Voxel-Based Lesion Mapping of Cryptogenic Stroke in Patients with Advanced Cancer: A Detailed Magnetic Resonance Imaging Analysis of Distribution Pattern

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Background: Ischemic stroke is one form of cancer-associated thrombosis that can greatly worsen a patient's performance status. The present investigation aimed to elucidate the characteristic distribution pattern(s) of cryptogenic stroke lesions using a voxel-based lesion-mapping technique and examine the differences in clinical manifestations between cryptogenic and conventional strokes in patients with advanced cancer. *Methods:* Data from 43 patients with advanced cancer who developed acute ischemic stroke were retrospectively collected. Stroke etiology was grouped into either cryptogenic or conventional stroke etiology according to the ASCO stroke score. Clinical data were reviewed, and voxel-based lesion mapping using diffusion-weighted imaging (DWI) was performed to visualize the cross-patient spatial distribution of the lesions. *Results:* Of the 43 patients, 25 were classified as having cryptogenic stroke etiology and 18 were classified as having conventional stroke etiology. Median survival time of patients from stroke onset was 96 days for cryptogenic stroke etiology and 570 days for conventional stroke etiology ($P = .01$). D-dimer of patients was significantly higher in cryptogenic stoke etiology than in conventional stroke etiology ($P = .006$). Voxel-based lesion mapping showed that DWI hyperintense lesions accumulated at cortical and internal watershed areas of the cerebrum and at the vascular border zone of the superior cerebellar and posterior inferior cerebellar arteries at the cerebellum. *Conclusions:* Voxel-based lesion mapping for cryptogenic stroke in patients with advanced cancer showed that lesions accumulated at vascular border zones within the brain both at the cerebrum and at the cerebellum, but not at perforating arterial territories.

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Introduction

Thrombosis has been a well-known complication in cancer patients since it was described by Trousseau in 1865.[1,2] Both arterial and venous thromboses could occur in patients harboring or being treated for cancer. In fact, thrombosis of unknown etiology is sometimes indicative of occult cancer.[1,3-6] Among several thrombotic complications, ischemic stroke is one form of cancer-associated thrombosis that can greatly worsen a patient's performance status and is also considered an indicator of a poor prognosis.[5-7] Although cancer-associated ischemic stroke is a clinically serious matter, there have been few studies that attempted to uncover the nature of this condition. Because conventional cancer-unassociated cerebrovascular ischemic diseases could also occur in cancer patients, it is important to correctly determine whether the etiology of ischemic stroke is attributable to the cancer itself. Correct diagnosis will lead to more appropriate treatments not only of ischemic stroke itself, but also of the underlying malignancy, which will require profound knowledge and understanding of the disease. In the past, Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[8] and ASCO classifications[6,9,10] were used to distinguish cryptogenic cancer-associated stroke from conventional cancer-unassociated stroke along with detection of D-dimer, a fibrin breakdown product.[8] However, investigation of cryptogenic stroke based on detailed MRI analysis has not been conducted. The aims of the present investigation were to elucidate the characteristic distribution pattern(s) of cryptogenic stroke lesions using a voxel-based lesion mapping technique[11-13] and to examine the differences in clinical manifestations between cryptogenic and conventional strokes.

Materials and Methods

Patient Selection

Data for all patients with active cancer and acute ischemic stroke were retrospectively collected at our institution from April 1, 2011 to December 31, 2015. The institutional review board approved the use of clinical data for this study and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institution is a designated prefectural cancer hospital, and all patients included for analysis were active cancer patients within the last 6 months before developing a stroke. An active cancer patient was defined as a cancer patient who was under treatment or had recurrent or metastatic cancer lesions. All types of cancer were included except for basal cell or squamous cell carcinoma of the skin, hematologic malignancies, and primary brain tumors.

Eligible patients were identified through an institutional medical record database search for International Classification of Disease, Tenth Revision codes for ischemic stroke (codes I43) and by reviewing the clinical database accumulated at the Department of Stroke and Neurological Diseases. The following 2 conditions were excluded in the analysis: (1) early-stage cancer patients not reaching stage 3 or 4 (locally advanced or metastatic)[14]; and (2) patients who had ischemic stroke during the perioperative period, that is, within 1 month after surgery, because it has been reported that patients are at a higher risk of stroke during the perioperative period than during the nonoperative period.[15]

Furthermore, to distinguish between cryptogenic stroke etiology and conventional cancer-unassociated stroke etiology such as atherothrombosis, cardioembolism, and small-vessel disease, patients were phenotypically classified according to the ASCO score.[6,9,10] The ASCO phenotypic classification of stroke has not only shown good concordance with TOAST,[8] but it also provides important additional information. The patient population of interest for this study was active cancer patients who developed stroke caused by unconventional stroke etiology. Such patients are designated as cryptogenic stroke etiology in this study. A total of 59 patients were first identified, and then 16 patients were excluded according to the abovementioned exclusion criteria. Among the 43 patients analyzed, 25 (58.1%) were assigned to the cryptogenic stroke etiology group and 18 (41.9%) were assigned to the conventional stroke etiology group. The detailed clinical characteristics of the patients are listed in Table 1 and Supplementary Table S1.

Clinical Data Measures

Data relating to cancer, including type, histopathology, extent, and presence of metastases, and prior therapies for cancer were recorded. Age, sex, and stroke risk factors were also collected for all patients. Patients were initially diagnosed as having ischemic stroke by magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), and underwent various vascular studies to identify the cause of stroke. The time point of MRI was defined by referring to the onset of symptomatic stroke as day 0. DWI was acquired using a 3.0- or 1.5-T MRI (Trio and Symphony, Siemens Healthcare, Erlangen, Germany). DWI