Trousseau’s Syndrome Causing Refractory Deep Venous Thrombosis

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Abstract:
A 66-year-old man, who had been diagnosed with deep venous thrombosis (DVT), and who was treated with a vitamin K antagonist (VKA) and who had undergone the implantation of an inferior vena cava filter, was admitted due to an exacerbation of DVT. VKA was administered again; however, the patient’s DVT worsened. Further examinations revealed colon cancer, which led to a diagnosis of Trousseau’s syndrome. The regression of the thrombi was confirmed after the administration of heparin and the resection of the tumors. Trousseau’s syndrome should always be kept in mind when patients present with refractory venous thrombosis. The administration of heparin, and cancer control are necessary for the effective treatment of thrombosis in such cases.

Key words: Trousseau’s syndrome, refractory deep venous thrombosis, colon cancer, inferior vena cava filter, heparin

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Introduction

In 1865, Armand Trousseau found that a relationship exists between venous thromboembolic events and malignancy (1). The co-occurrence of such events with malignant lesions is now referred to as Trousseau’s syndrome. In Trousseau’s syndrome, thrombosis cannot be adequately controlled via the administration of a vitamin K antagonist (VKA). The administration of heparin and the control of the underlying cancer are important therapeutic measures; however, the outcomes of such cases are generally poor (2). We herein report the case of a 66-year-old man who developed refractory deep venous thrombosis (DVT), despite receiving anticoagulant therapy with a VKA. There are numerous reported cases of Trousseau’s syndrome and thrombosis due to malignant disease; however, there are no reports of Trousseau’s syndrome involving refractory deep venous thrombosis.

A 66-year-old man presented with swelling of the left lower leg. Twelve years previously, he had undergone the installation of an inferior vena cava (IVC) filter due to DVT of the right leg. Anticoagulant therapy using a VKA was initiated, which resulted in the remission of his DVT. A physical examination, whole-body computed tomography (CT), and laboratory tests were performed but did not show any evidence of malignant disease or a predisposition to thrombosis at this time. Approximately 6 months before the current admission, he decided - of his own volition - to stop taking the VKA. Lower extremity venous ultrasonography performed after the cessation of the VKA revealed acute thrombosis from the left external iliac vein to the lower leg. An acute exacerbation of venous thrombosis due to the discontinuation of VKA therapy was suspected. The oral administration of the VKA was therefore resumed, and a continuous infusion of unfractionated heparin was initiated. At 1 week after admission, the patient’s prothrombin time-

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international normalized ratio (PT-INR) was prolonged to approximately 2.0; thus, the administration of heparin was terminated. The edema of the lower extremities resolved after these treatments. However, at 1 week after discharge the patient became aware of swelling of his bilateral lower extremities. Blood tests conducted on admission showed mild anemia (hemoglobin: 12.4 g/dL) and high lactate dehydrogenase (325 IU/L) and carinoembryonic antigen (CEA, 9.2 ng/mL) levels. The patient’s PT-INR was also markedly prolonged to 5.84 during oral VKA therapy, and his D-dimer level had risen to 12.7 μg/mL. No significant abnormalities related to a predisposition to thrombosis or collagen disease were noted (Table). Chest radiography, electrocardiography, and echocardiography did not reveal any significant findings. Lower extremity venous ultrasonography revealed thrombotic occlusion of the region from the inferior vena cava to the distal part of the femoral vein on the right side and thrombotic occlusion of the region from the inferior vena cava to the popliteal vein on the left side. Furthermore, contrast-enhanced CT showed large thrombi both within and on the proximal side of the IVC filter (Fig. 1). While no signs of pulmonary embolization were noted, a metastatic liver tumor was found in segment S8 of the liver (Fig. 2A). Colonoscopy showed a hemorrhagic type 2 advanced tumor in the descending colon (Fig. 2B). Pathologically, the tumor was diagnosed as an intermediate-to-well-differentiated adenocarcinoma. The patient was therefore diagnosed with descending colon cancer and liver metastasis complicated by Trousseau’s syndrome. Apart from DVT, no other types of thromboembolism were observed.

We initiated anticoagulant therapy with unfractionated heparin on the day of admission (Day 1). On Day 2, we implanted an additional retrievable IVC filter in the upper renal vein as it was necessary to discontinue anticoagulant therapy.

**Table.** Patient’s Laboratory Data (Obtained during Vitamin K Antagonist Treatment).

| Hematology    | Biochemistry       | Coagulation |
|---------------|--------------------|-------------|
| WBC 79 ×10⁹/μL | TP 7.1 g/dL        | PT-INR 5.84 |
| RBC 427 ×10⁹/μL | T-Bil 0.55 mg/dL   | APTT 51 sec |
| Hb 12.4 g/dL   | AST 20 IU/L        | D-dimer 12.7 μg/mL |
| Ht 37.7 %      | ALT 41 IU/L        | Anti-CLAb <8 U/mL |
| Pkt 32.9 ×10⁹/μL | LDH 325 IU/L      | LAC 0.94    |
| Serology       | BUN 11.9 mg/dL     | AT-III 115 % |
| CRP 0.17 mg/dL | Cr 0.94 mg/dL      | PIC 0.8 μg/mL |
| ANA <40 Fold   | Na 142 mEq/L       | TAT 3.4 ng/mL |
| CEA 9.2 ng/mL  | K 4.0 mEq/L        | Protein C 57 % |
| AFP 3.2 ng/mL  | Cl 106 mEq/L       | Protein S 73 % |

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Pkt: platelet, CRP: C-reactive protein, ANA: antinuclear antigen, CEA: carinoembryonic antigen, AFP: alpha-fetoprotein, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Anti-CLAb: anticardiolipin antibody, LAC: lupus anticoagulant, AT-III: antithrombin III, PIC: plasmin-α₂-plasmin inhibitor complex, TAT: thrombin antithrombin complex

**Figure 1.** Contrast-enhanced computed tomography performed on admission. Deep venous thrombosis was detected in both legs, and a large thrombus (yellow arrow) was found on the patient’s upper inferior vena cava filter.

**Figure 2.** (A) A metastatic liver tumor (yellow arrow) was detected on contrast-enhanced computed tomography (upper: early phase, lower: delayed phase). (B) Descending advanced colon cancer was detected by colonoscopy.
Figure 3. The changes in the patient’s D-dimer and CEA levels. CEA: carcinoembryonic antigen

Figure 4. The changes in the large thrombus (yellow dashed line) on the inferior vena cava filter (yellow arrow) after heparin-based anticoagulant therapy.

during the perioperative period. We performed surgery to treat the patient’s descending colon cancer on Day 8 and the metastatic liver tumor on Day 50; postoperative chemotherapy was also administered. The tumors were successfully controlled by surgery and chemotherapy, and the subcutaneous injection of heparin calcium (20,000 units/day) was continued. The patient’s D-dimer and CEA levels gradually decreased (Fig. 3). Serial contrast-enhanced CT confirmed that the large thrombus that adhered to the proximal side of the IVC filter and the venous thrombus on its distal side had both regressed (Fig. 4). On Day 199, we tried to retrieve the IVC filter but failed due to adhesion. At 1 year after the diagnosis of Trousseau’s syndrome, the patient remains alive without any recurrence of his thrombosis or cancer.

Discussion

Clinically, the complication of a malignant neoplasm by venous thrombosis is known as Trousseau’s syndrome (3). Regarding malignant neoplasms, in addition to mechanically compressing or damaging the local blood vessels, the cells of such tumors also produce and release various products that induce platelet aggregation and promote coagulation to cause systemic hypercoagulability (4). In previous studies, the incidence of thrombosis in cancer patients ranged from 1-11% (5), and it is considered to be high in gastrointestinal, gynecological, pancreatic, and lung cancer - and histologically, in adenocarcinoma, particularly mucin-producing adenocarcinoma (6). Embolisms due to arterial thrombosis or thromboendocarditis as well as venous thrombosis are often encountered in cases of Trousseau’s syndrome (7). During the treatment of Trousseau’s syndrome, it is important to control the malignant tumor and to provide immediate anticoagulant treatment.

In the present case, the cause of the lower extremity thrombosis that arose 12 years previously was unclear. At that time, an IVC filter was installed, and continuous VKA treatment was prescribed. The recent exacerbation of the patient’s venous thrombosis, was initially considered to have been caused by the cessation of the VKA therapy; thus, anticoagulant therapy was restarted. However, the patient soon developed refractory venous thrombosis (i.e., his condition
was aggravated despite the effects of VKA being sufficient. With the exception of D-dimer elevation, no significant findings related to coagulation, fibrinolysis markers, or collagen disease were detected during various examinations; thus, a malignant neoplasm was suspected, which led to a diagnosis of Trousseau’s syndrome. In addition to the exacerbation of the patient’s lower extremity venous thrombosis, this case - in which a giant thrombus was found to have adhered to a previously installed IVC filter during a CT examination - involved particularly interesting imaging findings. While anticoagulant therapy (continuous infusion of unfractionated heparin sodium) was initially administered, a new IVC filter had to be placed on the proximal side of the thrombus, as it was necessary to suspend the anticoagulant therapy during the perioperative period. After colectomy and hepatectomy had been performed to treat the patient’s cancer, the subcutaneous injection of unfractionated heparin calcium was started, and an appropriate activated partial thromboplastin time was successfully maintained with a dose of 20,000 units/day. Although the evidence concerning the efficacy of anticoagulant therapy in Trousseau’s syndrome is still insufficient, low molecular weight heparin has been reported to be more effective than unfractionated heparin as an initial treatment during the early period after the onset of the disease (8) and to be more effective than VKA or non-vitamin K oral anticoagulants (NOACs) in the subacute period (9). Various mechanisms have been reported to cause tumor-related thrombus formation; however, VKA and NOACs are not considered to be of great clinical use against such thrombi, because it is difficult to inhibit the pathways of thrombus formation with these agents. On the other hand, heparin’s anticoagulant effects occur via various mechanisms of action, including: 1) the activation of antithrombin, heparin cofactor II, and protein C inhibitor; 2) the inhibition of factor Xa; 3) the inhibition of the binding of mucin secreted by adenocarcinoma cells to P-selectin or L-selectin; and 4) the promotion of the secretion of tissue factor pathway inhibitor from the vascular endothelium. These heparin-specific mechanisms of action can contribute to the control of thrombosis in Trousseau’s syndrome (4). The evidence concerning the efficacy of anticoagulant therapy in the chronic period is insufficient, and there is concern that the protracted use of unfractionated heparin is associated with a greater risk of hemorrhagic events and heparin-induced thrombocytopenia in comparison to low molecular weight heparin treatment. However, we decided to treat the patient using unfractionated heparin because the use of low molecular weight heparin in patients with Trousseau’s syndrome is not covered by the Japanese medical insurance system. Fortunately, by performing careful dose adjustments, adverse events were avoided, the progressive regression of the thrombi was confirmed, and no new arterial or venous thromboembolism occurred. Although there have been a number of reports about cases in which Trousseau’s syndrome was diagnosed based on the presence of an arterial or venous thromboembolism, cases such as ours - in which Trousseau’s syndrome was diagnosed after the exacerbation of existing venous thrombosis led to a refractory condition - are considered to be rare.

Conclusion

We reported a case in which the development of refractory venous thrombosis led to a diagnosis of Trousseau’s syndrome. A malignant neoplasm should be suspected if venous thrombosis is aggravated despite the appropriate use of a VKA. The prognosis of such patients can be improved via cancer control and heparin-based anticoagulant therapy.

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

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