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Case Report Open Access

Recurrent Cerebral Infarctions in a Patient with Ovarian Cancer: A Fatal Case of Trousseau's Syndrome

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Abstract

Cancer patients are at increased risk of thromboembolic events, and the combination of these two pathological conditions is known as Trousseau's syndrome. Venous thromboembolisms (VTE) and pulmonary embolisms (PE) are the most common clinical features of Trousseau's syndrome. However, arterial thromboembolisms can also occur. We report the case of a 55-year-old ovarian cancer patient, who developed repeated cerebral infarctions with catastrophic consequences. The initial ischemic stroke developed in the right middle cerebral artery territory 4 days before she was scheduled to undergo surgery. Anticoagulation therapy involving unfractionated heparin was administered, and the patient underwent emergency surgery, during which the right ovarian tumor was completely removed. Under a diagnosis of stage Ic ovarian cancer, postoperative adjuvant chemotherapy consisting of carboplatin plus paclitaxel was initiated. During the course of the adjuvant chemotherapy, the patient developed recurrent ovarian cancer, and second-line chemotherapy involving single agent gemcitabine was scheduled. After two months of second-line chemotherapy, which was not effective, the patient developed a second cerebral infarction in her left middle cerebral artery despite continuing to receive anticoagulation therapy. She died 5 days after the second stroke. Given the fact that recurrent thromboembolic events can occur even during ongoing anticoagulation therapy, intensive cancer treatment, thromboprophylaxis, and careful follow-up for the early detection of recurrent stroke events are recommended.

Keywords: Pulmonary embolism; Ovarian cancer; Venous thromboembolisms

Abbreviations: VTE: Venous Thromboembolism; PE: Pulmonary Embolism; MRI: Magnetic Resonance Imaging; CA: Cancer Antigen; CT: Computed Tomography; MCA: Middle Cerebral Artery; PT-INR: Prothrombin Time-International Normalized Ratio; APTT: Activated Partial Thromboplastin Time; UFH: Unfractionated Heparin; OCCC: Clear Cell Carcinoma of the Ovary; TF: Tissue Factor; CP: Cysteine Proteinase; PAI-1: Plasminogen Activator Inhibitor-1; LMWH: Low-Molecular-Weight Heparin.

Introduction

Hypercoagulable states frequently develop in patients with malignant tumors, especially in those with advanced stage disease [1-3]. Idiopathic thromboembolic events including venous and arterial thromboembolisms that occur in cancer patients are referred to as Trousseau's syndrome after the French physician Armand Trousseau first described the association between neoplastic disease and thromboembolic disorders in 1865 [4,5]. In ovarian cancer patients, Venous Thromboembolisms (VTE) and Pulmonary Embolisms (PE) have been the most common clinical features reported as Trousseau's syndrome. However, arterial thromboembolisms, such as brain infarctions, can also occur in patients with ovarian cancer [6].

Herein, we describe our experience of a fatal case of Trousseau's syndrome, in which repeated cerebral infarctions developed during the course of chemotherapy for ovarian cancer.

Case Report

The first stroke

A 55 year old Japanese woman was referred to our hospital to have a right ovarian tumor investigated. She was a non-smoker, and her past surgical and medical history was unremarkable. A transvaginal ultrasound scan detected a 9×8 cm right-sided ovarian tumor. Contrast-enhanced pelvic Magnetic Resonance Imaging (MRI) demonstrated that the ovarian tumor had a solid component, which exhibited contrast enhancement. A pretreatment work-up did not detect any evidence of metastatic disease. Laboratory studies found that the patient's serum Cancer Antigen (CA) 125 and CA19-9 levels were elevated to 1042 U/ml (normal range <65 U/ml) and 1581 U/ml (normal range <40 U/ml), respectively. Hemoglobin level, white blood cell count, platelet count, and D-dimer level were 12.4 g/dl, 5720/μl, 210,000/ul, and 7.29 μg/ml (normal range <0.50 μg/ml), respectively. Searches for thromboembolisms based on lower leg venous ultrasonography, contrast-enhanced Computed Tomography (CT) scans, and a physical examination did not detect any evidence of endovascular thrombosis. The patient was strongly suspected of having ovarian carcinoma, and thus, a laparotomy was scheduled. Four days before the scheduled surgery, she suddenly presented with dysphagia and left hemiparesis. A brain MRI scan depicted multiple acute cerebral infarctions, especially in the right Middle Cerebral Artery (MCA) territory (Figure 1a and 1b), but showed no evidence of atherosclerosis in her carotid arteries. Contrast-enhanced CT scans did not show any evidence of VTE or PE, and transesophageal endocardiography did not demonstrate any findings that were suggestive of cardiogenic thrombosis. Echocardiographic evaluation revealed no patent foramen ovale. Prothrombin Time-International Normalized Ratio (PT-INR), Activated Partial Thromboplastin Time (APTT), and fibrinogen concentration were 1.12, 23 seconds (normal range 23-39 seconds), and 156 mg/dl (normal range 150-350 mg/dl), respectively. Her white blood cell count and D-dimer concentration had increased to 12,230/ul and 19.74 ug/ml, respectively. The patient

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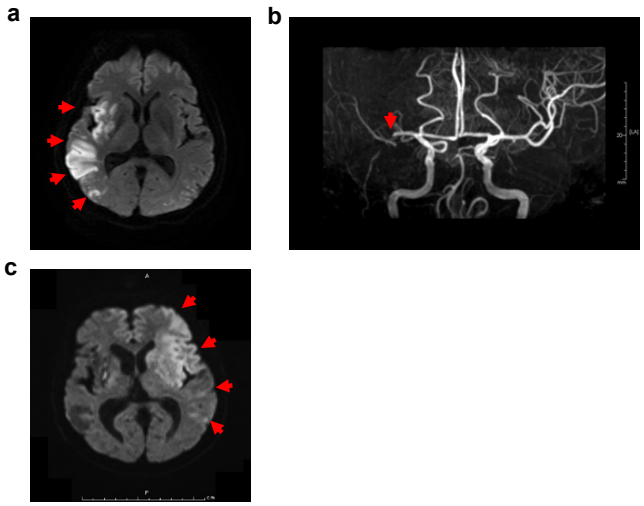

Figure 1: (a) Diffusion-weighted MRI image of the first stroke: Multiple infarctions were scattered in the right side of the insula, basal ganglia, temporal lobe, frontal lobe, and parietal lobe. **(b)** An image obtained using magnetic resonance angiography showing occlusion of the right middle cerebral artery. **(c)** Diffusion-weighted MRI image of the second stroke demonstrating the infarction of almost all of the left middle cerebral artery territory.

was diagnosed with ischemic stroke and admitted to the intensive care unit at our hospital. As an acute management, continuous intravenous administration of 10,000 IU/day of unfractionated heparin (UFH) had been immediately initiated. Four days after the stroke, a right salpingo-oophorectomy was performed. No gross residual disease was detected after the removal of the ovarian tumor. Four days after surgery, her D-dimer concentration decreased to 5.08 μg/ml. A pathological examination of the tumor demonstrated that it was a mixed endothelial tumor (a combination of clear cell adenocarcinoma and endometrioid adenocarcinoma), and a cytological examination of the peritoneal lavage produced a positive result. The patient was diagnosed with stage Ic ovarian cancer complicated by Trousseau's syndrome. Following the 10 days of intravenous injection of UFH, the patient started self-injections of 5000IU heparin sodium (subcutaneously, twice daily) as a thromboprophylaxis. She regained full neurological functions two months after the ischemic stroke. After the fourth course of the postoperative adjuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 5), she developed a recurrent tumor in her pelvis. Although second-line chemotherapy involving single agent intravenous gemcitabine (1000 mg/m^2 on days 1, 8 and 15 of a 4 week cycle) was initiated, the recurrent tumor progressed after two cycles of chemotherapy.

The second stroke

Twenty-seven days after the last dose of single agent gemcitabine had been administered, the patient suffered a second ischemic stroke and was admitted to the intensive care unit due to a sudden loss of consciousness. A neurological examination revealed Glasgow coma scale of 7 (E1, V2, M4), right hemiplegia, and right facial paralysis. In addition, a brain MRI demonstrated an infarction involving almost all of the left MCA territory (Figure 1c), magnetic resonance angiography indicated obstruction of the left MCA. A cerebral angiography performed immediately after the intravenous injection of 5,000 IU of UFH detected complete occlusion of the left MCA. The subsequent Merci mechanical thrombectomy achieved a partial recanalization of MCA. After the procedures, 10,000 IU of UFH had been continuously administered intravenously. However, despite intensive treatment the patient did not recover and died of ischemic stroke on the fifth day after her second stroke.

Discussion

Thromboembolic events have been a well-known complication in ovarian cancer patients [7-12]. Among the four histological subtypes of ovarian cancer, Clear Cell Carcinoma of the Ovary (OCCC) has been associated with unusually high rate of VTE [7]. Previous studies suggested that up to 40% of patients with OCCC develop VTE [7]. According to a multivariable risk assessment model for VTE that has been developed by Khorana et al in 2013 [13], our patient displaying Khorana score of 1 at the time of initial diagnosis had been at low risk for VTE. However, the patient developed the first ischemic stroke during the time between the diagnosis of ovarian cancer and surgery [13].

In a study of a large autopsy series, it was found that up to 14.6% of cancer patients suffered cerebrovascular complications [14]. In ovarian cancer, the precise incidence of cerebrovascular complications remains unknown. However, a recent nationwide population-based study revealed that ovarian cancer patients are at increased risk of developing ischemic stroke [6]. According to their report, the ischemic stroke incidence was 1.38-fold higher in the ovarian cancer cohort than in the matched control, with an HR of 1.49 (95% CI, 1.25 to 1.78; P<0.001). This is consistent with the findings of a previous report suggesting that gynecological malignancies have the greatest potential to induce ischemic stroke [15].

Cerebrovascular complications might not only impair cancer patients' quality of life, but also increase their mortality rate [16]. According to a previous study, among cancer patients the median survival period after cerebral infarction is only 4.5 months [16]. Therefore, it is of great importance to identify cancer patients who are at a high risk of ischemic stroke, which might enable physicians to conduct detailed follow-up examinations.

The risk factors for ischemic stroke among non-malignant populations include hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity [17]. A recent study focusing on ovarian cancer patients also produced similar results; hypertension (HR 1.84; P<0.001), diabetes mellitus (HR 1.71; P<0.001), and being aged ≥ 50 years (HR 2.21; P<0.001) were found to be independent risk factors for ischemic stroke, indicating that conventional stroke risk factors are important for the pathogenesis of ischemic stroke in ovarian cancer patients [14].

At the time of the initial thromboembolic event, our patient did not display any conventional risk factors for ischemic stroke, except untreated ovarian cancer. She did not receive anticoagulation therapy, as our institution does not recommend the use of anticoagulants during the time between the diagnosis of ovarian cancer and surgery. As previous studies have suggested that hypercoagulable states in ovarian cancer patients can only be abrogated through curative resection of the tumor and the patient's physicians were aware of the possibility of ischemic stroke, the physicians aimed to perform curative surgery as soon as possible [18,19]. Moreover, the role of prophylactic anticoagulation therapy during the waiting period prior to surgery should be investigated in future clinical trials involving patients with ovarian tumors.

The biological basis for the systemic coagulopathy in cancer patients has yet to be defined, but it is presumably multifactorial. The main causes of arterial or venous thrombosis in patients with Trousseau's syndrome seem to be prothrombotic factors such as Tissue Factor (TF), mucin, Cysteine Proteinase (CP) and Plasminogen Activator

Inhibitor-1 (PAI-1), which are produced by tumor cells. Mucin can interact with P-selectin and L-selectin, inducing the formation of platelet-rich microthrombi. Secreted TF induces fibrin formation and platelet aggregation by thrombin production. CP activates factor X to generate thrombin. Elevated levels of PAI-1 which is the inhibitor of plasminogen activator result in deficient plasminogen activation and are related to a predisposition to thrombosis. Moreover, the hypoxic condition within the tumor enhances production of TF and PAI-1. Although the present case was not a mucin-producing ovarian cancer, all of these mechanisms contribute to various extents toward the systemic coagulopathy in cancer patients [5].

Regardless of the underlying mechanisms, in the acute phase the primary approach to treating Trousseau's syndrome involves eliminating the causative tumor and administering systemic anticoagulation therapy. In this case, we performed right salpingo-oophorectomy alone to avoid the lengthy staging surgery which might be a cause of another thromboembolic event. As previous investigations have suggested that Trousseau's syndrome tends to recur soon after the discontinuation of anticoagulation therapy [20], long-lasting prophylactic anticoagulation is also necessary. The administration of UFH or low-molecular-weight heparin (LMWH) for the first 6 months after thromboembolic events is generally recommended to prevent recurrent events [21]. In Japan, as the health insurance system only allows the use of LMWH during the perioperative period UFH is generally subcutaneously administered to prevent recurrent thromboembolic events, as was done in our case. Although Trousseau's syndrome is treated using a uniform approach, due to the multiple interacting causative mechanisms of the condition the optimal management strategy might differ between cases involving cancers originating in different organs. Thus, further studies are needed to investigate the optimal anticoagulation therapy and treatment duration to employ in cases of Trousseau's syndrome involving ovarian cancer patients.

Our patient developed repeated episodes of ischemic stroke during the course of anticoagulation therapy and eventually died 5 days after her second stroke, which strongly indicates that in ovarian cancer hypercoagulable states cannot be completely abrogated by anticoagulation therapy.

Due to the rarity of reported cases, the risk factors for recurrent stroke in ovarian cancer patients are unknown. However, it has been reported that the annual recurrent risk of stroke is 3-4% [22], and hypertension, hyperglycemia, dyslipidemia, atrial fibrillation, alcohol, and smoking were found to be risk factors for recurrence in non-malignant populations [23]. Our patient did not display any of these risk factors, and showed Khorana score of 1 during the courses of front-line and second-line chemotherapies, indicating that the patient had been at low risk for VTE. However, a previous study revealed that ovarian cancer patients receiving chemotherapy are at increased risk of stroke [6]. The chemotherapy administered just before the second stroke in this patient was gemcitabine, which has been reported to have vascular toxicity which might be a cause of VTE or acute arterial events [24]. Moreover, it was reported that thromboembolic events can occur despite satisfactory levels of anticoagulation being achieved, especially in patients with persistent, progressive, or recurrent ovarian cancer [25]. Thus, in the present case the existence of recurrent disease and the administration of chemotherapy might have facilitated the development of a hypercoagulable state and caused the recurrent thromboembolic event. Our case strongly indicates that careful attention should be paid to ovarian cancer patients, especially those receiving chemotherapy for primary or recurrent tumors. More studies are needed to investigate whether it is necessary to perform prophylactic anticoagulation therapy during chemotherapy.

In summary, we have described a fatal case of Trousseau's syndrome, in which repeated cerebral infarctions occurred in a patient with ovarian cancer. Given the fact that recurrent thromboembolic events can occur in such patients even during ongoing anticoagulation therapy, intensive cancer treatment, thromboprophylaxis, and careful follow-up for the early detection of recurrent stroke events are recommended. In addition, considering the rarity of cancer-associated arterial thromboembolisms, we consider that it is important to report even individual cases so that an optimal management strategy for Trousseau's syndrome can be established.

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