnosis following a stroke. The reported specificity is notably high at 92%, surpassing the predictive value of the

Occult-5 Score by Beyeler et al. in 2022[10]. However, it is important to note that this combination exhibits a lower sensitivity of 43%[11]. In light of these results, there is merit in exploring the addition of advanced investigations such as TEE and thoraco-abdominal-pelvic CT or PET scans. Conducting a comprehensive cost-benefit analysis study would offer valuable insights into the potential advantages of integrating these advanced investigations into the predictive model.

In the context of available resources, individuals with a suspected cancer-associated embolic stroke of undetermined source are advised to undergo additional targeted test modalities for cancer screening. This involves Thoraco-abdominal-pelvic CT or PET scans during the initial one-year follow-up, with the option to extend to a three-year follow-up based on individual cancer risk. Despite the absence of specific guidelines in widely recognized sources for cancer screening in these patients, a systematic review emphasizes that integrating extensive cancer screening, including CT of the abdomen/pelvis, increases occult cancer detection by almost 20% compared to limited screening involving medical history, physical examination, routine blood tests, and chest radiography. Notably, ultrasound of the abdomen/pelvis and screening for carcinoembryonic antigen (CEA) and prostate -specific antigen (PSA) do not significantly enhance cancer detection beyond the scope of limited screening alone. It is important to note that this review focused specifically on patients with venous thromboembolism (VTE)[18]. Regarding the screening period, evidence suggests that 2-10% receive a cancer diagnosis within the year following the stroke event[1, 2]. Data from the large Zurich Swiss Stroke Registry (2014-2016) reveal that out of 1157 patients, 2.9% were diagnosed with cancer within one year after a stroke, with a modest 2% increase (totaling 4.8%) in cancer detection over the three-year follow-up period post-stroke[11].

b.) Patients with known active malignancy

For patients with a known active malignancy who experience arterial ischemic stroke or transient ischemic attack, a standard etiological work-up for their stroke is recommended. This includes a comprehensive assessment involving detailed clinical history, diffusion-weighted imaging magnetic resonance imaging (DWI-MRI) vascular imaging, and cardiac rhythm monitoring. D-dimer plays a crucial role as a diagnostic, prognostic, and monitoring tool after initiating antithrombotic therapy, with its value potentially re-escalating in the recurrence of cancer[19]. TEE is considered more beneficial than TTE for determining etiological factors, including non-bacterial (marantic) endocarditis. Additionally, investigations into hypercoagulability, paradoxical embolism from venous thrombosis, tumor-related vascular compression, and strokes associated with anti-cancer treatments may be worthwhile considerations.

Future trend in investigation in Cancer-associated ischemic stroke

- ***A machine learning-based prediction model using immunohistochemically stained thrombi obtained from thrombectomy***

  In the latest study by Heo et al., a machine learning model was employed to predict cancer as the underlying cause or to detect occult cancer. The study used immunohistochemical slide images of thrombi obtained during endovascular thrombectomy, which were stained with platelet, fibrin, and erythrocyte markers. The results showed that the platelet

model consistently demonstrated high accuracy in classifying patients with cancer, achieving an area under the receiver operating characteristic curve of 0.986 (95% CI, 0.983–0.989) during training, 0.954 (95% CI, 0.937–0.972) during internal validation, and 0.949 (95% CI, 0.891–1.000) during external validation. When applied to patients with occult cancer, the model accurately predicted the presence of cancer with high probabilities ranging from 88.5% to 99.2%20.

Conclusion

Patients with active malignancy experiencing arterial ischemic stroke or transient ischemic attack should undergo a thorough diagnostic work-up, including clinical history assessment, DWI-MRI vascular imaging, and cardiac rhythm monitoring. Additional tests for occult cancer investigation supplements standard stroke guidelines. In addition to standard stroke guidelines, supplemental tests for investigating occult cancer are advised. These supplementary tests encompass blood tests, including D-dimer, fibrinogen level, hs-CRP, as well as transthoracic echocardiogram followed by transesophageal echocardiogram, and thoraco-abdominal-pelvic computed tomography

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