Pleural Effusion After Spontaneous Abortion in Two Young Women with Essential Thrombocythemia

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Abstract

Essential thrombocythemia (ET) is one of the myeloproliferative disorders characterized by an elevated platelet count and either hemorrhagic or thrombotic tendency. ET in pregnancy may be complicated by recurrent abortion. In this paper, we reported pleural effusion following spontaneous abortion in two young women with ET in the third trimester. Both patient's chest roentgenograms showed pleural effusion. Platelet counts were $1120x10^9$/L and $1200x10^9$/L, respectively. Bone marrow biopsy revealed increased megakaryocytes. Both patient's lung perfusion scans revealed perfusion defects. The platelet count and pleural effusions decreased gradually with hydroxyurea and heparin. To our knowledge, there is no reported case of essential thrombocythemia and spontaneous abortion associated with pleural effusion in the literature.

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Key words: *Essential thrombocythemia, pleural effusion, spontaneous abortion*

Introduction

Essential thrombocythemia, a chronic myeloproliferative disorder (MPD), is predominantly a disease of middle and old age in which the physical signs and symptoms result from a predisposition to both thrombosis and haemorrhage (1). There is no test that can be used to establish the diagnosis of ET with certainty. For these reasons, a set of diagnostic criteria for ET has been proposed (Table 1). ET can also occur in a younger age group in which pregnancies can be very difficult to manage (2). Occurence of ET in pregnancy has been reported to be complicated by recurrent abortion and fetal growth retardation (3-6). Occlusion of large arterial vessels, venous thromboembolic complications and microvascular occlusions are frequent complications in these patients (7). Only one case of pleural effusion without spontaneous abortion has been reported in literature occuring in an elderly woman (8). In this paper, we reported two young female patients with ET who had spontaneous abortions and pleural effusions.

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Table 1. Diagnostic criteria for essential thrombocythemia

1. Platelet count >600,000/μL.
2. Hemoglobin ≤13g/dL or normal red cell mass (males: <36 mL/kg, females: <32 mL/kg).
3. Stainable iron in marrow or failure of iron trial (<1 g/dL rise in hemoglobin after 1 month of iron therapy).
4. No Philadelphia chromosome.
5. Collagen fibrosis of marrow
   a. Absent, or
   b. <1/3 biopsy area without both splenomegaly and leukoerythroblastic reaction.
6. No known cause for reactive thrombocytosis.

Case 1

A 34-year-old multigravida woman (5 gravidities, 2 abortions) was admitted to a community hospital at 32 weeks gestation because of spontaneous abortion, shortness of breath at rest and at minimal exercise and back pain. Her previous pregnancy had ended with a spontaneous abortion after approximately 24 weeks gestation at 27 years of age. Since two weeks prior to admission, the patient had been suffering from dyspnea, diaphoresis and back pain. On admission, the patient had a temperature of 37°C, a heart rate of 112-beat/min^{-1}, and a respiratory rate of 22 per minute. Her blood pressure was 130/80 mmHg. There was no finding of preeclampsia or eclampsia. The notable abnormalities on physical examination were decreased movement of chest wall, respiratory sounds and thoracic vibration besides dullness on percussion on right hemithorax. The chest x-ray showed a normal sized heart and right pleural effusion. The computed tomography (CT) scan revealed right pleural effusion and compression atelectasis (Figure 1). Ultrasonography of abdomen was normal. Trans-oesophageal echocardiography showed slight aortic and mitral valve regurgitation, and diastolic dysfunction of the left ventricule. However, systolic function of left ventricule was normal. No intraventricular or atrial thrombi could be detected. Electrocardiography showed sinus tachycardia. Platelet count was 1120x10^9/L, haemoglobin value 11,4 g/dL, haematocrit 33%, red blood cell count: 4.11x10^6/μL, and white blood cell count 6x10^9/L. Erythrocyte sedimentation rate (ESR) was 70 mm/hour. The urinalysis showed 3+ protein, and 0-2 red blood cells and 5-6 white blood cells on microscopic examination. Biochemistries of blood was normal. Owing to lack of edema, ascites, hypertension, hypoalbuminemia and hypercholesterolemia and the temporary nature of proteinuria, this proteinuria was considered to be due to concentrated urine or functional proteinuria. Serum levels of antitrombin III, protein S and protein C were normal. The perfusion scans of the lung revealed perfusion defects. The perfusion defects were depicted in the middle and lower zones of right lung, ventilation scintigraphy could not be made. Antinuclear antibodies, anti-DNA antibodies, anti-neutrophil cytoplasmic antibodies, antiglomerular basal membrane antibodies, serum IgG anticardiolipin antibody, IgM anticardiolipin antibody and rheumatoid factor were negative. Forced vital capacity (FVC) was 87% predicted, and forced expiratory volume in one second (FEV_1) was 85% predicted. Arterial blood gas values were shown to be normal. Thoracentesis

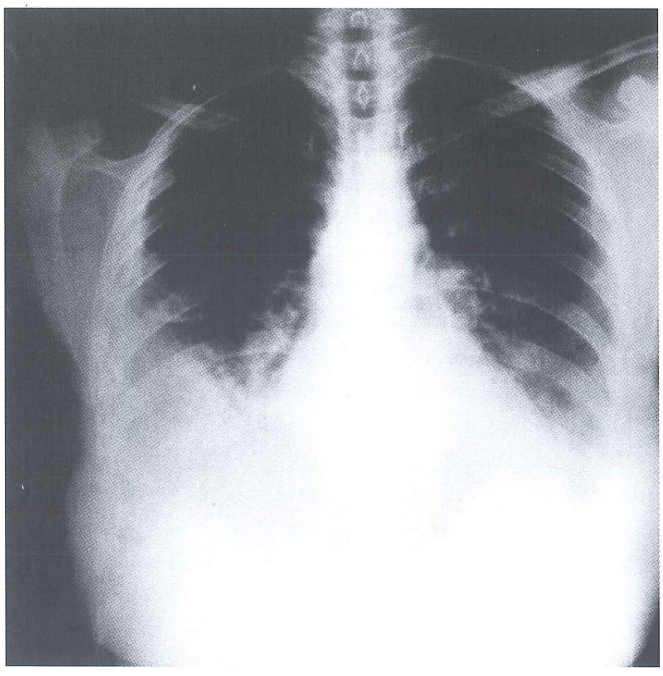

Figure 1. *CT scan: right pleural effusions.*

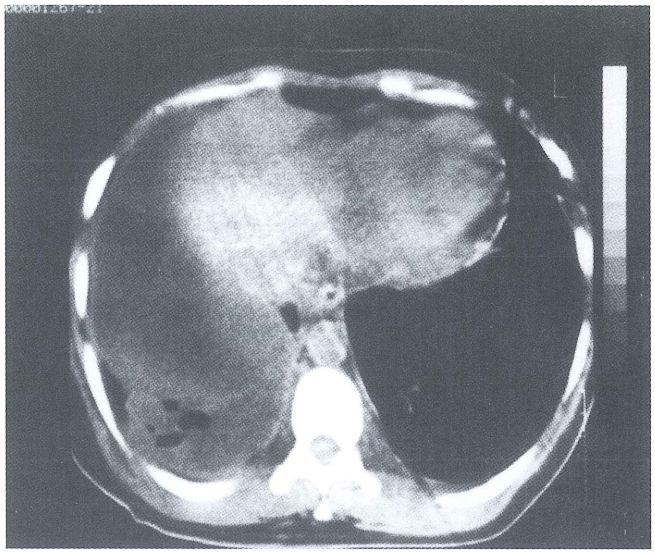

Figure 2. *Clusters of dysplastic megakaryocytes in the bone marrow (Hematoxylin-eosin x 50)*

was performed. White blood cell was $0.7x10^9$/L (56% neutrophil, 42% lymphocyte), red blood cell $0.03x10^{12}$/L, and haemoglobin value 0.3 g/dL in pleural fluid. Examination for malignant cells was negative, as were stains and cultures for bacteria, mycobacteria and fungi. Pleural fluid analysis showed an exudative effusion according to Light's criteria, and diuretics had not been used before thoracentesis. The color of pleural fluid was yellow. Bone marrow biopsy revealed clusters of atypical megakaryocytes and the presence of iron (Figure 2). According to polycythemia vera study group criteria, ET was diagnosed (2). After heparin was started immediately by the intravenous route in therapeutic doses, the patient's condition improved dramatically. Myelosuppressive therapy with hydroxurea was started. During the following days, peripheral platelet counts gradually decreased. One year later after the cessation of drug treatment, the patient was in good health and platelet count was $600x10^9$/L.

Case 2

A 25-year-old primigravida was admitted to the hospital because of dyspnea, haemoptysis, fever, palpitation, back pain and diaphoresis. There had been no complication during her pregnancy until the 20th week. The patient was admitted to the hospital because of spontaneous abortion at 24-week gestation. The temperature was 38°C, the pulse rate was 130/min, and the respiratory rate 30/min. The blood pressure was 110/70 mm Hg. On physical examination, decreased respiratory sounds and thoracic vibration accompanying percussion dullness were remarkable on the left hemithorax, but cardiac examination was normal. The chest x-ray revealed left pleural effusion. Electrocardiog-raphy showed sinus tachycardia. Transoesophageal echocardiographic and Doppler ultrasonographic studies of the lower extremities were normal. The CT scan of the chest revealed bilateral pleural effusions and compressive atelectasis of left lower lobe, but no lymphadenopathy. Haemoglobin value was 8.7 g/dL, haematocrit 25.6%, red blood cell count: $3.35x10^6$/μL,white blood cell $9.3x10^9$/L, ESR 54 mm/hour and the platelet count $1200x10^9$/L. Partial thromboplastin and prothrombin times were normal. On biochemical analysis, total and indirect bilirubin levels were both elevated at 2.4 mg/dL and 2.1 mg/dL, respectively. Serum total protein was 4g/dL, albumin was 1.8 g/dL. But, urinalysis was normal. Due to exudative nature of the pleural fluid and lack of edema and ascites, hypoalbuminemia was not considered as the cause. The probable reason of this hypoalbuminemia may be nutritional deficiency associated with poor social status and pregnancy. The perfusion scans of the lung revealed unilateral perfusion defect in lower zone of the left lung, ventilation scintigraphy could not be made. Antinuclear antibodies, anti-DNA antibodies, anti neutrophil cytoplasmic antibodies, antiglomerular basal membrane antibodies, and rheumatoid factor were all negative. Pleural fluid analysis showed an exudative effusion according to Light's criteria, and no diuretics had not been given before thoracentesis. The color of pleural fluid was yellow. White blood cell was $2.0x10^9$/L (55% neutrophil, 31% lymphocyt, 8.6% monocyt, 2.3% eozinophil), red blood cell $0.03x10^{12}$/L, and haemoglobin value 0.2 g/dl in pleural fluid. All bacteriologic cultures were negative, and cytologic study of pleural effusion was reported to be benign. Pleural biopsy was nonspecific. Bone marrow biopsy revealed increased number of atypical megakaryocytes. Based on these data, ET was diagnosed (2). Hydroxyurea and heparin were started. During the following days, peripheral platelet counts gradually decreased. The patient's condition improved after the treatment. The albumin was also increased to 3.6 g/dL at discharge. One year later after the cessation of drug treatment, the patient was in good health, and platelet count was $585x10^9$/L.

Discussion

Pleural effusion is found in almost 10% of patients who have internal diseases, and the main cause in 30-40% of them is cardiac failure. Among the noncardiac effusions, parapneumonic effusions are the most common at 48%, of which approximately 75% are of bacterial, and 25% of viral origin. Malignant pleural effusions follow with an incidence of 24% of cases, more than half of which are caused by lung or breast cancer. Pleural effusion is secondary to pulmonary embolism in 18% of noncardiac cases, to liver cirrhosis in 6%, and to gastrointesitinal diseases, mainly pancreatitis, in 3% of cases. Idiopathic pleural effusions are seen at 15% (9). Investigators reported that pleural effusion, pulmonary embolism and spontaneous abortion were also seen in antiphospholipid syndrome. But, this syndrome is associated with thrombocytopenia and antiphospholipid antibodies (10,11). Also, postpartum pleural effusion was reported. In a study, the rate of postpartum pleural effusion within 1-24 h of normal delivery was 23 %, but of no clinical significance (12). In our report, the nature of pleural effusions according to Light's criteria was exudative in both patients. Also, diuretic had not been given to the patients, and cardiac size was normal. Any pneumonic infiltration was not seen on chest radiograph and CT scan of the both patients. The biopsy of parietal pleura did not reveal any evidence of malignancy. Antiphospholipid antibodies were negative and thrombocytosis was present. Perfusion

scans of the lung showed perfusion defects in both cases. Thus, pulmonary embolism was considered. However, Doppler ultrasonography of the lower extremities for deep venous thrombosis was normal. For these reasons, pulmonary embolism was the most probable cause of these pleural effusions. ET is characterised by a persistent elevation of platelet count above $0.6x10^{12}$/L, and generally over $10x10^{12}$/L (2) in the absence of reactive thrombocytosis and other MPD. Clinical problems encountered by patients with ET involve either hemorrhage or microvascular thrombosis. Many patients, however, are entirely asymptomatic for long periods of time (13). The arterial thrombotic manifestations of ET in 809 patients from 11 retrospective studies were described as major arterial thrombosis in 20 % and microcirculatory disturbance in 41% of the patients (24 % in extremities and 17% in the cerebral circulation). The incidence of deep venous thrombosis including portal and splenic vein thrombosis in the above-mentioned 809 ET patients was as low as 4 % (14). Placental infarctions due to thrombosis leading to chronic placental insufficiency, intrauterine fetal growth retardation and even fetal death seem to be the most consistent pathological events in pregnant women with ET (15).

Shimomoto, et al., (8) reported bilateral pleural effusions due to pulmonary embolism in a 79-year-old woman with ET. In our cases, there were pleural effusions with findings of pulmonary embolism after spontaneous abortion, and they were pregnant young females. A review of the literature identifying only 34 women with ET concluded that many adverse outcomes during pregnancy were possible; including abortion, intrauterine death, abruptio placentae, fetal growth retardation, and premature delivery (16). Griesshammer et al., (15) reported the rate of abortion 43 % in women with ET. The most of the spontaneous abortions were seen in the first trimester. In Bangerter's study (17), spontaneous abortion rate was 35%. In another study, the rate of abortion was 45% (18). In our cases, according to their medical history, there were abortions in the third trimester. It is possible that these abortions could have been related to ET.

The question about the ideal therapy in these patients remains unresolved, and acetylsalicylic acid, heparin, dipyridamole, busulfan, hydroxyurea, anagrelid, sulfinpyrasone sodium phosphate and interferon-alpha have been suggested. Complete abstention from pregnancy or platelet apheresis before delivery was also suggested (19-21). In all reports, the treatment of ET was given at prepregnancy period. But for our cases, the diagnosis was established following abortion, and hydroxyurea and heparin were started. The symptoms of patients, pleural effusion and platelet counts decreased gradually after the treatment. Anticoagulation therapy was continued for six months.

In conclusion, in case of pleuropulmonary manifestations such as pleural effusions and/or pulmonary infiltrates in pregnant ET patients, pulmonary embolism should be taken into account. Futher diagnostic investigation such as spiral CT, ventilation-perfusion scintigraphy, D-dimer, and Doppler ultrasonography must be done. Anticoagulant therapy may be indicated for cases with suspected thromboembolism to prevent morbidity and mortality.

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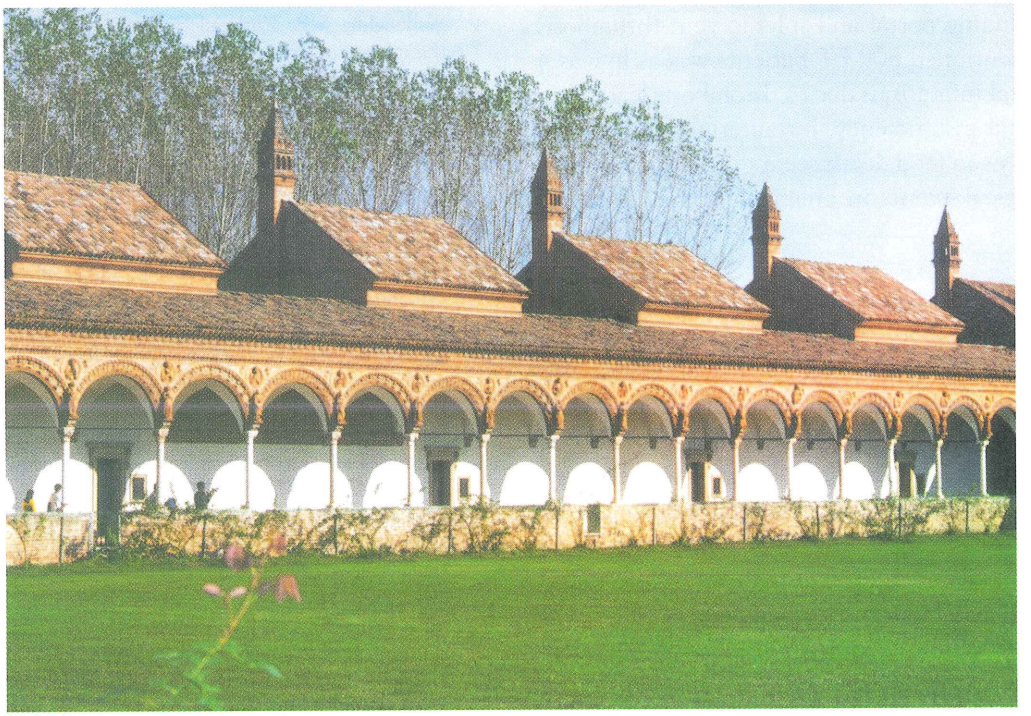

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