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CASE REPORT

Characteristics and Management of a Cancer Patient with Stroke: A Case Report

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Background: The onset of stroke in patients with cancer worsens their performance status and affects the treatment strategy for cancer. Nonetheless, intensive rehabilitation may be able to restore the once-lost therapeutic indications of cancer patients who have suffered a stroke. However, because the mechanism of stroke in patients with cancer varies widely, it is necessary to understand the patient background, including the cause of stroke, the control of the primary cancer, and the patient's overall condition, so as to determine the appropriate rehabilitation regimen. **Case:** A 65-year-old man presented with cerebral infarction. He was suspected of having recurrence or metastasis of bladder cancer just before the stroke. Because the patient's performance status worsened with the onset of stroke, it was judged that there was no indication for further investigation and treatment of the bladder cancer, and priority was given to improving his physical function through rehabilitation. Rehabilitation improved the patient's physical function, but in the meantime, the cancer progressed, and he died of cancerous pleural effusion. **Discussion:** Intensive rehabilitation can be an effective treatment for patients with stroke associated with cancer, but in convalescent rehabilitation wards, it is not possible to combine rehabilitation and cancer treatment. Therefore, for patients whose physical function takes a long time to recover or whose cancer is not under control, it is necessary to make a careful decision on whether intensive rehabilitation is the optimum approach. To facilitate informed decision making, it is important to share information across departments.

Key Words: cancer patients; convalescent rehabilitation ward; performance status; stroke; Trousseau's syndrome

INTRODUCTION

Recent developments in cancer management, such as early diagnosis and treatment, have improved the survival rate of cancer patients,[1)] and the number of cancer survivors is increasing. However, these cancer survivors have an increased medium- to long-term risk of cardiovascular disease compared with the general population.[2)] It has been reported that about 15% of patients with cancer develop cerebrovascular disease during the course of their disease,[3)] and the number of patients with cancer who develop cerebrovascular disease is expected to increase as the number of cancer survivors increases. Complications of cerebrovascular disease in patients with cancer are directly related to deterioration of their performance status (PS), which may sometimes affect the treatment strategy for their cancer. The convalescent rehabilitation ward is a specialized ward unique to Japan that was initiated in 2000 with the aim of discharging patients home through intensive rehabilitation; such wards play an important role in stroke treatment in Japan. However, it is impossible to continue detailed examinations and intensive treatment in parallel with rehabilitation. Therefore, depending on the condition of the primary cancer, the cause of the stroke, and the patient's condition, the cancer treatment may be curtailed. We experienced a patient who was suspected of having recurrent bladder cancer just before the onset of

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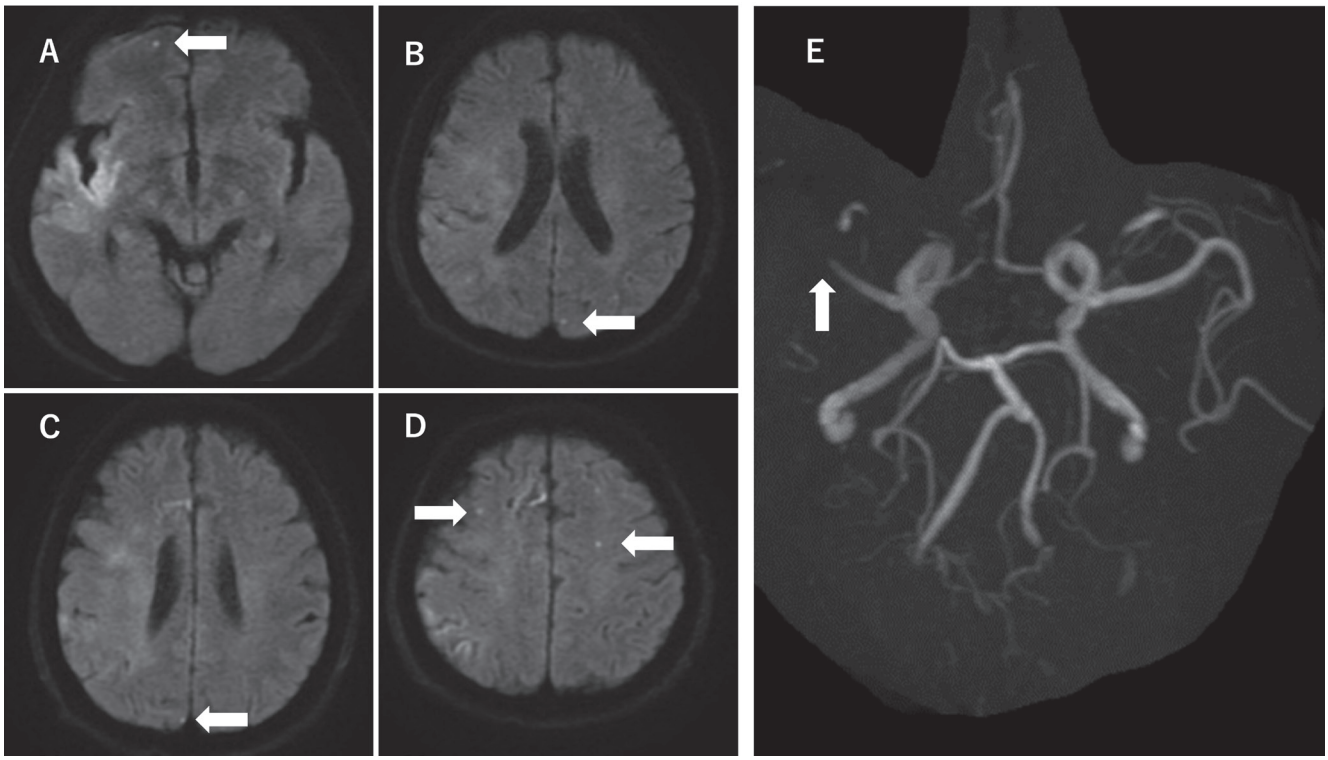

Fig. 1. (A-D) Head magnetic resonance imaging diffusion-weighted images. High signal intensity was seen in the dorsal area around the right sylvian fissure, the right corona radiata, and the right centrum semiovale, indicating acute cerebral infarction, mainly in the right middle cerebral artery territory. Multiple subcortical microinfarcts (arrows) are detected in the bilateral frontal and occipital lobes. (E) Magnetic resonance angiography. The area distal to the right middle cerebral artery M1 is poorly delineated (arrow).

cerebral infarction. However, because of the resulting hemiplegia, the patient's PS worsened and he was transferred to a convalescent rehabilitation ward because it was determined that there was no indication for treatment of his cancer; consequently, rehabilitation was performed prior to the start of cancer treatment. This report will consider the characteristics and management of cerebrovascular disease in patients with cancer, Trousseau's syndrome, and the problems that the onset of stroke poses for cancer treatment.

CASE

A 65-year-old man was admitted to the emergency hospital (1st day of the stroke) with difficulty in speaking and weakness in the left lower extremity. Head magnetic resonance imaging (MRI) revealed extensive cerebral infarction in the right middle cerebral artery territory and multiple acute to subacute cerebral infarctions in the frontal, temporal-occipital, and occipitoparietal subcortical regions (**Fig. 1**). The administration of recombinant tissue plasminogen activator was not indicated because too much time had already passed since the onset of stroke; endovascular surgery was performed, but it was completed without recovery of the thrombus. The patient was treated conservatively, but on the fifth day after onset, consciousness disorder caused by cerebral edema appeared, and external decompression was performed. For secondary prevention, the patient was diagnosed with embolic stroke and was administered 10 mg/day of apixaban. The patient had undergone total cystectomy and cutaneous ureterostomy for bladder cancer 9 years previously. He had also suffered multiple cerebral infarctions 1 year previously, but was still able to live independently. At that time, Trousseau's syndrome was suspected; the patient underwent detailed examination, but no tumor was found. Approximately 2 weeks before the onset of stroke, the patient had come to the hospital because of redness and swelling of the bilateral lower legs. Blood tests showed hypercoagulability, with a D-dimer level of 11.5 μg/mL, fibrinogen/fibrin degradation products of 69 μg/mL, prothrombin time-international normalized ratio of 1.96, and a platelet

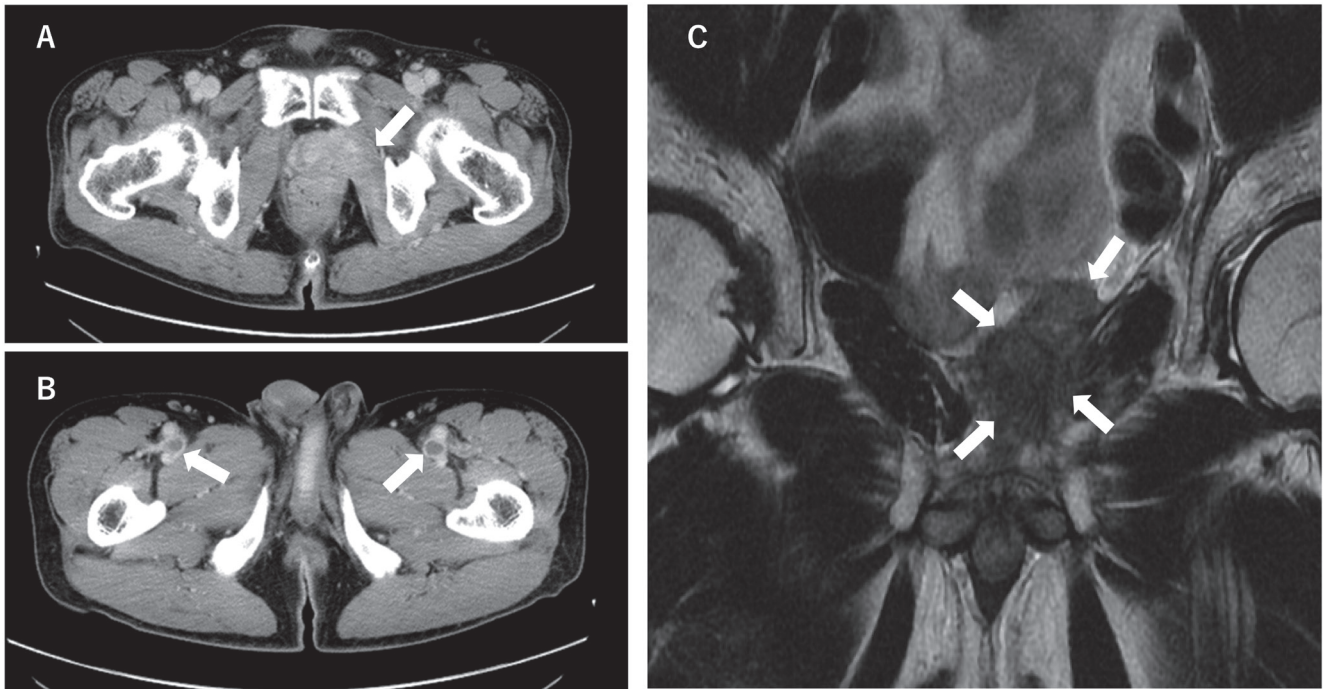

Fig. 2. (A) Contrast-enhanced computed tomography. A mass was detected that extended from the left side of the prostate to the left obturator internus muscle (arrow). (B) Contrast-enhanced computed tomography. Bilateral femoral deep venous thrombosis was detected (arrows). (C) Magnetic resonance imaging T2-weighted image coronal section at 4 months after stroke onset. Solid tumor is detected from the prostate base to the apex, mainly in the left peripheral zone and the transitional zone (arrows).

count of $15.6\times10^4/\mu L$. A systemic evaluation was performed using contrast-enhanced computed tomography (CT), which showed deep vein thrombosis in the bilateral lower limbs and a tumor extending from the prostate to the obturator internus muscle (**Fig. 2**). Based on the patient's medical history, the pelvic tumor was suspected to be a recurrence or metastasis of bladder cancer, but it was judged that there was no indication for its treatment at that time because the stroke had resulted in deterioration of the patient's physical function. Therefore, the patient was transferred to our hospital on the 56th day after stroke onset with a plan to examine and treat the tumor depending on the improvement of physical function achieved through rehabilitation.

At the time of admission to our hospital, the patient had left hemiparesis, sensory impairment on the left side, and higher brain dysfunction, such as left hemispatial neglect and mild disorientation. The Functional Independence Measure (FIM) at admission was 31 points for motor items and 20 points for cognitive items, totaling 51 points. Blood analysis revealed normocytic anemia, renal dysfunction, and high D-dimer levels (**Table 1**). From the beginning, the patient's level of wakefulness was unstable, but he cooperated with rehabilitation. Gradually, voluntary movements in hip flexion were confirmed, and gait training was started on the 64th day. On the 84th day, an ankle–foot orthosis was provided. On the 103rd day, the patient was able to walk about 10 m with a four-point cane and an ankle–foot orthosis with assistance. Although memory and attention deficits remained, wakefulness levels stabilized, and communication skills improved during the same period. On the 126th day, the patient's continuous walking distance had increased to 30 m with light assistance. At this time, the FIM score was 41 points for motor items and 27 points for cognitive items, giving a total of 68 points.

Because the patient's ability to perform activities of daily living had improved, it was decided to make a diagnosis of the pelvic tumor. On the 142nd day, he was transferred to the hospital and a transrectal retroperitoneal biopsy was performed. Retroperitoneal recurrence of bladder cancer was diagnosed. The patient was transferred to our hospital again on the 147th day to continue rehabilitation with a plan for chemotherapy, pending further improvement of his physical functions.

At night on the 157th day, the patient suddenly complained

Table 1. Laboratory data on admission

WBC	5230/μL	AST	26 U/L	TP	7.5 g/dL
Neut	61.2%	ALT	17 U/L	Alb	3.7 g/dL
Eosi	13.6%	LDH	261 U/L	T-Chol	223 mg/dL
Baso	0.6%	T-Bil	0.2 mg/dL	TG	149 mg/dL
Lymph	21.0%	ALP	213 U/L	HDL-C	40 mg/dL
Mono	3.6%	γ-GTP	19 U/L	FBS	110 mg/dL
RBC	328×10^4/μL	BUN	29.7 mg/dL	HbA1c	5.6%
Hb	9.3 g/dL	Cr	1.50 mg/dL		
Ht	30.3%	Na	140 mEq/L	CRP	0.43 mg/dL
MCV	92 fL	K	4.9 mEq/L		
MCH	28.4 pg	Cl	104 mEq/L	PT-INR	0.95
MCHC	30.7%			D-dimer	8.6 μg/mL
Plt	19.3×10^4/μL				

WBC, white blood cells; Neut, neutrophils; Eosi, eonsinophils; Baso, basophils; Lymph, lymphocytes; Mono, monocytes; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Plt, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; T-Bil, total bilirubin; ALP, alkaline phosphatase; γ-GTP, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; TP, total protein; Alb, albumin; T-Chol, total cholesterol; TG, triglyceride, HDL-C, high density lipoprotein cholesterol; FBS, fasting blood sugar; HbAlc, hemoglobin Alc; CRP, C-reactive protein; PT-INR, prothrombin time-international normalized ratio.

of dyspnea. The respiratory status was SpO_2 78% and the respiratory rate was 24 breaths/minute. Arterial blood gas analysis with the patient breathing room air was as follows: pH 7.464, $PaCO_2$ 29.2 Torr, PaO_2 48.5 Torr, HCO_3^- 20.5 mEq/L and base excess −3.6 mEq/L. Chest radiography revealed pneumonia, pulmonary edema, and acute heart failure. The patient was transferred to an acute care hospital (**Fig. 3**). He was treated at the hospital to which he was transferred but died on the 184th day of respiratory failure due to cancerous pleural effusion from recurrence of bladder cancer. For this report, we provided sufficient explanation to the patient and he gave consent in writing.

DISCUSSION

Cerebrovascular diseases are causally related to malignant tumors,[4] and cerebrovascular diseases occur at a higher rate in cancer patients than in the general population.[5] There are various causes of cerebrovascular disorders associated with malignant tumors, such as intratumoral hemorrhage, and diseases that cause stroke symptoms due to hypercoagulability induced by malignant tumors, which is known as Trousseau's syndrome. However, due to recent advances in treatment technology, the number of patients surviving cancer is increasing. Nonetheless, among patients with cancers who develop cerebrovascular disease, the cause is not necessarily related to the malignant tumor, and there is likely a mix of cases, among which the main cause is atherosclerotic disease due to hypertension, diabetes, or atrial fibrillation.[6] In a report of 3426 consecutive autopsies of patients with malignant tumors, cerebral infarction was found in 256 cases. Among

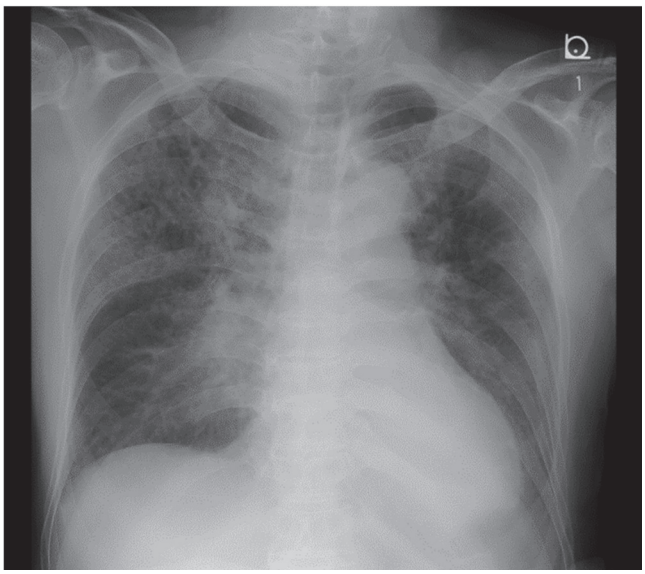

Fig. 3. Chest radiograph. Enlarged cardiac shadow and enhanced vascular shadows in bilateral lung fields indicate pulmonary edema.

these, cerebral infarction resulting from atherosclerosis was the most common, with 73 cases.[3] Therefore, because some cerebrovascular diseases in patients with cancer are not directly related to malignancy, it is necessary to consider the treatment plan depending on the cause of the disease.

In the current patient, multiple infarction foci in several vascular territories were observed on imaging, in addition to subcortical microinfarcts. Although the patient had mild hypertension and abnormal lipid metabolism, which are risk factors for cerebral infarction, they were well controlled by oral medication. Carotid artery ultrasonography showed no significant stenosis or plaque, and the ankle–brachial pressure index was 1.35 on the right side and 1.16 on the left, which are within the normal range. There was no enlargement of the left atrial diameter on echocardiography and no atrial fibrillation on electrocardiography. Consequently, it was difficult to determine whether the cause of cerebral infarction was lacunar infarction, atherothrombotic cerebral embolism, or cardiogenic cerebral embolism: the patient was ultimately classified as having stroke of more than one likely etiology according to the Trial of ORG 10172 in Acute Stroke Treatment classification.[7] Furthermore, considering that the bladder cancer had metastasized to the retroperitoneum and was at an advanced stage (stage IV), the deep vein thrombosis occurring immediately before stoke onset is suggestive of thrombophlebitis caused by the cancer, and the subsequent stroke was most likely the result of Trousseau's syndrome in the context of cancer-induced hypercoagulability.

The brain tends to be a target for disseminated intravascular coagulation because it is rich in thromboplastin, which triggers the extrinsic coagulation system, and poor in thrombomodulin, which acts as an antagonist.[8] Therefore, cerebral infarction is likely to occur in patients with Trousseau's syndrome. Consequently, anticoagulant therapy is recommended for the treatment of Trousseau's syndrome. Because hypercoagulability is caused by a variety of mechanisms, heparin, which inhibits coagulation via multiple pathways (including inhibition of secretin-mediated coagulation and inhibition of activated factor Xa), is the first choice.[9] However, warfarin is not effective as an oral anticoagulant for secondary prevention,[10,11] and dabigatran, a direct oral anticoagulant, is reportedly ineffective in preventing recurrence of stroke.[12] Therefore, challenges remain in the management of the long-term prevention of stroke recurrence. Moreover, the treatment of complicating cerebrovascular disease alone does not improve prognosis: the condition of the malignant tumor and the treatment of the primary disease also affect prognosis.[10] Furthermore, Trousseau's syndrome is often associated with advanced cancer, with a median survival time of 4.5 months and with 25% of patients dying within 30 days[13]; therefore, the prognosis is generally poor. As an exception, if the primary tumor is ovarian clear cell carcinoma, cerebral infarction is likely to occur at an early stage, and the onset of cerebral infarction may trigger the early diagnosis of cancer, allowing cancer treatment to be started as soon as possible. Therefore, compared to other cancers, the recurrence of cerebral infarction is less frequent and the survival time is longer for ovarian clear cell carcinoma.[14] Therefore, depending on the type of primary tumor and the patient, the onset of Trousseau's syndrome could be an opportunity for early detection of the primary tumor, which could facilitate control of the disease and lead to a good prognosis.

PS is an important factor when considering the suitability of cancer treatments. Therefore, if a patient with cancer suffers a stroke, the indication for cancer treatment may be lost. In studies of Japanese patients, the following prognostic factors before primary treatment for stage IV bladder cancer treated with systemic chemotherapy have been established: sex (male), Eastern Cooperative Oncology Group (ECOG) PS ≥1 or PS ≥2, hemoglobin <10 g/dL, white blood cell count ≥8000/μL, liver metastasis, and multi-organ metastasis.[15,16] In the current patient, cancer treatment was not indicated at the time of stroke onset because he had an ECOG PS of 4 as a result of cerebral infarction. Accordingly, it was decided to provide rehabilitation before the start of cancer treatment. Intensive rehabilitation in the convalescent rehabilitation ward resulted in a certain degree of improvement in the patient's physical function. However, because he had had a severe stroke, it took more than 2 months for his physical functions to improve, and during that time, the bladder cancer progressed. While it is true that the improvement of physical function through rehabilitation can be expected to increase a patient's resilience to withstand cancer treatment and, depending on the situation, restore the indication for treatment, current convalescent rehabilitation wards have limitations in their ability to combine rehabilitation and cancer treatment and are not able to control the progression of cancer. In the current case, assuming that the patient was a general stroke patient, satisfactory improvement in physical functions could have been expected with an appropriate amount of time spent on rehabilitation. However, because the survival of patients with advanced cancer is relatively limited, prolonged hospitalization shortens the time they can spend at home. Therefore, it was necessary to determine the effect of rehabilitation on the treatment plan at an earlier time than usual. If we reconsider this case, because the patient

was unable to walk even after 1 month of rehabilitation, after clearly explaining the prognosis with untreated cancer, it may have been ethically desirable to present the patient and family with different management options, such as continuing intense rehabilitation in the hospital or returning home to live out the rest of his life. Indeed, if physical function recovery is not expected in a relatively short period of time or if the cancer is not under control, the indication for admission to the convalescent rehabilitation ward should be fully considered. This case highlights that when a patient with cancer has a stroke, it is necessary to develop an individualized treatment and rehabilitative strategy in close cooperation with other departments. This is desirable because of the complexity of various factors such as the condition of the primary tumor, the cancer type, the treatment plan, the cause of the stroke, and the severity of the stroke. Currently, the Japanese Guidelines for the Management of Stroke 2021 and Clinical Guidelines for Cancer Rehabilitation in Japan, 2nd Edition, do not specifically address treatment strategies for such patients. For this reason, a detailed understanding of the clinical picture and the background of patients with cancer complicated by stroke should be shared among medical departments to develop a comprehensive mid- to long-term treatment strategy.

CONCLUSION

With the development of cancer treatment, the number of patients surviving with cancer is increasing; therefore, the number of cases of cancer complicated with stroke is expected to rise. To provide an appropriate treatment strategy for each patient, it is necessary to elucidate the overall clinical picture of stroke patients with cancer and to use this information to inform the development of a comprehensive treatment strategy.

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CONFLICTS OF INTEREST

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