Trousseau Syndrome with Nonbacterial Thrombotic Endocarditis in a Patient with Uterine Cancer

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Abstract

This paper aims to describe the usefulness of transthoracic echocardiography in the follow-up of recurrent nonbacterial thrombotic endocarditis (NBTE) associated with neoplastic conditions. A 60-year-old woman with advanced uterine cancer developed recurrent areas of aseptic vegetation on the mitral valve along with cerebral, renal and splenic embolisms. Echocardiographic assessments revealed vegetation and thrombotic events on three occasions. In this case, transthoracic echocardiography was effective in following the decreased frequency of attachment of the NBTE vegetation to the mitral valve and reductions in the size of the area of vegetation following treatment with unfractionated heparin infusion, hysterectomy and chemotherapy.

Key words: aseptic vegetation, recurrent stroke, unfractionated heparin, cancer


Introduction

Since originally described in 1865 (1), many studies have confirmed the association between cancer and thromboembolism. Approximately 15% of cancer patients experience thromboembolic events during the course of their disease, and as many as 50% exhibit evidence of venous thromboembolism on postmortem examinations (2). Although most cancer-associated thromboembolic events are venous in origin, arterial thromboembolic events may also occur (3). Nonbacterial thrombotic endocarditis (NBTE) is one of the mechanisms of arterial thromboembolism encountered in patients with neoplastic disease (3). NBTE has been reported to be associated with Trousseau syndrome (4). NBTE is characterized by small, broad-based and irregularly shaped areas of vegetation along coaptation lines without destruction of valvular tissue (5).

No study to date has described the time course and morphological assessment of NBTE and its response to therapy in detail using transthoracic echocardiography.

We herein describe the case of 60-year-old woman with advanced uterine cancer who developed aseptic vegetation on the mitral valve along with recurrent embolism. Echocardiographic assessments showed aseptic vegetation with thrombotic events on three occasions. Unfractionated heparin infusion, hysterectomy and chemotherapy suppressed the frequency and size of the areas of aseptic vegetation attached to the mitral valve.

Case Report

A 60-year-old woman with advanced uterine cancer was admitted to our hospital for treatment of cancer. She had no history of symptomatic thromboembolism. We observed a large tumor extending through the patient’s abdominal cavity and supraclavicular lymph nodes. The serum carbohydrate antigen 19-9 (CA19-9) concentration was 2,232 U/mL (normal range, 0 to 37 U/mL), the serum carcinoembryonic antigen (CEA) concentration was 10.7 U/mL (normal range,
0 to 5.0 U/mL), the carbohydrate antigen 125 (CA125) concentration was 745 U/mL (normal range, 0 to 35.0 U/mL) and the serum D-dimer concentration was markedly elevated (22.5 μg/mL). The serum thrombin-antithrombin-complex (TAT) level was 5.4 ng/mL (normal range, <3.0 ng/mL). A clinical examination performed on admission revealed a systolic heart murmur at the apex. The patient had no neurological deficits and no fever. Chest radiography showed slight congestion. Venous ultrasonography of the lower extremities revealed venous thrombosis in the right soleus; however, lung perfusion scintigraphy showed no evidence of pulmonary thromboembolism.

Transthoracic echocardiography performed on day 7 showed vegetation on the mitral valve with severe regurgitation (Fig. 1). A further cardiac assessment using transesophageal echocardiography revealed mitral valve lesions with vegetation attached along the mitral valve coaptation lines and some mobile structures; however, no evidence of leaflet destruction was observed (Fig. 2). The largest area of vegetation was 13 mm in size. Cerebral, right renal and splenic infarctions were detected (Fig. 3) on the same day (day 7). The patient did not complain of any symptoms. Magnetic resonance angiography (MRA) showed no obstruction in the carotid artery. Infective endocarditis or NBTE was suspected, leading to the initiation of empiric therapy with intravenous antibiotics and unfractionated heparin. Three sets of blood cultures were negative. An extensive thrombophilic evaluation was conducted, including assays for antinuclear antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies (ANCA), lupus anticoagulant, anti-cardiolipin antibodies, protein S and protein C. Blood cultures and serology showed no evidence of infective endocarditis or Libman and Sacks syndrome. Due to the likelihood of NBTE embolism and the presence of advanced ma-

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**Figure 1.** Transthoracic echocardiography showing vegetation on the mitral valve (→: arrow) on hospital day 7. (a) Parasternal long axis view. (b) Apical 2-chamber view. (c) Apical 3-chamber view showing severe mitral valve regurgitation. LA: left atrium, LV: left ventricle, Ao: aortic valve

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**Figure 2.** Transesophageal echocardiography showing vegetation on the mitral valve on hospital day 7. (a) Long axis view on transesophageal echocardiography showing vegetation attached to the anterior and posterior mitral leaflets (→: arrow). The largest area of vegetation, 13 mm in length, was attached to the anterior leaflet. (b) Commissure view showing thickening of the anterior mitral leaflet. Many mobile structures were attached to the mitral valve leaflet, although no destruction of the leaflet was observed. Mitral regurgitation was severe (color). LA: left atrium, LV: left ventricle
Thromboembolism associated with malignancy was first described in 1865 as “migratory thrombophlebitis as a presenting sign of visceral malignancy,” a condition still referred to as Trousseau syndrome (1). Although most cancer-associated thromboembolic events are venous in origin, arterial thromboembolic events may also occur (3). In some series, arterial thromboembolic events were reported to account for 10-30% of thrombotic complications in cancer patients (3). NBTE is another mechanism underlying arterial thromboembolism encountered in patients with neoplastic diseases (3). NBTE is associated with many types of primary carcinomas, with lung, pancreatic and ovarian adenocarcinomas being the most frequently observed (6). An echocardiographic study of 200 living patients with various cancers found evidence of NBTE in approximately 19% of the patients, and evidence of NBTE was 10-fold higher in these patients than in a control group (7). Postmortem ex-

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Figure 3. Cerebral, renal and splenic infarctions were detected on hospital day 7. (a) Diffusion-weighted magnetic resonance imaging (DWI) showing a high-intensity signal lesion in the right frontal lobe (centrum semiovale). (b, c) Contrast-enhanced computed tomography (CT) scan showing low-density areas in the (b) right kidney and (c) spleen.

After four courses of adjuvant chemotherapy, we were unable to detect any areas of vegetation on the mitral valve (Fig. 5). Continued infusion of unfractionated heparin, extended hysterectomy and chemotherapy reduced the patient’s serum concentrations of D-dimer and tumor markers and contributed to the suppression of recurrent NBTE thromboembolism. The frequency of attachment of vegetation to the mitral valve decreased, and the size of the areas of vegetation decreased. The mitral regurgitation improved from severe to mild. Fortunately, the patient exhibited no neurological deficits while in the hospital. We changed the infusion of unfractionated heparin to subcutaneous heparin calcium (10,000 U/day) at discharge (Fig. 6), which maintained the serum D-dimer concentration at 0.5-1.8 μg/mL. The patient was discharged from the hospital on day 125.

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aminations have detected NBTE in 0.9-1.3% of patients who have died of cancer (3).

NBTE is the cardiac manifestation of systemic hemostatic activation in cancer patients, resulting in the formation of platelet and fibrin vegetation on cardiac valves with no evidence of inflammation or bacteria (3). Echocardiography shows valvular lesions associated with NBTE in 32%, 63% and 19% of patients with primary antiphospholipid syndrome, myeloproliferative disorders and solid malignant tumors, respectively (8). Our patient exhibited no evidence of infective endocarditis or Libman and Sacks syndrome on blood cultures or serology, resulting in a diagnosis of NBTE associated with cancer.

NBTE is characterized by small, broad-based, irregularly shaped areas of vegetation along coaptation lines without destruction of valvular tissue (5). NBTE lesions are usually found in high-flow areas, such as the distal portion of the leaflets, the atrial surface of the mitral valve and the ventricular aspect of the aortic valve, and in areas damaged by intracardiac lines (7). The most commonly affected valves are the aortic valve, the mitral valve and a combination of both the aortic and mitral valves (2). Involvement of the right-sided heart valves, while less common, has also been reported (2). Our patient exhibited areas of vegetation along

Figure 4. Panels (X), (Y) and (Z) in Figure 4 correspond to panels (X), (Y) and (Z) in Figure 5, respectively. (X) Transthoracic echocardiography performed on hospital day 7 showing vegetation on the mitral valve ((X)-left) and that performed on hospital day 9 showing that the largest area of vegetation had disappeared ((X)-middle) in association with a new left renal infarction ((X)-right). Contrast-enhanced CT scan showing a low-density area in the left kidney ((X)-right). (Y) Transthoracic echocardiography performed on hospital day 19 showing a new area of vegetation attached to the posterior mitral leaflet ((X)-left). This area of vegetation disappeared on day 20 ((X)-middle), and a new cerebellar infarction was detected ((X)-right). DWI showing a high-intensity signal lesion in the left cerebellar hemisphere ((X)-right). (Z) Transthoracic echocardiography performed on hospital day 57 showing a new area of vegetation attached to the posterior mitral leaflet ((Z)-left). This area of vegetation disappeared on hospital day 61 ((Z)-middle), and a new cerebral infarction was detected ((Z)-right). DWI showing a high-intensity signal lesion in the left parietal lobe ((Z)-right). CT: computed tomography, MRI: magnetic resonance imaging, DWI: diffusion-weighted imaging.

the mitral coaptation lines with no destruction of tissue. Thromboembolisms associated with NBTE are frequently asymptomatic or mildly symptomatic and may be easily missed unless they are specifically assessed (8). Embolization of nonbacterial thrombotic lesions frequently occurs, most likely due to the lack of a tissue response (8). Recurrent NBTE vegetation and several embolization events were detected in our patient. However, she exhibited no neurological deficits.

The pathogenesis of NBTE in patients with malignancy remains partially elusive, although it is intimately related to cancer-associated thrombophilia, originally described as Trousseau syndrome (2, 6). In the presence of excessive clotting factor activity, endothelial damage caused by circulating cytokines, such as tumor necrosis factor and interleukin-1, can trigger platelet deposition in areas of high blood flow (2, 5, 6). However, the pathogenesis of Trousseau syndrome may be more complicated, in that it may involve tissue factor and tumor-associated cysteine proteinase activity, tumor hypoxia, carcinoma mucin activity associated with platelet aggregation dependent on P- and L-selectins and oncogene activation related to hypercoagulability (9). In our patient, a pathologic examination showed that the tumor was a Grade I adenocarcinoma, endometrioid type, which seldom produces mucin. However, mucin was detected using mucicarmine staining in our case. Mucin may be associated with hypercoagulability.

The primary approach to treating Trousseau syndrome is to eliminate the causative tumor, if possible. Because this is often not feasible, unfractionated heparin is the preferred treatment (2, 9). Indeed, when our patient was switched from unfractionated heparin to warfarin, her serum D-dimer concentration increased markedly and a new area of vegetation attached to the posterior mitral leaflet was detected and disappeared. After four courses of adjuvant chemotherapy, the serum D-dimer and CA125 levels were suppressed, and the frequency of attachment of vegetation to the mitral valve was reduced. When unfractionated heparin was changed to warfarin as anticoagulation therapy, the D-dimer levels immediately increased. CA125: carbohydrate antigen 125.

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**Figure 5.** Time course of the recurrent mitral valve vegetation and thrombosis, the serum concentrations of D-dimer and CA125 and the course of treatment. Panels (X), (Y) and (Z) in Figure 5 correspond to panels (X), (Y) and (Z) in Figure 4, respectively. × mark indicates that no areas of vegetation were detected on transthoracic echocardiography. (X) On hospital day 7, transthoracic echocardiography showed vegetation on the mitral valve with severe regurgitation. The largest area of vegetation disappeared on day 9. (Y) On hospital day 19, a new area of vegetation attached to the mitral valve leaflet was detected and disappeared. (Z) On hospital day 57, soon after switching from warfarin to unfractionated heparin, a new area of vegetation attached to the posterior mitral leaflet was detected and disappeared. When unfractionated heparin was changed to warfarin as anticoagulation therapy, the D-dimer levels immediately increased. CA125: carbohydrate antigen 125.
effectiveness of unfractionated heparin in patients with Trousseau syndrome, it can be assumed that unfractionated heparin has a variety of biological activities other than inactivating thrombin since it is a complex and heterodisperse mixture of glycosaminoglycans extracted from certain animal sources (9). Unfractionated heparin is reported to inhibit heparin cofactor II and protein C and blocks the binding of L- and P-selectins to their natural and pathologic ligands (9). Heparin can also bind and potentially neutralize a wide variety of cytokines and chemokines (9).

To our knowledge, this is the first case report to describe the detailed course of recurrent NBTE vegetation and its response to therapy using transthoracic echocardiography in a Trousseau syndrome patient.

Conclusion

Echocardiography was useful for monitoring a patient with NBTE associated with Trousseau syndrome.

Therefore, it is desirable to apply echocardiography in neoplastic patients suspected of having NBTE, whether or not they exhibit clear symptoms.

The authors state that they have no Conflict of Interest (COI).

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