Diagnostic Laparoscopy of Patient with Deep Vein Thrombosis before Diagnosis of Ovarian Cancer : A Case Report

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Venous thromboembolism (VTE) is a common complication in patients with malignant disease. Epidemiological studies have demonstrated an increased risk of subsequent cancer in the patients who are diagnosed with idiopathic venous thrombosis. Cancers of the breast, lung and ovary in women and adenocarcinomas of an unknown primary cancer are most strongly associated with thrombosis. Mucin-producing cancers are most often associated with VTE and the highest rates of VTE were found for cases of ovarian cancer, but the absolute risk of cancer after thrombosis is relatively low (about 2% over the first year) and so the benefit of screening for cancer in thrombosis patients seems limited. But as this case, the association between thrombosis and occult cancer shows the importance of this association for patients who have thrombosis that is unresponsive to anticoagulant therapy. Especially, we should recognize that such patients can undergo investigation for an underlying malignancy. Diagnostic laparoscopy of an adnexal mass for confirming cancer in the acute setting of deep vein thrombosis (DVT) was performed for our patient. We report here on a case of a patient with DVT in the upper and lower extremities before the diagnosis of ovarian cancer, and we briefly review of the relevant literature.

Key words

Idiopathic thrombosis, Ovarian neoplasms, Laparoscopy

Introduction

The association between venous thrombosis and malignancy was first described by Trousseau in 1865 and this has been confirmed by several clinical, pathologic and laboratory studies (1). Ovarian cancer has a poor prognosis, and it is frequently complicated by venous thromboembolic events (VTE) (2). A previous report suggests that VTE may occur as a consequence of underlying cancer, and VTE can be detected prior to the diagnosis of cancer. Some authors estimate that as many as 15% of the patients with ovarian cancer will have a thromboembolic event, with higher percentages for certain histological types, including mucinous adenocarcinoma (3). Ovarian cancer cells are capable of thrombin formation and thrombin degradation. This, along with the increased fibrinolytic activity seen in many gynecologic malignancies, may be associated with the spread of disease and a poor prognosis (4), as well as the prothrombotic process. The general prothrombotic mechanisms are related to the host's response to cancer. A prominent part is played by tumor specific clot-promoting mechanisms that are the result of the prothrombotic

properties expressed by the tumor cells. Malignant cells can activate blood coagulation in several ways: by producing procoagulant, fibrinolytic, and proaggregating activities; by releasing proinflammatory and proangiogenic cytokines; and by interacting directly with the host's vascular and blood cells, such as endothelial cells, leucocytes and platelets, by means of adhesion molecules. Cancer procoagulant is a cysteine proteinase that directly activates factor X independently of factor VII (5). Tumor cells produce and release various cytokines, including $\text{TNF}\alpha$, interleukin 1β and vascular endothelial growth factor (VEGF), and these can be involved in the development of thrombotic disorders in patients with cancer. Tumor-specific prothrombotic properties contribute to the process of tumor growth and dissemination. The formation of thrombin, which is the final effector enzyme of the clotting cascade, and the production of fibrin, which is the final product of the activation of blood coagulation, are coagulation-dependent mechanisms of tumor progression (6). Epidemiological studies have demonstrated an increased risk of subsequent cancer in the patients diagnosed with venous thrombosis or thromboembolism (2). The spectrum of thrombosis-associated second cancers is very similar to that for the original cancers and so

similar etiologic factors may be at play. These risk factors could be smoking, obesity and hormone replacement therapy since these factors are the suggested or established risk factors for both VTE and cancer. However, the cancers that have increased relative risks of venous thrombosis (ovary, prostate, liver, biliary and pancreas cancer) do not share these lifestyle risk factors. One study suggested that a second cancer is most likely occult and it causes venous thrombosis through changes in the clotting pathway (7). In one study, the median survival from the first thrombotic event in patients with solid tumors was 8.5 months (8). Another recent study found that only 12% of patients diagnosed with cancer at the time of primary DVT were alive at 1 year (2). Iliofemoral venous thrombosis in gynecologic cancer patients may be more a result of tumor-related obstruction of venous flow (9). Although it is probably more common in patients with advanced or recurrent gynecologic cancer, iliofemoral thrombosis may be a presenting feature. Primary surgical therapy in this situation is problematic because therapeutic anticoagulation must be interrupted and the manipulation or relieved compression of clotted veins may precipitate embolization. Some of these patients are not treated aggressively because of their poor prognosis and surgical risks. We performed diagnostic laparoscopy of an adnexal mass in the acute setting of DVT. We report a case of patient with DVT in the upper and lower extremities before the diagnosis of ovarian cancer was made, and we also review the relevant medical literature.

Case Report

The patient is a 44-year-old female who presented to her physician with complaints of reddish swelling and pain in her left leg that had

Fig. 1. Left ascending leg venography revealed DVT involving the lower leg and the popliteal and femoral veins.

occurred for the previous 7 days. Left ascending leg venography revealed deep vein thrombosis (Fig. 1). The patient was admitted to the general surgery department under impression of migrating phlebitis. Pelvic computed tomography revealed multiple intramural myomas and several well defined hypodense lesions with enhancement in the pelvic cavity and there was thrombus in the left proximal deep femoral vein (Fig. 2). Hypercoagulation studies were done, including protein S, protein C, antithrombin III, lupus anticoagulant, the platelet count, the prothrombin time, the activated partial thromboplastin time and the levels of coagulation factors VIII and X and Von-willebrand's factor. The increased prothrombin time (31.9 sec) and activated partial thromboplastin time (42.0 sec) and the decreased coagulation factor X (12%) and the decreased protein S (26%) and protein C (46%) activity were all noted. She then underwent heparin anticoagulation therapy. However, the patient's symptoms didn't improve after 3 weeks' continuous therapy and they were even aggravated to involve the upper extremity. The CA 125 antigen level was 360 μ /L. We then sought consultation with the Gynecologic Oncology Department. She had no history of trauma, surgery, immobilization, hormone therapy or smoking. Her family history was negative for clotting disorders. She was single and didn't have a past history of pregnancy. Transvaginal sonography revealed multiple myomas and a 3.5 $\times$ 3.1 cm hyperechoic mass in the left ovary (Fig. 3). The ovarian mass was hard to recognize on pelvic CT, and multiple subserosal myoma was suspected. The pelvis dynamic MRI revealed a left ovarian mass with cystic and solid portions (Fig. 4), and this was suspicious for being carcinoma. Echocardiography revealed no intracardiac emboli and no cardiac abnormalities. She underwent diagnostic laparoscopy in January 2007 (Fig. 5) and we performed washing cytology, left oophorectomy and right ovary biopsy. On intraoperative inspection, the other internal organs were grossly tumor free. The pathology was confirmed to be moderate differentiated mucinous cyst adenocarcinoma (Fig. 6). Aggressive surgical exploration was not performed because the patient was in an active thrombosis state. We performed oophorectomy to prevent the possi-

Fig. 2. Computed tomographic scan showing multiple myomas & several hypodense lesions in the pelvic cavity.

Fig. 3. Transvaginal ultrasonography showing a hyperechoic mass in the left adnexae.

Fig. 4. Pelvis dynamic MRI revealed left ovarian carcinoma with cystic and solid portions.

Fig. 5. Laparoscopy shows a small sized mucinous cystadenocarcinoma in the left ovary.

Fig. 6. The histologic presentation of moderate differentiated mucinous cystadenocarcinoma (H&E, $\times 200$).

bility of ovary cyst rupture and uncontrolled bleeding. Intraoperative bleeding was absent. The postoperative staging workup was normal. The patient was restarted on heparin immediately after the operation and this was followed by coumadin. The symptoms of her leg and arm were decreased after diagnostic laparoscopy. A decision was made to proceed with combination chemotherapy with plans for interval debulking, if feasible. The patient was continued on warfarin oral anticoagulation and the international normalized ratio (INR) was kept in the treatment range of 2.0 to 3.0. The patient received three cycles of postoperative adjuvant therapy with carboplatin and taxol. The follow up CA 125 level was 45 μL after her first cycle of chemotherapy. After three cycles, we performed complete surgical staging with the rapid normalization of the CA 125 level. An exploratory laparotomy was performed in April 2007. Total hysterectomy, left salpingectomy, right salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node dissection and appendec-

tomy were done. The initially decreased coagulation factor X and protein S and protein C activity were normalized on the postoperative follow up. She was optimally debulked with exploration, and this revealed a normal liver, pancreas, gall bladder, stomach, small and large bowel and appendix, and there was no gross evidence of abdominal or retroperitoneal disease. The histologic examination was free of tumor. She received perioperative anticoagulation. The stage of the patient was stage Ia. The patients with VTE before the diagnosis of cancer appear to have reduced survival regardless of the initial stage, and VTE reflects the emergence of an aggressive and more thrombogenic cancer phenotype, which can lead to earlier death (10). So postoperatively, she received six additional cycles of chemotherapy. In July 2007, the patient's anticoagulant therapy was halted. She remains without evidence of disease 23 months after completion of chemotherapy.

Discussion

Malignancy is generally associated with a hypercoagulable state (11). Activated factor X and procoagulant tissue factor are directly produced by tumor cells. The host immune response to tumor cells also causes the release of cytokines IL-1 and tumor necrosis factor, and both of which may induce a tissue factor expression in macrophages and endothelial cells. Measurable changes in hemostasis occur in 50% of cancer patients and in 90% of those with metastatic disease. Cancer growth is associated with the development of a hypercoagulable state. Patients with malignant disorders, but no thrombosis, commonly present with abnormalities on the laboratory coagulation tests, which suggest a continuous process of fibrin formation and removal at different rates (5). Fibrin and other clot components have roles not only in thrombogenesis, but also in tumor adhesion, spread and metastasis (6). Cancer-associated venous thrombosis has a multifactorial pathophysiology. Either invasion or compression of vessels is a common event. The clotting cascade can be activated by malignant cells (4). The plasma levels of factors I, V, VII, IX and XI may be increased in patients with cancer and such inhibitors as antithrombin III, protein C and protein S may be low due to poor synthesis. The mechanism for this has not been clearly elucidated, but it is thought to result from the release of procoagulants such as tumor factors that activate a high turnover of clotting factors in the face of depleted inhibitors. These tissue factor materials directly activate clotting cascades and this initiates thrombotic events (12). For example, the sialic acid moiety of secreted mucin from mucinous adenocarcinoma can non-enzymatically activate factors X to Xa and so initiate thrombin formation. Thus, there is a high risk of thromboembolic disease with pulmonary, gastrointestinal, pancreatic and ovarian mucinous adenocarcinomas (13). This patient was examined for all coagulation factors except sialic acid. She displayed decreased factor X, protein C and protein S. Her manifestation was a result of high consumption and low synthesis of coagulation factors that was due to a tumor factor activating the clotting cascade. In a recent study of 13,031 women with epithelial ovarian cancer, 5.2% were diagnosed with a VTE event within 24 months after the diagnosis. The cumulative incidence varied from 1.4% among the women with local stage disease to 6.7% among the women with advanced disease. The development of VTE was a strong independent predictor of reduced survival. VTE was associated with a 3.2-fold higher risk of death in the patients with regional stage cancer and a 4.7-fold higher risk of death in the patients who presented with local stage cancer. VTE was associated with a 2.5-times higher risk of death (10). For all the combined malignancies, there was a high excess risk of being diagnosed with cancer (SIR 4.2, CI 3.9~4.5) within 1~6 months after the diagnosis of VTE, with a slowly declining but still significant excess risk for each 6-month follow-up period for up to 2 years (14). The risk of subsequent cancer after diagnosis of VTE was significantly raised for all individual malignancies calculated, but of particular note with SIRS greater than 5.0 were cancers of the ovaries

(14). The diagnosis of VTE should include routine coagulation studies, as well as evaluation of levels of several factor and antithrombin III, protein C or protein S deficiencies, echocardiography to detect a cardiac origin and venography to localize the thrombus (15). The levels of certain anticoagulant proteins may be altered in the setting of acute thrombosis. Therefore, the coagulation evaluation and follow-up can be safely done at a time remote from the initial event. Acute VTE can be the first manifestation of an occult malignancy, and patients presenting with idiopathic VTE are more likely to have underlying cancer than those patients in whom a secondary cause of thrombosis is apparent. Based on a prospective medical database of a county population in the United States, a rough estimate of the annual incidence of VTE in a cancer population is approximately 1/200. About 10% of the patients with idiopathic VTE were diagnosed with subsequent cancers over the next 5~10 years. Levitan et al found the highest rates of VTE in patients with mucinous ovarian cancer (1.2%) (3). More than 75% of these cases were reported within the first year after the diagnosis of DVT (8). Extensive screening for cancer in patients with idiopathic VTE is not routinely warranted (3). If the patient has normal inherited clotting studies, then anticoagulation can be discontinued if the disease is in remission. The standard treatment for femoral venous thrombosis has been 5~10 days of intravenous heparinization followed by 3~6 months of oral warfarin. Low-molecular-weight heparin administered subcutaneously has recently been shown to be an effective and convenient alternative to intravenous heparinization. The patient presenting simultaneously with femoral venous thrombosis and an operable gynecologic cancer poses a dilemma. The problems with heparin therapy in such patients include a delay in the surgical therapy, reduced effectiveness of the heparin therapy in the face of malignancy or extrinsic venous occlusion (3), the occasional development of heparin-associated thrombocytopenia, the need for perioperative anticoagulation with its attendant complications and an increased risk of bleeding complications in cancer patients. In the current case, the patient suffered from phlebitis in the upper and lower extremities despite continuous anticoagulation therapy. Therapy should be based on the most appropriate treatment for the patient, including surgery if feasible. In a recent study, women undergoing laparoscopic surgery also appeared to be at a lower risk for VTE (10). We needed a definite diagnosis of the patient's adnexal mass in the acute setting of DVT. So, a less invasive diagnostic laparoscopy was performed. This is the first Korean case report of DVT before the diagnosis of cancer. Reduction of the tumor burden with surgery and chemotherapy and the prolonged anticoagulation was followed by a resolution of the abnormal laboratory blood values, indicating that this thrombotic event was not incited by a genetic cause. Neoadjuvant chemotherapy can be an option that would allow more time for treating the thrombosis before a staging operation. In our patient, the CA125 level and the symptoms were normalized after one cycle of chemotherapy. Venous thrombosis is not only a poor prognostic indicator for patients with gynecologic cancer, but it is also the manifestation of a pathophysiologic process that contributes to the aggressiveness of the

cancer. The patient was alive at time of writing this report (23 months after the last chemotherapy).

In conclusion, ovarian cancer that is diagnosed less than 4 months after VTE is associated with an advanced stage and the prognosis tends to be poorer than that for ovarian cancer patients without VTE

(7). So, the patients with thrombosis that is unresponsive to anti-coagulant therapy should be suspected of having occult cancer. We suggest investigating for an underlying malignancy in such patients. Additionally, we recommend treating this patient population as aggressively as is indicated.

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