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A case of recurrent stroke with underlying adenocarcinoma: Pseudo-cryptogenic stroke

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Abstract:

Stroke is the most common neurological disorders leading to early death. Early recognition of underlying mechanisms and etiology of stroke is important to prevent recurrence, mortality and disability. The term cryptogenic stroke or embolic stroke of undetermined sources is used where no etiology could be detected. We are describing this rare case of "recurrent stroke with undetermined etiology" finally proved to have an uncommon underlying etiology.

Keywords:

Cryptogenic stroke, paraneoplastic stroke, recurrent stroke

Introduction

Stroke is leading cause of death and disability among all medical condition. Cryptogenic stroke (undermined etiology) is challenging condition for the stroke physicians and prevention of recurrence is often based on antiplatelates. Through our case report we are presenting the same challenge and recommend that searching for the underlying cause in stroke patients is important for prognosis.

Case Report

This 62-year nonsmoker female admitted with us in October 2017 with sudden onset right hemianopia caused by left parieto-occipital infarction in posterior cerebral artery (PCA) territory [Figure 1]. She was not having any old medical history of any systemic disease like diabetes, hypertension or coronary artery disease. She was investigated and found to have normal echocardiography, normal brain and neck angiography by computerized tomography (CT) and 24 h holter monitoring. Her glycoselated hemoglobin, lipid profile and thyroid profile was normal. Her erythrocyte sedimentation rate (ESR) was 56 mm/h and X-ray chest posteroanterior (PA) view was normal. Then she was put on antiplatelates and rosuvastatin and discharged with diagnosis of cryptogenic PCA stroke. About 2 months later this female had sudden speech arrest and found to have left middle cerebral artery infarction in superior division [Figure 2]. This time we put on double antiplatelates and checked for thrombophilia profile that also came negative. Within 1 week of dual antiplatelates therapy patient had developed third stroke in right PCA territory and became blind now she was put on enoxaparin 0.6 mg subcutaneous twice a day. Another new infarction occurred in right middle cerebral artery infarction on all treatment [Figures 3 and 4]. Now our focus was to do trans-esophageal echo for persistent foramen ovale and aorta screening for any plaque. Trans-esophageal

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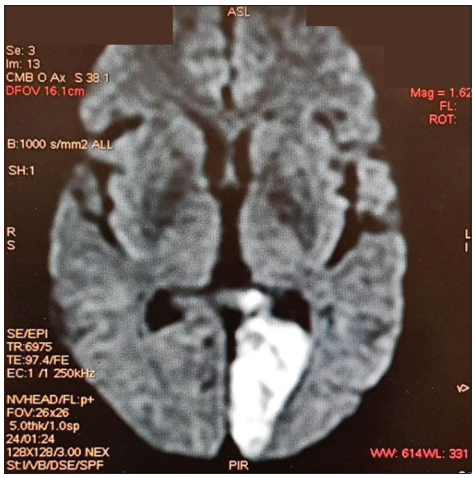

Figure 1: Diffusion weighted imaging – Magnetic resonance imaging showing left posterior circulation stroke

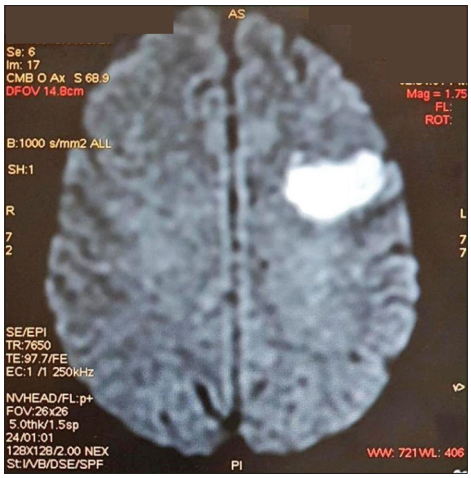

Figure 2: Diffusion weighted imaging – Magnetic resonance imaging showing left middle cerebral artery stroke

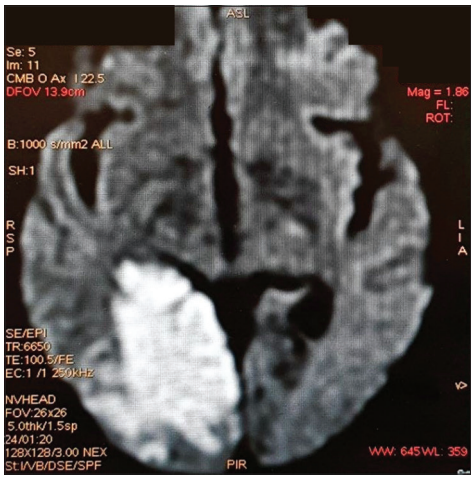

Figure 3: Diffusion weighted imaging – Magnetic resonance imaging showing right posterior circulation stroke

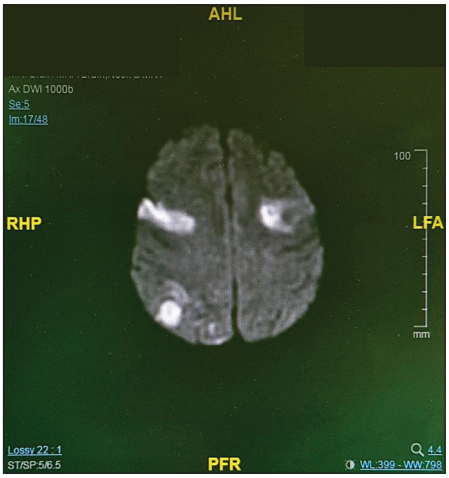

Figure 4: Diffusion weighted imaging - Magnetic resonance imaging showing right middle cerebral artery stroke

Figure 5: Computerized tomography abdomen showing spleen infarction

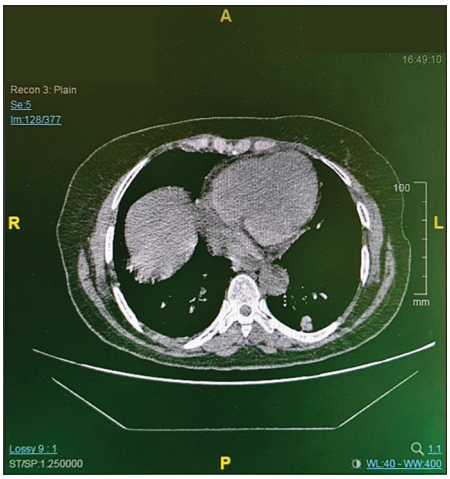

Figure 6: Computerized tomography chest showing lung nodule

echo done outside was normal. CT Aortography was done which was also normal but accidently we found splenic and right renal infarction [Figure 5]. Additional finding was suspected and lung nodules were seen in the basal areas bilaterally [Figure 6]. X-ray chest PA view

was repeated which was again normal. We sent vasculitis and para neoplastic profile of the patient and planned for biopsy. Her vasculitis profile was negative and her CEA and CA 125 were highly positive. Her biopsy from chest nodule showed anaplastic adenocarcinoma. Finally the patient proved to have recurrent stroke with underlying anaplastic adenocarcinoma. Even after extensive investigations exact mechanism of stroke could not be established, although we have ruled out prothrombotic state (negative) but we have not estimated D-dimer level.

Discussion

In Indian literature 20%–27% patients suffers from stroke due to undetermined etiology classified as cryptogenic stroke (CS).[1,2] The rate of CS has been quoted rather more frequently (26%–40%) in patients of recurrent embolic stroke.[3-6] The current stroke guidelines recommended antiplatelates for secondary stroke prophylaxis in patients with undetermined etiology. But there is no specific guidance for those patients who have recurrent stroke (cryptogenic) on antiplatelates. One nonsystemic review suggests long duration holter recording (72 h) to rule out paroxysmal atrial fibrillation.[7] Our case was difficult to manage for us as she had recurrent episodes in-spite of all treatment and we could not find the etiology initially so labeled as CS. In TOAST classification system, stroke with undetermined etiology also includes patients of stroke with incomplete work-up.[8] In year 2014, the term embolic stroke of undetermined sources (ESUS) was coined by CS/ESUS international working group.[9] ESUS term can be used with nonlacunar stroke in absence of; (1) intracranial/extracranial atherosclerosis causing more than 50% luminal stenosis supplying to symptomatic zone; (2) major cardio-embolic sources including permanent/paroxysmal atrial fibrillation; and (3) no other specific cause of stroke. The specific investigations for long list of uncommon causes of stroke are very costly and not available everywhere especially in countries like India therefore, CS/ESUS is commonly used after common causes have been ruled out in clinical practice. In our cases infarctions were bilateral and were in both anterior as well as posterior circulation territories. This multifocal distribution is only possible when embolization occurs from either heart or arch of aorta. We planned for trans-thoracic echocardiography and CT aortography. It was accidental detection of pleural nodules during arotography which led to accurate diagnosis of the case.

Stroke in cancer can be divided into three categories; (1) those who have typical vascular risk factors for stroke with cancer; (2) those who have no other risk factor but only malignancy that diagnosed prior to the stroke and (3) those who diagnosed as CS initially and later found to have underlying malignancy. Therefore, many cases with unknown malignancy presenting with stroke can be classified as CS/ESUS. Till date several studies have tried to correlate the specific cancer type having strong association with stroke. In one study, among 1,274 patients of stroke 12% had additional diagnosis of cancer, with uro-genital, gastrointestinal and breast being the most common.[10] In other studies patients with lung, pancreas, colorectal, breast, and prostate had higher incidence of stroke.[11]

Multiple mechanisms may be linked in stroke with cancer like hypercoagulability, paradoxical emboli, nonbacteriral thrombotic endocarditis (NBTE), and direct tumor effects. In one study 8 of 24 patients with cancer were found to have NBTE which was frequently associated with adenocarcinoma.[12] It is common to presume a diagnosis of hyper-coagulability in patient with recurrent stroke of undetermined etiology till they found underlying cancer as etiology.[12,13] In NBTE, sterile vegetations develop on aortic and/or mitral valve. Transesophageal echocardiography (TEE) is thought to be more sensitive for diagnosis.[14] We could not found any evidence of NBTE on TEE done in our patient. Systemic emboli occur in nearly 50% of patients with NBTE with cerebral emboli being quite common.[14,15] The diffusion magnetic resonance imaging pattern in patients with NBTE was uniformly found to have multiple widely distributed small and large strokes while those with bacterial endocarditis had more varied stroke patterns.[16]

As such it is unclear that which subset of patients should be considered for screening of cancer in CS. Existing reports indicates that elderly patients with (1) recurrent embolic stroke without stroke related risk factors, (2) patients with cerebral and systemic emboli, (3) patients with stroke in presence of "B" symptoms such as unexplained fever, weight loss and malaise, (4) high serum markers known to correlate with the diagnosis of cancer (such as D-Dimer, Ferritin and ESR of >100).

Our patient had continued to have new strokes while getting antiplatelates and low molecular heparin. In patients with cancer and stroke, having classical risk factors for stroke like hypertension, diabetes, atrial fibrillation, or carotid artery disease follow same protocols for disease modification as in without cancer. It remains to be seen whether there is a role for antiplatelates or anticoagulants in the secondary prevention of cancer related stroke. Based on limited data available it can be assumed that anticoagulation is superior for the prevention of hyper-coagulability induced stroke in cancer patients if associated with high D-dimer level. D-dimer level was not estimated in our case so again we can't associate the results of failed anticoagulation in our case.

The case presented here convey the important message that any elderly patient presenting with new onset or recurrent stroke without known risk factors of stroke underlying malignancy should be ruled out before labeling the case as cryptogenic.

Conclusions

Our case present the diagnostic and therapeutic challenges related so called "cryptogenic stroke" with underlying occult malignancy. Systemic and cerebral embolic stroke in short duration without classical risk factors of stroke needs detail evaluation for underlying malignancy.

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Conflicts of interest
There are no conflicts of interest.

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