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Ischemic stroke as an initial presentation of primary bone marrow lymphoma

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Abstract

Various cancer types have been associated with cancer-related cerebral infarction. In this study, we describe the first case of cancer-related cerebral infarction in which the underlying disease was primary bone marrow lymphoma (PBML). A 79-year-old man presented with abruptly developed bilateral lower extremity weakness and confusion. Diffusion-weighted imaging on admission showed multiple cortical and subcortical embolic infarction lesions in multiple vascular territories. Diagnostic evaluations to determine the embolic source revealed no abnormalities. Laboratory testing demonstrated elevated D-dimer (2.59 μg/mL) but no other prothrombotic abnormalities. In suspicion of cancer-related stroke, we performed chest CT, abdomen CT, and FDG-PET to detect the hidden malignancy. Findings revealed no evidence of cancer; however, they did reveal signs of anemia (hemoglobin 9.0 g/dL). Bone marrow aspiration biopsy showed large atypical B cell involvement suggestive of high-grade B cell lymphoma. The patient was diagnosed with primary bone marrow diffuse large B-cell lymphoma initially presenting with ischemic stroke. Our case suggests that primary bone marrow cancer may be a candidate for the differential diagnosis of hidden malignancy in patients with suspected cancer-related stroke. Bone marrow biopsy may be essential for establishing an appropriate differential diagnosis in patients with abnormal hematologic findings.

Keywords: Bone Marrow Neoplasm; Bone Marrow Examination; Diffuse large B cell lymphoma; Embolism and Thrombosis; Stroke

INTRODUCTION

Active systemic cancer increases the risk of stroke.[1] The prevalence of cerebrovascular disease is as high as 7.4% in patients with cancer.[2] The exact mechanism of increased risk of cerebral infarction in cancer patients is uncertain and likely a combination of multiple factors.[1] Plausible mechanisms include hypercoagulability, nonbacterial thrombotic endocarditis (NBTE), tumor embolism, paradoxical embolism through the right-to-left shunt, and direct compression of a cerebral artery by the tumor.

Overall survival after stroke is poor in patients with cancer. Predictors of mortality in cancer-associated stroke include systemic metastases, lung cancer, cryptogenic mechanisms, and elevated D-dimer level.[1] Patients with cancer-related stroke have a higher risk of stroke recurrence than in general stroke population, even though life expectancies are short.[3] Treatment of anti-thrombotic, such as anticoagulants or antiplatelets, is considered important to prevent recurrence of cerebral infarction, but there are no definitive guidelines. The co-morbidities and condition of patients should determine the treatment strategy for cancer-related stroke. Early recognition of underlying cancer and stroke mechanism is crucial in guiding the extent of investigation and management of stroke.

Sometimes ischemic stroke occurs as the first clinical manifestation of cancer.[4] It is essential to search for hidden malignancy in acute cryptogenic stroke patients with distinctive characteristics of the cancer-related mechanism. However, in cases of cancer with low incidence, general screening tests may be insufficient to diagnose occult disease. Here we report the first case of stroke as an initial manifestation of primary bone marrow lymphoma (PBML) identified only by bone marrow biopsy.

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CASE REPORT

A 79-year-old man presented with abruptly developed bilateral lower extremity weakness and confusion. Diffusion-weighted imaging on admission showed multiple cortical and subcortical acute ischemic lesions that involved multiple vascular territories (Figure 1). Magnetic resonance angiography and computed tomography (CT) angiography demonstrated normal findings for both the intracranial and extracranial arteries. Diagnostic evaluations to find an embolic source, including electrocardiography and echocardiography, yielded no abnormalities. Laboratory testing demonstrated elevated D-dimer (2.59 μg/mL) but no other prothrombotic abnormalities. In peripheral blood testing, leukocyte count was 4,080/mm^3, hemoglobin level was 9.0 g/dL, and platelet count was 134,000/mm^3, while normal rages of mean cell volume and mean cell hemoglobin were observed during initial testing.

Cancer-related cerebral infarction was suspected based on the patient's ischemic lesion distribution and abnormal laboratory findings. However, chest CT and abdominal CT showed no evidence of cancer and only pulmonary thromboembolism was confirmed on chest CT. Whole-body ^{18}F-fludeoxyglucose (FDG) positron emission tomography (PET) was performed to detect hidden malignancy. The PET scan showed increased diffuse uptake of FDG in both humeri and femurs, suggesting a reactive inflammatory change. There was no evidence of abnormal hypermetabolic lesion suggesting malignancy.

To specify the etiology of anemia, an esophagogastroscopy and colonoscopy were performed. However, no active bleeding lesions or cancer were observed. Initial peripheral blood smear showed mild anisocytosis without any other hematologic abnormal findings. Follow-up laboratory testing revealed the presence of anemia (hemoglobin 7.5g/dL) and mild agglutination. Both direct and indirect Coomb's tests showed

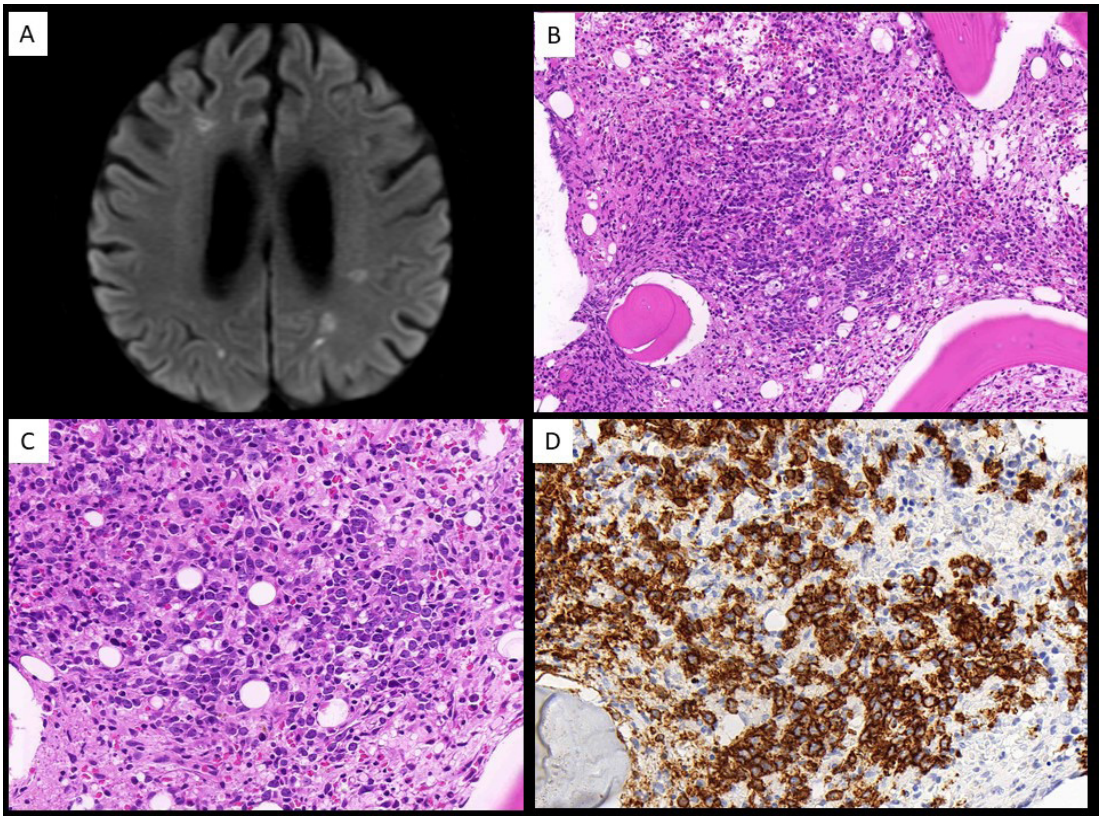

Figure. 1. Cerebral infarction lesion and histologic features of diffuse large B cell lymphoma in the bone marrow. (A) Diffusion-weighted imaging showed multiple embolic ischemic lesions involving multiple territories. (B) Bone marrow biopsy showed multiple lymphocytes. (Hematoxylin & Eosin [H&E] stain, ×100). (C) Bone H&E × 400. (D) Immunohistochemical staining was positive for CD20 and consistent with B-cell lymphoma.

positive results. Autoimmune hemolytic anemia or related conditions were suspected.

Bone marrow aspiration biopsy showed large atypical B cell involvement suggesting high-grade B cell lymphoma. Immunohistochemical studies revealed that the neoplastic cells were positive for CD20 (Fig. 1). Morphologic features, together with immunohistochemical results, were consistent with diffuse large B-cell lymphoma. Given the absence of systemic involvement or other solid masses, the patient was diagnosed with primary bone marrow lymphoma presenting with acute ischemic stroke. Subsequently, he was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. Following two months of chemotherapy, the patient's clinical manifestation and abnormal laboratory findings resolved.

DISCUSSION

Our patient presented with multiple ischemic lesions involving multiple vascular territories, laboratory testing demonstrated elevated D-dimer only. A previous study demonstrated that elevated D-dimer levels in conjunction with multiple embolic lesion patterns could be used as a predicting marker for occult cancer in a patient with cryptogenic cerebral infarction.[4] D-dimer is the degradation product of cross-linked fibrin that is formed by coagulation system activation. Evidence indicates that the level of D-dimer correlates with advanced cancer stage, progression rate and survival in patients with cancer.[5,6] The plasma D-dimer concentration, a marker of hypercoagulability, is associated with cryptogenic embolic mechanism and embolic signal on transcranial Doppler in a patient with cancer-related ischemic stroke.[7] High D-dimer levels may be predictive of early neurological deterioration and death in cancer-associated stroke.[6,8] A study showed that D-dimer levels dramatically reduced during anticoagulation therapy, which can also be used to determine the effectiveness of treatment.[7] Furthermore, D-dimer measurements might be useful for finding underlying cancer-related hypercoagulability mechanism in cryptogenic stroke patients.[4] Based on these findings, clinicians agreed to perform a screening test to find hidden primary malignancy if the patient demonstrates a distinctive D-dimer elevation and characteristic infarction lesion pattern in cryptogenic cerebral infarction.

Screening for a hidden malignancy involves chest and abdominal CT, gastrointestinal endoscopy, and PET CT, as adenocarcinoma is the most common pathology in cancer-related ischemic stroke.[9,10] In addition to a solid tumor, cerebral infarction was also reported in hematologic malignancy such as leukemia or systemic lymphoma. However, there was no report of cerebral infarction associated with isolated bone marrow malignancy.

PBML is an extremely rare disease and < 50 cases have been previously reported in the literature.[11] It is challenging to diagnose or suspect PBML due to its vague clinical manifestation and the absence of solid mass lesions. In previous reports, hematologic abnormalities including anemia were frequently associated with PBML, but there was no report of thrombosis.[12] In this study, it was difficult to identify the mechanism of cerebral infarction or pulmonary thromboembolism in the patient. Tissue factors derived from abnormal cells or endothelium might lead to a hypercoagulable state similar to other hematologic malignancies.[1] NBTE associated with hypercoagulability should be considered as a source of embolism in our patient. NBTE is defined as non-infectious, sterile cardiac valvular platelet-thrombin vegetations with negative blood cultures. In our case, echocardiography did not confirm vegetation, but NBTE would not be excluded due to the high false-negative rate.[13]

Our case suggests that primary bone marrow cancer, although rare, should be considered for differential diagnosis of hidden malignancy in patients with suspected cancer-related stroke. Bone marrow biopsy may be essential for establishing an appropriate differential diagnosis in patients with abnormal hematologic findings.

DISCLOSURE

Conflicts of interest: None.

REFERENCES

1. Navi BB, Iadecola C. Ischemic stroke in cancer patients: A review of an underappreciated pathology. *Ann Neurol* 2018;83:873-83.
2. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine (Baltimore)* 1985;64:16-35.
3. Navi BB, Singer S, Merkler AE, *et al*. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology* 2014;83:26-33.
4. Kim SJ, Park JH, Lee MJ, Park YG, Ahn MJ, Bang OY. Clues to occult cancer in patients with ischemic stroke. *PLoS One* 2012;7:e44959.
5. Dirix LY, Salgado R, Weytjens R, *et al*. Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer. *Br J Cancer* 2002;86:389-95.

6. Lee MJ, Chung JW, Ahn MJ, *et al*. Hypercoagulability and Mortality of Patients with Stroke and Active Cancer: The OASIS-CANCER Study. *J Stroke* 2017;19:77-87.
7. Seok JM, Kim SG, Kim JW, *et al*. Coagulopathy and embolic signal in cancer patients with ischemic stroke. *Ann Neurol* 2010;68:213-9.
8. Nam KW, Kim CK, Kim TJ, *et al*. D-dimer as a predictor of early neurologic deterioration in cryptogenic stroke with active cancer. *Eur J Neurol* 2017;24:205-11.
9. Bang OY, Ovbiagele B, Kim JS. Evaluation of cryptogenic stroke with advanced diagnostic techniques. *Stroke* 2014;45:1186-94.
10. Dearborn JL, Urrutia VC, Zeiler SR. Stroke and cancer- A complicated relationship. *J Neurol Transl Neurosci* 2014;2:1039.
11. Bhagat P, Sachdeva MU, Sharma P, *et al*. Primary bone marrow lymphoma is a rare neoplasm with poor outcome: case series from single tertiary care centre and review of literature. *Hematol Oncol* 2016;34:42-8.
12. Kim MS, Cho YU, Jang S, Seo EJ, Lee JH, Park CJ. A Case of primary bone marrow diffuse large B-cell lymphoma presenting with fibrillar projections and hemophagocytic lymphohistiocytosis. *Ann Lab Med* 2017;37:544-6.
13. el-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. *Oncologist* 2007;12:518-23.