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Differentiation of cancer from atrial fibrillation in patients with acute multifocal stroke

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ABSTRACT

Objective: Acute multifocal embolic infarction (AMEI) is conventionally caused by etiologies such as cardioembolism due to atrial fibrillation (Af), but can also be caused by serious underlying diseases such as cancer. We characterized cancer-related AMEI and identified useful indicators for cancer-associated strokes.
Methods: A retrospective analysis was performed on 35 patients with Af-related AMEI and 35 patients with cancer-related AMEI selected from 1235 consecutive patients with acute infarcts. All patients received diffusion-weighted magnetic resonance (MR) imaging. Cerebral MR angiography, carotid and cardiac ultrasonography, electrocardiogram-monitoring and whole body computed tomography were also performed on these patients. D-dimer levels were evaluated on admission, and were measured during the sub-acute phase in 19 of the patients with Af and 27 of the patients with cancer.
Results: Acute phase D-dimer levels were significantly higher in patients with cancer than in patients with Af alone. The cut-off D-dimer value to identify cancer-associated infarcts was 2.0 μg/mL. D-dimer levels during the sub-acute phase remained elevated in the cancer patients.
Conclusions: We may differentiate cancer-associated AMEI from Af using a D-dimer level ≥ 2.0 μg/mL, which does not decrease during the sub-acute phase.

1. Introduction

The major causes of acute multifocal embolic infarction (AMEI) are cardioembolism due to atrial fibrillation (Af) [1]. Less common cases include more serious etiologies such as cancer.

Cancer is an important cause of embolic strokes of undetermined source (ESUS). ESUS due to cancer have a poor prognosis because of its strong resistance to anticoagulation therapy [2]. In an autopsy study by Graus et al. [3], 15% of patients had evidence of cerebrovascular disease, only half of whom were previously symptomatic; in only a few of these cases were the lesions of the first presentation of cancer. In some cases, cerebral infarction is the initial manifestation of cancer [4]. Therefore, special attention should be paid to cancer-associated strokes in patients with AMEI, not only by neurologists but by any clinician who treats cancer patients.

Prior magnetic resonance imaging (MRI) studies have suggested that cancer-associated strokes are characterized by acute multifocal simultaneous infarcts [5–8]. There is also a higher prevalence of adenocarcinoma (e.g. pancreatic, lung, gastric and colorectal cancers) among patients with AMEI [5,6,8–12]. Various mechanisms have been proposed to explain the high incidence of cancer-associated hypercoagulation、which is known as Trousseau's syndrome [13]. One theory suggests that the small fraction of mucin secreted by adenocarcinomas interact with P- and L-selectins, thereby inducing platelet-rich microthrombi through platelet-neutrophil interaction [10,14]. Other considerable mechanisms include release of tissue factor, cancer procoagulant activation of factor X, and platelet activation. Although previous studies suggest that patients with advanced-stage cancer present with AMEI and high D-dimer levels [11,12], no useful biomarker is available to predict cancer-related strokes in patients with AMEI.

In this study we analyzed the D-dimer levels of patients with AMEI, and calculated threshold of D-dimer value on admission followed by the serial determination of D-dimer values during the sub-acute phase.

2. Methods

2.1. Patients

A total of 1235 patients with acute strokes were consecutively admitted to our university hospital stroke care units between April 2011

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and November 2015. In the present study, we defined AMEI as multifocal infarcts detected with diffusion-weighted imaging (DWI) of MRI within 48 h after onset without carotid and/or vertebrobasilar arterial stenosis more than 50% which is considered a likely major embolic source without hypercoagulable state. Seventy AMEI cases due to Af or cancer were identified, who did not receive recombinant tissue plasminogen activator or endovascular therapy. All patients prospectively provided informed consent, and the study was approved by the ethical review board of Fujita Health University.

2.2. Patient evaluation

Precise inclusion and exclusion criteria are shown in Fig. 1. All patients were examined with diffusion-weighted imaging (DWI) with a 1.5 T MRI system within 48 h of AMEI onset. Infarct sizes were measured using the TFS-01 DV-R Ver. 1.95 medical viewer (Toshiba Medical Systems Corporation, Tochigi, Japan), by which infarct sizes can be measured automatically. Head and neck magnetic resonance (MR) angiography and carotid ultrasonography (USG) were also performed. A total of 134 patients who exhibited >50% carotid or vertebrobasilar arterial stenosis based on the North American Symptomatic Carotid Endarterectomy Trial criteria were excluded from the study. MRI analysis was sequentially performed by certified neurology and stroke experts, and was double-checked by the neuro-radiologists at our university hospital. Routine laboratory tests and coagulation studies, including D-dimer, PT and APTT measurements, as well as a survey of known risk factors, were performed in all cases within 8 h of admission. In 70 patients with Af or cancer, serial D-dimer measurements were performed on 46 (66%) patients during the sub-acute phase (more than 7 days after onset). Reasons why these tests could not be performed were because of transfers to other hospitals or clinics from mainly economic reasons irrespective of their severities of the disease. D-dimer levels were measured with the latex agglutination method using a STACIA automatic coagulation analyzer (Mitsubishi Chemical Medience, Tokyo, Japan). We also performed cardiac USG, identified a history of previous anticoagulant therapy and underlying diseases, and determined the localization and maximum size of the infarction on DWI. Af was diagnosed by continuous telemetry monitoring of electrocardiogram (ECG) and Holter ECG. The monitoring of ECG was performed as long as possible (at least 72 h) to detect paroxysmal Af. Whole body computed tomography (CT) was performed on all AMEI patients with Af or cancer. Most cancer patients were diagnosed using whole body gallium scintigraphy, abdominal and pelvic USG and tumor marker measurements (CEA, CA19-9, CA15-3, CA125, ProGRP, SCC, CYFRA and PSA) as well as whole body CT. Final cancer diagnoses were confirmed in all cases following histopathologic biopsy or resected sample examination. Patients with complex cardiac thromboembolic sources (left atrial or ventricular thrombus, aortic or mitral stenosis, aortic or mitral valve replacement and bacterial or non-bacterial thromboendocarditis) were diagnosed and excluded from the study based on a combination of ECG, myocardial damage biomarker level (CK-MB, myoglobin, troponin I), transthoracic cardiac USG and brain natriuretic peptide elevation. Some patients who had suspicious findings on transthoracic cardiac USG were received additional examinations of transesophageal cardiac USG. Deep vein thrombosis (DVT) was detected using USG and CT. Other associated diseases were identified using serum biochemical and immunologic markers and enhanced whole-body CT. 47 AMEI patients of others group in Fig. 1 had other underlying diseases, and 30 (64%) patients of them received serial D-dimer measurements.

2.3. Statistical analysis

Statistical analysis was performed using the JMP10 statistical software (SAS Institute Inc., Cary, NC, USA). D-dimer levels between groups were compared using the Mann–Whitney *U* test. This was an exploratory analysis of a convenience sample and therefore no prespecified power calculation was performed. To calculate the D-dimer cut-off value to differentiate cancer-associated infarcts from cardioembolism due to Af, a receiver operator characteristic (ROC) curve was configured

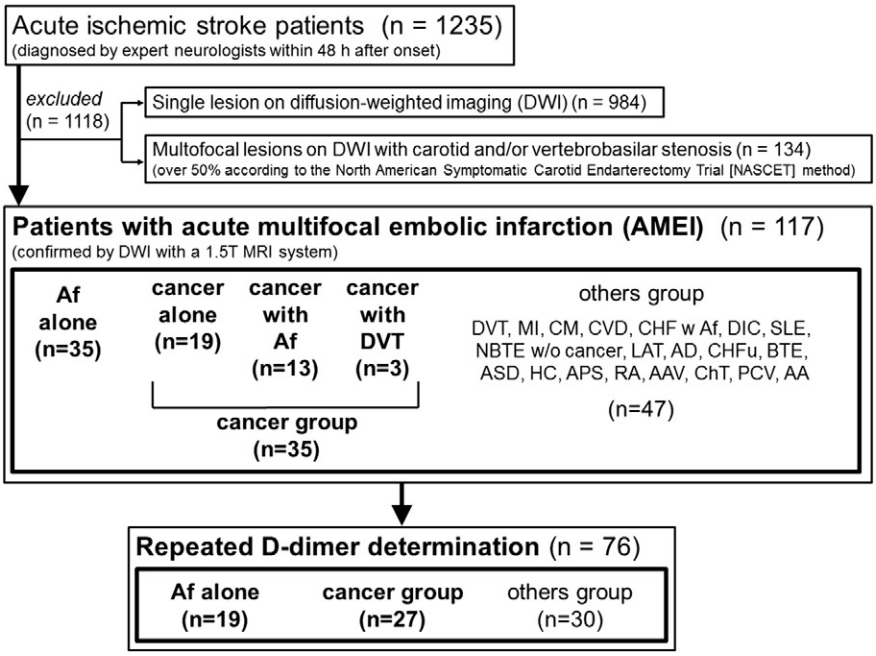

Fig. 1. Patient Selection. Forty-seven patients of others group included various underlying diseases such as deep venous thrombosis (DVT) in six patients, myocardial infarction (MI) in five, cardiomyopathy in five, cardiac valvular disease (CVD) in five, chronic heart failure due to atrial fibrillation (Af) (CHF w Af) in three, infectious disseminated intravascular coagulation (DIC) in three, systemic lupus erythematosus (SLE) in two, non-bacterial thrombotic endocarditis without cancer (NBTE w/o cancer) in two, left atrial thrombus (LAT) in two, aortic dissection (AD) in two, and one case each of CHF with unknown etiology (CHFu), bacterial thrombotic endocarditis (BTE), atrial septal defect (ASD), hypercoagulopathy associated with hepatic cirrhosis (HC), antiphospholipid antibody syndrome (APS), rheumatoid arthritis (RA), anti-neutrophil cytoplasmic antibody (ANCA) -associated vasculitis, chronic thyroiditis (ChT), polycythemia vera (PCV) and amyloid angiopathy (AA); two cases were from an unknown associated disease. Af, atrial fibrillation; DVT, deep venous thrombosis.