*Neurology Asia 2013; 18(2) : 153 – 158*

# Usefulness of CEA and CA19-9 for detecting a previously undiagnosed cancer in patients with acute ischemic stroke

[1]Akiyuki Hiraga *MD*, [1]Ikuo Kamitsukasa *MD*, [1]Saiko Nasu *MD*, [2]Satoshi Kuwabara *MD*

*[1]Department of Neurology, Chiba Rosai Hospital, Chiba; [2]Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan*

## Abstract

*Background:* Ischemic stroke can occur in patients with an underlying or undiagnosed malignancy. We aim to report the clinical features of ischemic stroke patients in whom a previously undiagnosed cancer was detected after stroke onset. *Methods:* Clinical and laboratory records of 28 consecutive ischemic stroke patients with cancer were reviewed retrospectively. The analysis was made focused on the differences between patients who were already diagnosed as having cancer before ischemic stroke (Group A) and those in whom a previously undiagnosed cancer was detected after ischemic stroke onset (Group B). *Results:* There were 18 patients in the Group A and 10 in the Group B. In Group B patients, the indicators that led to the detection of cancer were as follows: ascites (n=2), liver enzyme elevation (n=2), anemia (n=2), hematemesis (n=1), hematochezia (n=1), and sore throat (n=1), and autopsy (n=1). Nine of the 10 patients (90%) in Group B, and 6 of the 18 (33%) in Group A had a gastrointestinal cancer. In Group B, 8 of the 9 patients showed elevated serum carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19-9 (CA19-9). Stroke relapse, prognosis, diffusion-weighted imaging patterns and laboratory findings were not different between the 2 groups.
*Conclusions:* Gastrointestinal cancer was frequent in ischemic stroke patients with newly diagnosed malignancy after stroke onset in this study among Japanese patients. Physicians should be aware that underlying cancer may be present particularly in ischemic stroke patients whose stroke etiology is unclear or who have anemia or liver dysfunction. In such cases, measurements of CEA and CA19-9 levels are easy and useful screening for the detection of occult malignancies.

## INTRODUCTION

Cerebrovascular disease is second only to metastases in the frequency of central nervous system lesions in large autopsy series of patients with cancer, and in one series, 14.6% of the patients had pathological symptomatic evidence of cerebrovascular disease.[1] Cancer-related stroke can occur at any point during the course of malignancy. Moreover, stroke can be the first manifestation of occult malignancy in a few patients.[2] Previous studies have shown that 0.4%–3% of ischemic stroke (IS) patients had occult malignancies.[2,3] However, most previous studies of IS patients with cancer did not focus on the timing of the detection of the associated cancer. Furthermore, studies that compared IS patients who were diagnosed as having cancer before IS onset with those who had newly detected a previously undiagnosed cancer after IS onset have been rare.

The purpose of this study was to evaluate the clinical features of cancer patients presenting with IS particularly focusing on the comparison between IS patients with active cancer prior to IS onset and those in whom a previously undiagnosed cancer was detected after IS onset.

## METHODS

### *Patients*

We retrospectively studied the case records of 28 consecutive IS patients with cancer who were admitted to the Neurological Department of our institution. The patients were followed-up for at least 2 months after IS onset. The criteria for inclusion in this study were as follows: (1) presence of cancer that is not in remission, or recurrent, and/or metastatic or was diagnosed after IS onset and (2) acute IS confirmed both clinically and radiologically by cranial diffusion-

*Address correspondence to:* Akiyuki Hiraga, MD, Department of Neurology, Chiba Rosai Hospital, 2-16 Tatsumidai-Higashi, Ichihara-shi, Chiba 290-0003, Japan. Tel: +81-436-74-1111, Fax: +81-436-74-1151, e-mail: hiragaa@yahoo.co.jp

weighted imaging (DWI). Hemorrhagic stroke (subarachnoid hemorrhage and intracranial hemorrhage) were excluded. Disease disabilities at admission, 1 month and 2 months after admission were evaluated according to the modified Rankin Scale (mRS).

The patients were divided into 2 groups: Group A comprised patients with active cancer before IS onset and group B comprised a previously undiagnosed cancer detected after IS onset. Age, sex, cancer diagnosis and laboratory data (basic chemistries, blood cell count and coagulation studies, including prothrombin time, activated partial thromboplastin time and fibrinogen) were collected. D-dimer and fibrinogen degradation products were not evaluated in this study. In selected patients, carcinoembryonic antigen (CEA) and serum carbohydrate antigen 19-9 (CA19-9) levels were measured.

*Neuroimaging*

Magnetic resonance imaging was performed in the acute phase. Cranial DWI was performed using a 1.5-Tesra Siemens Magnetom Vision (repetition time/echo time = 3900/100 ms). All images obtained were 6-mm thick with 1.25-mm interslice gaps for all scans. One patient had undergone DWI in another clinic before admission.

*Statistical analysis*

Differences in proportions were tested with the chi-square test or Fisher's exact test, and differences in means were tested with Student's *t*- test. Results with $P < 0.05$ were considered to be significant.

## RESULTS

*Patients and malignancy*

The patients included 17 men and 11 women with a mean age of 70.9 years (range, 44–95 years). Group A had 18 patients, and Group B had 10. The clinical features and underlying malignancies are summarised in Table 1. Nine of the 10 patients (90%) in Group B had gastrointestinal cancer (pancreas, 4; gastric, 3; colon, 1 and duodenum, 1), whereas 6 of the 18 (33%) patients in Group A had gastrointestinal cancer (gastric, 3; hepatic, 2 and colon, 1). In the 10 Group B patients, the indicators that led to the detection of undiagnosed cancer were as follows: ascites (n=2), liver enzyme elevation (n=2), anemia (n=2), hematemesis (n=1), hematochezia (n=1), and sore throat (n=1), and autopsy (n=1). In 1 patient of Group A, who had prostate cancer before IS onset, gastric cancer was discovered 5 days after IS onset because of tarry stool and anemia (double cancer). Two patients who had prostate cancer in Group A were treated with estrogen before IS onset, which can cause coagulopathy. One patient with uterine cancer in group A had metastasis and invasion of the cervical vein, which caused cerebral venous thrombosis. In Group B, surgery or chemotherapy could be used to treat only 3 of the 10 patients with newly diagnosed cancer after IS onset; the remaining 7 patients could not be treated for their cancer because of stroke severity or advanced cancer. The mRS scores at admission and at 1 and 2 months after admission and the survival rates at 2 months after stroke onset were not significantly different between groups A and B, which indicated that stroke severity and prognosis were not different between the 2 groups.

*Neuroimaging*

DWI patterns were classified as single/multiple lesions involving 1 arterial territory and multiple lesions involving multiple arterial territories. DWI lesions that involved multiple vascular territories were observed in 3 of the 18 patients in Group A and 4 of the 10 in Group B, but the difference was not statistically significant.

*Laboratory findings*

Transaminase, hemoglobin, platelets, prothrombin time, activated partial thromboplastin time and fibrinogen were not different between the 2 groups. In Group B, serum CEA and/or CA 19-9 levels were measured in 9 of 10 patients, and 8 of those 9 patients had elevated CEA and/or CA19-9 levels (CEA: mean, 987; median, 45.3 range, 1.9–7480; CA19-9: mean, 45 672; median, 48.5 range, 0.7–357 000). Moreover, in Group A, the patients with prostate cancer who had gastric cancer newly diagnosed 5 days after IS onset had elevated CEA and CA19-9 levels.

*Autopsy case*

An 83-year-old man was brought to our department's medical emergency room with acute onset of impairment of consciousness and left hemiparesis. He also had a 2-month history of gait disturbance. Cranial DWI showed multiple high signal intensities in multiple vascular territories (Figure 1). The patient died 12 days after admission. Autopsy revealed an invasive

**Table 1 Clinical features and malignancies**

| | Group A (n = 18) | Group B (n = 10) | *P* |
|---|---|---|---|
| Age, mean (y) | 68.4 | 75.4 | NS |
| Sex, M/F | 11:7 | 6:4 | NS |
| Complicated malignancy (n): | | | |
| Stomach | 3 | 3 | |
| Prostate | 5 | 0 | |
| Pancreas | 0 | 4 | |
| Lung | 3 | 0 | |
| Breast | 2 | 0 | |
| Liver | 2 | 0 | |
| Colon | 1 | 1 | |
| Uterus | 1 | 0 | |
| Ovary | 1 | 0 | |
| Kidney | 0 | 1 | |
| Duodenum | 0 | 1 | |
| mRS at admission | 3.7 | 3.6 | NS |
| mRS 1 month after admission | 3.7 | 3.9 | NS |
| mRS 2 months after admission | 3.7 | 4.6 | NS |
| 60-day survival after stroke onset (n) | 12 | 7 | NS |
| Stroke recurrence (n) | 2 | 3 | NS |
| DWI patterns (n) | | | |
| Single vascular territory | 15 | 6 | NS |
| Multiple vascular territories | 3 | 4 | NS |
| Laboratory findings | | | |
| Hemoglobin (g/dL) | 11.1 | 11.8 | NS |
| Platelet ($\times 10^4/\mu L$) | 25.1 | 28.3 | NS |
| AST (U/L) | 27.1 | 29.0 | NS |
| ALT (U/L) | 21.3 | 23.8 | NS |
| PT (sec) | 11.9 | 12.1 | NS |
| APTT (sec) | 26.4 | 27.0 | NS |
| Fibrinogen (mg/dL) | 302 | 354 | NS |

Group A: Patients had active cancer before the onset of ischemic stroke. Group B: A previously undiagnosed cancer was discovered after ischemic stroke onset.
NS, not significant; mRS, modified Rankin Scale; DWI, diffusion-weighted imaging; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time.

ductal carcinoma of the pancreatic head and body with extensive metastasis to the liver and vessels. Vegetations of nonbacterial thrombotic endocarditis attached to the mitral, aortic, pulmonary and tricuspid valves were confirmed. Multiple fibrin microthrombi were also observed in the small arteries of the heart, liver, lungs, prostate and kidney. Although a brain autopsy was not allowed, the other findings suggested that this patient's stroke was caused by embolism due to nonbacterial thrombotic endocarditis.

## DISCUSSION

Our study found that gastrointestinal cancer was frequent (90%) in IS patients who were newly diagnosed as having occult malignancies after stroke onset and that CEA and CA19-9 levels were frequently elevated in these cases.

In previous studies of IS with cancer, the underlying malignancies varied between studies; the most common associated cancers have been reported as lung[4-8], gynecological[9], urogenital[10], prostate[11] or gastrointestinal.[6] Gastrointestinal cancer accounted for 6%–31% of underlying

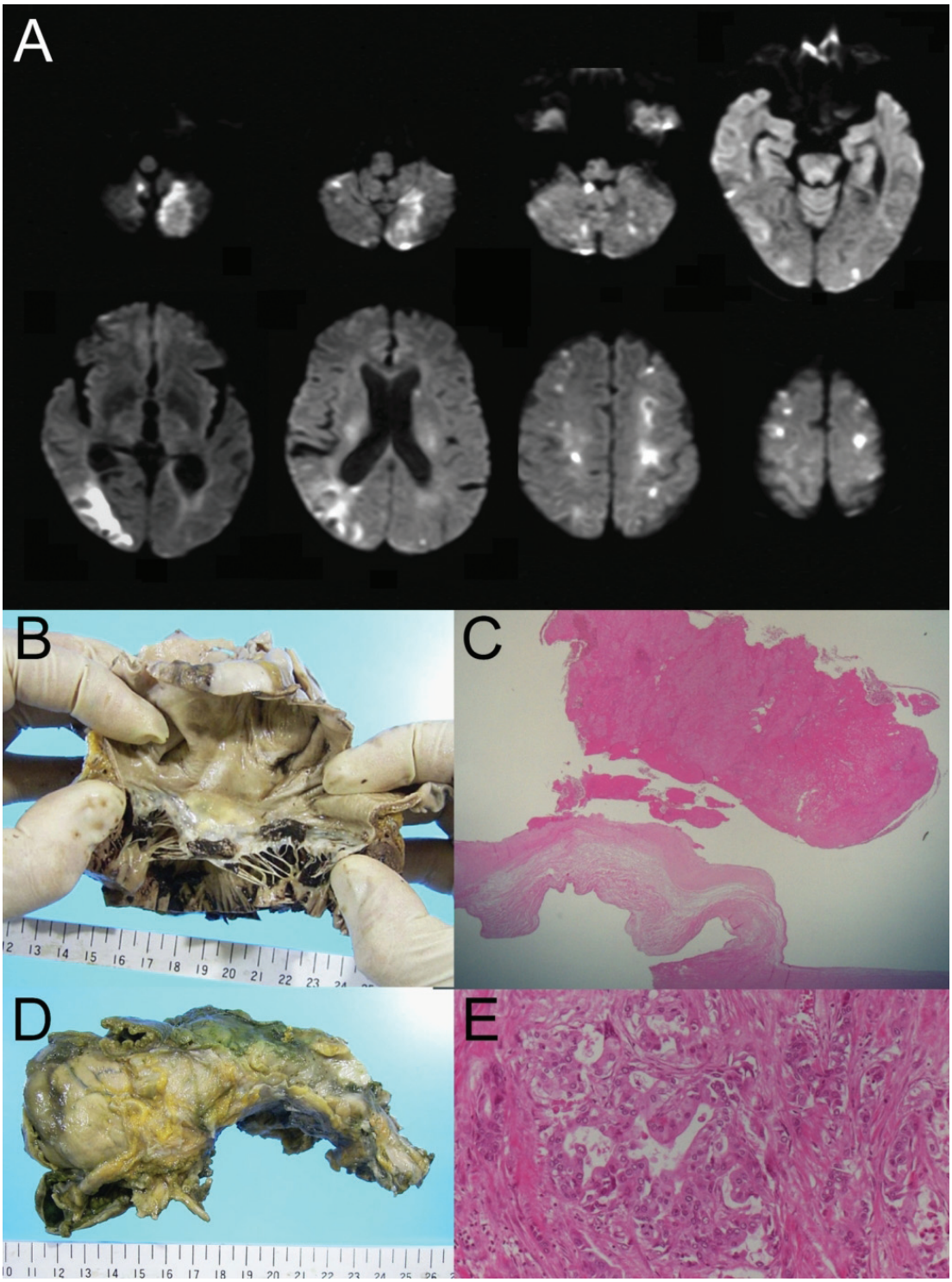


Figure 1. Autopsy case of ischaemic stroke with pancreatic cancer. The cancer was detected by autopsy. (A) A diffusion-weighted magnetic resonance image shows infarcts of the multiple vascular territories. (B) Gross photography of mitral valve vegetations of nonbacterial thrombotic endocarditis. (C) Histological section through part of the vegetation. The vegetations appear to have a uniform eosinophilic appearance. There are no significant inflammatory cells and no microorganisms visible. (D) Pancreatic cancer of the pancreatic head and body with diameters of 3.5 × 2.2 cm. (E) Microscopic examinations of the pancreas shows invasive ductal carcinoma.

cancers in IS patients with malignancies.[4,6,9,10] In two previous studies of IS patients who were newly diagnosed as having concealed cancer after IS onset, the Belgium study showed that the underlying malignancies were as follows: breast (n=4), small cell lung cancer (n=3), prostate (n=2), ovarian (n=2), uterine (n=1), leukaemia (n=2), lymphoma (n=1), intravascular lymphoma (n=1), melanoma (n=1), sarcoma (n=1), pancreatic (n=1) and adenocarcinoma of unknown origin (n=1).[3] Another study from Korea showed that the underlying malignancies were as follows: pancreatic (n=3), lung (n=3), ovarian (n=1), leukemia (n=1), cholangioadenocarcinoma (n=1) and adenocarcinoma of unknown origin (n=1).[12] The findings from these studies suggested that lung cancer was the most frequent cancer in IS patients with newly diagnosed concealed cancer after stroke onset, however, the underlying malignancies varied. A recent study from Japan found that 51 of 1,714 (3%) IS patients were newly diagnosed as having occult malignancy during hospitalisation.[2] In that study, the underlying cancers were as follows: colon (n=13), stomach (n=10), lung (n=6), pancreatic/bile duct (n=4), liver (n=4), prostate (n=4), kidney (n=3), uterine (n=3), ovarian (n=2), breast (n=1) and bladder (n=1). In total, 31of the 51 patients had gastrointestinal cancers, which suggests that the frequency of gastrointestinal cancer in IS patients who have occult malignancies is high. These previous 3 studies did not focus on comparisons of patients with cancer detected before IS and those with newly detected previously undiagnosed cancer after IS onset. Our study compared these patient groups, and our findings strongly suggest that gastrointestinal cancer is a common underlying malignancy in IS patients with newly detected cancer after stroke. The differences of underling malignancy between studies (e.g. lower rate of lung cancer in our study) may depend on countries where the study was conducted. The incidence and frequency of cancers differ between countries, which may be due to differences of genetic factors, lifestyles or environmental factors. In Japan, the leading site of cancer is stomach, followed by colon and rectum, lung, breast, and liver (http://ganjoho.jp). Cancer incidence rate of stomach cancer in Japan is higher than Western countries, whereas lung cancer is lower than Western countries. This may be an explanation of our results. As for the reason for the high rate of gastrointestinal cancer in IS patients with newly diagnosed occult malignancies after IS onset, one possible explanation is that pancreatic cancer is very difficult to detect in the early stage, and advanced cancer causes cancer-related thromboembolisms before occurrence of symptoms for primary pancreatic cancer such as pain, body weight loss or jaundice.

It is very important to know when occult cancer should be considered in IS patients. This knowledge may depend on an understanding of the stroke mechanism of IS in cancer patients. Systemic cancer is related to IS via various mechanisms.[5] In addition to conventional stroke mechanisms, cancer-related mechanisms of IS patients with cancer include coagulopathy, tumour occlusion or tumour embolism, vessel compression or infiltration and treatment-related mechanisms.[7] However, autopsy studies have demonstrated that the most common cause of IS in patients with cancer was atherosclerosis.[1] Moreover, a recent study showed that 60%–68% of cases involved conventional stroke mechanisms.[5,8] We did not systematically perform magnetic resonance angiography, Holter electrocardiography, ultracardiography, cervical echography or D-dimer evaluations in all patients, which was a limitation of our study because we could not clearly divide each patient's IS subtype. A previous study demonstrated that concealed cancer should be considered in patients who exhibit multiple infarcts on DWI with unknown stroke etiology[12], elevated D-dimer levels, low hemoglobin levels[2] or early vascular recurrence.[3] Moreover, a recent study showed that DWI patterns and D-dimer levels may be helpful in early identification of nonconventional stroke mechanisms (particularly, coagulopathy) in cancer patients with IS.[5] However, conventional stroke mechanisms were more frequent than cancer-associated mechanisms, as previous studies have shown, and DWI multiple lesions were not frequent in our study. These findings suggest that, in patients whose stroke etiology is unknown, it is not reasonable to only consider DWI multiple vascular lesions as indicators of possible concealed cancer in IS patients. Besides DWI multiple lesions, elevated D-dimer level, early stroke relapse, anemia or elevated liver enzymes may be indicators of occult malignancies in IS patients. Of course, routine cancer work-ups in all IS patients are unreasonable; therefore, tumour marker tests provide easy tools for use in selective cases before systemic cancer work-ups are considered.

Mucinous cancer is associated with coagulopathy that causes IS.[13] Jovin et al. reported that 4 patients with metastatic cancer, IS and other thromboembolic disease had markedly

elevated levels of the mucinous tumour marker CA-125 and suggested its possible association with IS.[14] Moreover, another study showed that marked elevation of CA-125 level may cause IS even under benign conditions.[15] These findings suggest a possible role of mucin in IS associated with coagulation abnormalities in patients with cancer. CEA is a general oncofoetal antigen that is a historical and basic tumour marker of gastrointestinal tumours, whereas CA19-9 is also a 'mucinous marker' as is CA125, and CA19-9 is the most commonly used marker for gastrointestinal tumours.[16] Although a direct association of CA19-9 with thromboembolism is unknown and CEA and CA19-9 levels are not elevated in early malignancies and occasionally elevated in benign disease, these tumour markers can be effective tools for indicating cancer in selective IS patients because these markers are easily measured.

In conclusion, gastrointestinal cancer was frequent in IS patients with newly diagnosed occult malignancies after stroke onset. Physicians should be aware of the possibility of underlying cancer, particularly gastrointestinal malignancy, in IS patients whose stroke etiology is unclear or in those who have DWI multiple vascular lesions, early relapse, anemia or elevated transaminase. In such cases, measurements of CEA and CA19-9 levels are easy and useful screening for the detection of occult malignancies.

## DISCLOSURE

Conflict of interest: None

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