Massive pulmonary embolism in a woman with leiomyomatous uterus causing pelvic deep venous thrombosis

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Deep venous thrombosis (DVT) is a serious illness sometimes causing death due to acute pulmonary thromboembolism (PTE). Blood stasis of the pelvic vein is a major etiologic factor for DVT. Occasionally a large myomatous uterus can cause compression of the pelvic venous system leading to DVT. We describe a very rare case of massive pulmonary embolism in a 39-year-old woman with multiple uterine myomas and no other recognized risk factors for PTE and DVT. The patient was successfully treated with thrombolytic and anticoagulation therapy associated with total hysterectomy.

Key words: Heparin resistance; Pulmonary embolism; Uterine leiomyoma.

Introduction

Intravascular deep venous thrombosis (DVT) is a serious illness that sometimes causes death due to acute pulmonary thromboembolism (PTE). DVT has been reported to be caused by pregnancy, surgical procedures, long-term bed rest, bone fractures, cancer, antiphospholipid syndrome, use of oral contraceptives, and long-haul air travel1-4. Obesity is not a clear risk factor1. Very rarely a large myomatous uterus can determine a compression of the pelvic venous system causing DVT5-7. However to the best of our knowledge there are only a very few English language previous reports of PTE associated with uterine myomas8,9. We report an additional case of massive pulmonary embolism in a 39-year-old woman with multiple uterine myomas and no other recognized risk factors for PTE and DVT. The patient was successfully treated with thrombolytic and anticoagulation therapy associated with total hysterectomy. No relapse has been observed after a 16-month follow-up.

Case report

A 39-year-old woman was admitted to our Department for acute dyspnea and palpitation onset associated with pain and swelling of the right leg. The patient was nulliparous, non-smoker, and denied alcohol or illicit drug use. No history of oral contraceptive use, prior surgery, as well as a personal or family history of coagulopathies were documented. During the 5 months prior to admission, she has been reporting recurrent right leg swelling and menorrhagia that was not investigated by a gynecologist. On admission the patient was dyspnoic, her pulse rate was 104 b/min, respiratory rate 36 breaths/min, blood pressure 140/80 mmHg. Breath sounds were normal, and cardiac examination was not remarkable. A unilateral edema of the right ankle and calf was noted as well as a positive Homan’s sign of the right leg. Her body mass index was 35.7 kg/m2. Due to her large abdomen circumference no masses were palpable on the lower abdomen. Arterial blood gas analysis (room air) showed: PaO2 69 mmHg, PaCO2 33 mmHg, pH 7.45, HCO3− 26.5 mEq/L. An ECG revealed normal sinus rhythm. Chest X-ray showed a clear lung field without cardiomegaly. Laboratory findings revealed a hemoglobin level 8.9 g/dL with indices demonstrating an iron deficiency anemia, platelet count 293 000/mm3 and a normal coagulation profile. However, since D-dimer levels were elevated (988 µg/L), a pulmonary embolism was suspected. A spiral computed tomography (CT) of the chest with contrast medium showed tapering of the right pulmonary artery and a normal left pulmonary artery. Abdominal CT scan showed an enlarged right shifted uterus (Fig. 1) with three voluminous lesions (probably referred to myomas) determining compression on the right pelvic veins. At Doppler flow ultrasonography, a thrombus was found in the right leg at the level of the popliteal vein. On the basis of these findings anticoagulation therapy was started with intravenous heparin (1100 U/hour) and oral warfarin (2 mg/day).

However, during the days following admission, the patient required > 40 000 U/24 hours (up to 1800 U/hour) heparin to prolong the activated partial thromboplastin time added to the therapeutic range. On day 4, despite intensive
and prolonged anticoagulation, an acute dyspnea relapse, associated with tachypnea, hypotension, pleuritic chest pain, and jugular vein distension was observed. Arterial blood gas analysis (room air) showed: PaO₂ 44 mmHg, PaCO₂ 29.9 mmHg, pH 7.48, HCO₃⁻ 22.3. The ECG revealed inverted T waves in leads V₁-V₄, while a transthoracic echocardiogram revealed a dilated and hypokinetic right ventricle with a 68 mmHg pulmonary artery systolic pressure calculated using the Bernoulli formula. An urgent chest CT scan showed the presence of “saddle” emboli at the bifurcation of the main right and left pulmonary arteries (Fig. 2). The abdominal CT scan also showed a proximal deep vein thrombosis extended to the right femoral and external iliac veins. A catheter-directed thrombolytic therapy with intrapulmonary artery infusion of recombinant tissue plasminogen activator plus urokinase was performed. This procedure was associated with mechanical thrombus fragmentation and insertion of an inferior vena cava filter. After this treatment the patient’s respiratory status dramatically improved, and approximately 24 hours later pulmonary angiography showed a bilateral clot resolution.

Histologic examination showed uniform, benign cells consistent with leiomyomata.

The patient’s clinical conditions definitively improved and she was discharged without symptoms of respiratory impairment on hospital day 38. No relapse has been observed after a 16-month follow-up.

Discussion

Although DVT and PTE are known to be complications of gynecologic surgery, particularly during hysterectomy¹⁰, hysterectomy performed to treat thromboembolic disease is a very rare phenomenon. Large uterine tumors, such as leiomyoma, can cause a compression of the surrounding structures and cause various clinical syndromes, such as hydroureter and hydronephrosis, mesenteric vein thrombosis, acute intestinal gangrene, and cases of acute abdomen¹¹,¹². However, a large leiomyomatous uterus occasionally can determine DVT due to the pelvic venous system stasis secondary to compression⁵-⁷. The occurrence of PTE secondary to DVT and uterine myoma has been reported only twice in the English literature⁸,⁹.

Myomas are rare before menarche, often enlarge during pregnancy, and diminish in size following menopause or castration, which is accompanied by a significant reduction in circulating estrogen. This is why the probability of intraperitoneal organ compression by uterine myomas is particularly high in the reproductive period. In fact, as confirmed by literature data, an association of DVT or PTE with myomatous uterus occurs in pre-menopause patients (range 39-51 years⁸,⁹).
In the classic triad of Virchow, the factors of stasis, disruption of the vascular endothelium and changes in the coagulation pathways have all been recognized as risks for DVT developing. Some recent experimental reports of women with uterine myomas and DVT were complicated by risk factors, such as high-dose norethisterone acetate, history of venous insufficiency, prior DVT or lower extremity vein stripping. On the contrary in our patient the unique predisposing factor for DVT was the large myomatous uterus that induced chronic venous stasis in the pelvis and lower limbs.

Intravenous heparin is the recommended drug to start anticoagulation in patients with PTE. However, a special feature of this case was the low effectiveness of intravenous heparin during the first days of treatment, a fact that probably favored the recurrence of PTE 4 days after presentation. There is a considerable in vivo variation in response to a fixed dose of heparin among individuals; this is partly due to the pharmacokinetic limitations of heparin, in addition to the difficulties encountered in measuring its desired anticoagulant effect. In the context of venous thromboembolism, heparin resistance is defined as the need for > 35 000 U/24 hours to prolong the activated partial thromboplastin time added to the therapeutic range. Pharmacokinetic limitations are caused by the binding of heparin to plasma proteins including platelet factor 4, fibrinogen, factor VIII and histidine-rich glycoprotein. As many heparin-binding proteins are acute-phase reactants, heparin resistance is often encountered in acutely ill patients, in patients with malignancies, and during pre- or post-partum periods. Heparin resistance has also been associated with drug-induced causes including aprotinin and nitroglycerin (although the latter is controversial), and low antithrombin levels. None of these recognized risk factors for heparin resistance was present in our patient.

Pelvic vein compression by an enlarged myomatous uterus is a strict indication for hysterectomy. However, the existence of PTE may often require thrombolytic therapy and inferior vena cava filters (Table I), and the management of such cases could be more difficult than those without pre-operative DVT. In our case the catheteter-directed thrombolysis associated with embolus fragmentation rapidly reestablished pulmonary blood flow. Catheter fragmentation followed by intrapulmonary thrombolytic infusion is an aggressive technique used to achieve a rapid thrombus resolution, improving hemodynamic conditions in most patients. Recent experimental in vitro and in vivo evidence suggests that, in case of a massive pulmonary occlusion due to an embolus, a vortex proximal to the occluding embolus can form, and any fluids infused proximally to the pulmonary artery occlusion will make only evanescent contact with the thrombus edge, and the fluid is washed into the non-occluded ipsilateral and contralateral pulmonary arteries. After embolus fragmentation the infused fluid is completely carried into the formerly occluded artery. It should be outlined that this technique is not routinely used, and should be considered only when facilities and expertise are readily available. However, our case and some evidence support this practice, especially in cases of massive bilateral life-threatening PTE.

In conclusion we have described a rare case of massive pulmonary embolism due to a large leiomyomatous uterus. The patient was successfully treated with anticoagulation and direct thrombolytic therapy followed by hysterectomy and no relapse occurred during a 16-month follow-up.

Table I. Accepted indications for inferior vena cava filter insertion.

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<tr>
<th>Indication</th>
<th>Contraindications to anticoagulation</th>
<th>Anticoagulation complications</th>
<th>Anticoagulation failure</th>
<th>Recurrent PTE despite adequate therapy</th>
<th>Inability to achieve adequate anticoagulation</th>
<th>Massive pulmonary embolism with residual deep venous thrombus in a patient at risk for further PTE</th>
<th>Free-floating iliofemoral or inferior vena cava thrombus</th>
<th>Severe cardiopulmonary disease and DVT (cor pulmonale with pulmonary hypertension)</th>
<th>Poor compliance with anticoagulation therapy</th>
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<td>DVT = deep venous thrombosis; PTE = pulmonary thromboembolism. From Grassi et al., modified.</td>
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