

A 53-year-old woman with thrombocytosis and pulmonary embolism

Eftychia Demerouti¹, Athanassios Manginas², Evangelos Leontiadis¹, Theodoros Hatzis³, George Athanassopoulos¹, Konstantinos Mihos⁴, Gregory Pavlides¹

¹Onassis Cardiac Surgery Center, Athens, Greece

²Mediterraneo Hospital, Athens, Greece

³Mitera Hospital, Athens, Greece

⁴Kymi General Hospital, Evia, Greece

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Corresponding author:

Eftychia Demerouti Dr,
Med SC, MD

Onassis Cardiac Surgery
Center

Syngrou Avenue 356

17674 Athens, Greece

Phone: +306947721793

Fax: +302109493336

E-mail: efidemer@otenet.gr

A 53-year-old woman was referred to our cardiology clinic for evaluation of severe exertional breathlessness of 3 months duration, after an episode of pulmonary embolism. Her medical history began in 1995 when the diagnosis of essential thrombocythemia was established, treated with hydroxyurea. The diagnosis was based on bone marrow biopsy. The specimen showed proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. The findings did not meet the World Health Organization (WHO) criteria for polycythemia vera, primary myelofibrosis or other myeloid neoplasm. Splenectomy was performed in 2004. Deep vein thrombosis occurred in 2006 and since then the patient has remained on anticoagulation therapy. Acute myeloid leukemia was diagnosed in 2007 and isolated 20q deletion was identified. A Hickman catheter, which was implanted for chemotherapy (the patient received three courses of anthracycline monotherapy), was removed by the end of 2008 after a first episode of pulmonary embolism.

On the day of the patient's admission, the vital signs were: blood pressure 100/60 mm Hg, heart rate 90 beats/min, respiratory rate 16/min and room air oxygen saturation 92%. Clinical examination was nearly normal and among the laboratory findings, thrombocytosis (600 000/ml) and an increased value of N-terminal pro-brain natriuretic peptide (3221 pg/ml, upper normal limit: 125 pg/ml) were identified. The hemoglobin levels, the leukocytes and the erythrocytes were within normal limits. The liver and renal function were normal.

The electrocardiogram revealed sinus rhythm (102 bpm) with signs of right ventricular hypertrophy. The echocardiogram demonstrated right ventricular dilatation with mild impairment of systolic function, systolic pulmonary arterial pressure at 70 mm Hg and a 3 cm × 2 cm mural mass, adjacent to the inferior vena cava. A cardiac magnetic resonance image identified the thrombus in the right atrium but also confirmed the reduced systolic function of the dilated right ventricle. The 6-minute walk distance was 297 m, associated with reduction of oxygen saturation from 92% to 71%.

Right heart catheterization (RHC) was performed with the following values: mean pulmonary arterial pressure (mPAP) 40 mm Hg, pulmonary artery systolic pressure (PASP) 64 mm Hg, pulmonary capillary wedge pressure (PCWP) 7 mm Hg, cardiac output (CO) 4.1 l/min, and pulmonary vascular resistance (PVR) 6.7 WU.

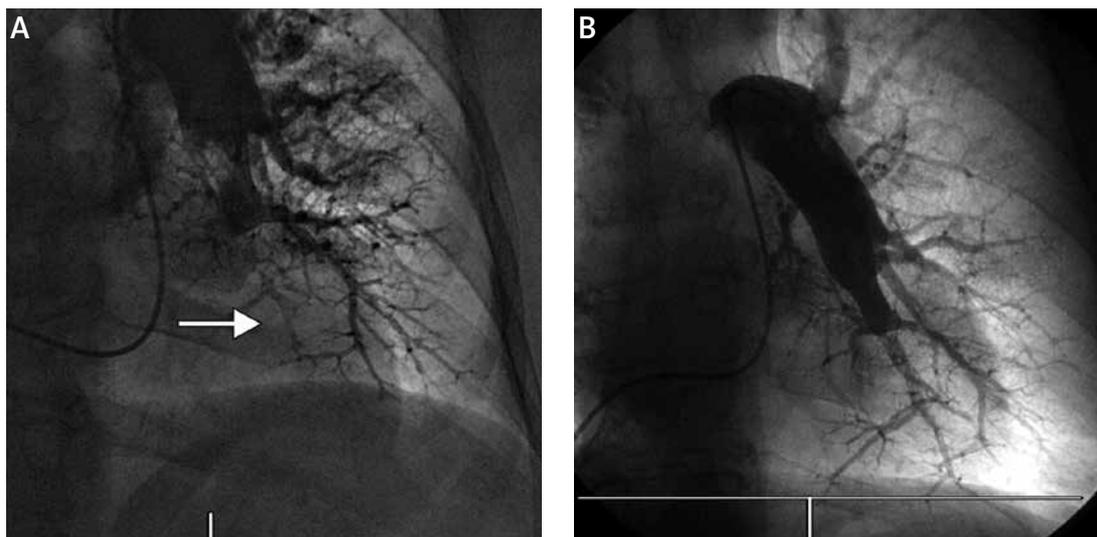


Figure 1. A – Pulmonary angiography. B – Pulmonary angiography 1 year later

Pulmonary angiography was performed and bilateral occlusions in lobar, segmental and sub-segmental arteries were identified. Pulmonary angiography for the left lung (Figure 1 A) revealed a thrombus in the pulmonary artery for the left lower lobe and thrombi with calcification, suggesting the chronicity of the disease. The ventilation/perfusion lung scan (Figure 2) identified two large mismatch defects in the right superior and the left inferior lobe.

The patient was referred for pulmonary endarterectomy in combination with surgical excision of the right atrial thrombus. Due to severe comorbidities, she was deemed an unsuitable surgical candidate, and after hematological assessment, she was treated with busulfan, fondaparinux and bosentan.

Twelve months later, a second pulmonary angiography (Figure 1 B) demonstrated the recanalization of the pulmonary artery for the left lower lobe. The perfusion improvement, attributed to recanalization, was verified in a second ventilation/perfusion lung scanning. A new RHC revealed mPAP at 28 from 40 mm Hg, CO 4 l/min and PVR 5.2 WU.

Two years after the initial presentation, the patient is in functional status WHO class I, with a 6-minute walk distance of 459 m. On echocardiogram the size of the right atrial thrombus decreased (2 × 1.5 cm) and the PASP was estimated at 40 mm Hg, with normal right ventricular systolic function.

Pulmonary hypertension is a severe pathophysiologic and hemodynamic disorder characterized by elevated pulmonary artery pressure and pulmonary vascular resistance. It is a progressive disease leading to right ventricular failure.

Chronic thromboembolic pulmonary hypertension (CTEPH), an infrequent form of pulmonary hypertension, is characterized by intraluminal thrombus organization and fibrous stenoses, or complete

obstruction of pulmonary artery branches, and represents the only curable form of the disease [1].

A majority of patients (50–70%) demonstrate persistent abnormalities on computed tomography (CT) pulmonary angiography (CTPA) several weeks after an acute pulmonary embolism, even if adequately anticoagulated. Unresolved pulmonary emboli after an embolic event cause vascular obstruction of the vessel lumen, and CTEPH occurs in up to 4% of patients after an acute pulmonary embolism [2]. The recurrence of embolism is estimated as 2.5% to 7% of adequately treated pulmonary embolic events. Ventilation/perfusion lung scanning is proposed to be performed 3 months after an episode of PE in patients with persistent pulmonary hypertension, to exclude CTEPH. Pulmonary angiography is the gold standard for CTEPH diagnosis and all CTEPH patients must be evaluated for pulmonary endarterectomy, which represents the treatment of choice [3]. In case of inoperable CTEPH, medical therapy remains the only option, based on pulmonary arterial hypertension specific drug therapy [3].

The prevalence of a right heart thrombus in the setting of an acute pulmonary embolism is 7–18% [4]. Mobile right heart thrombi are potentially hazardous because they can embolize at any time, with a high risk of recurrent pulmonary embolism and a death rate in the range 80–100%. Immediate therapy is advised, although the issue of choice between thrombolysis and surgery has not been resolved [5].

Essential thrombocytosis represents a myeloproliferative neoplasm (MPN), with a 5-year survival of 74% to 93% and a 10-year survival of 61% to 84% [6]. The possibility of progression to either acute myeloid leukemia or myelofibrosis is unusual [7] but exists. Essential thrombocythemia has an inherent tendency to evolve into acute leukemia, even in the

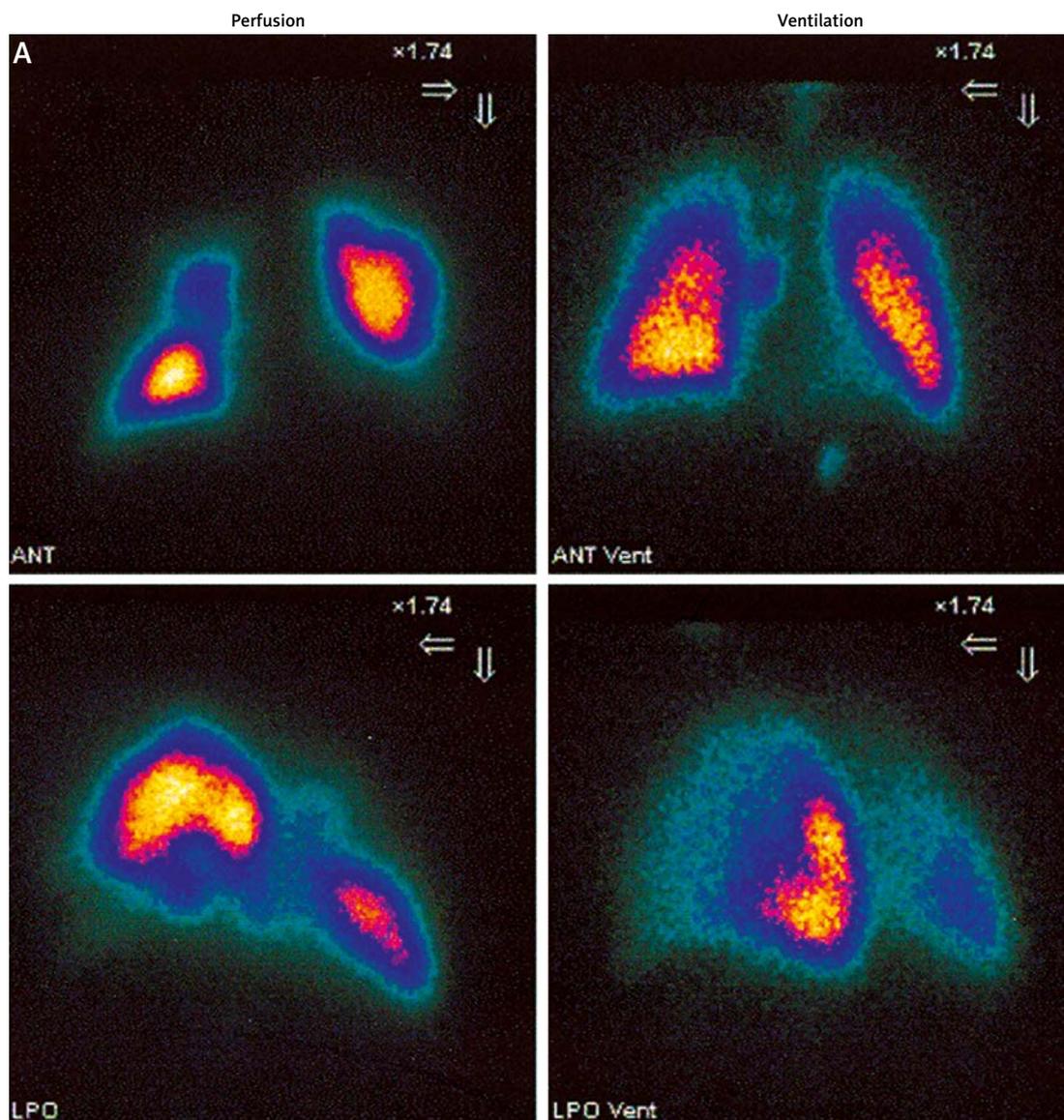


Figure 2. A – Lung V/Q scan

absence of specific therapy. The risk of acute myeloid leukemia development after MPN diagnosis is significantly associated with high exposures of radioactive phosphorous (P(32)) and alkylators, but not with hydroxyurea treatment, which our patient received [7]. Pulmonary hypertension is the most prominent cardiac pathology in patients with chronic myeloproliferative neoplasms [8]. Thromboembolic episodes are the most common complications, with an incidence of 15%, due to an inappropriate state of platelet activation. It has been hypothesized that control of platelet count might play an important role in the progression of CTEPH; however, there is no clear evidence of symptom amelioration or pulmonary hypertension reversibility. Our patient, 2 years after the diagnosis of CTEPH, remains on anticoagulation therapy with subcutaneous fondaparinux (a direct thrombin inhibitor) and not heparin, thus avoiding heparin-induced thrombocytopenia [9], with the aim of lifelong treatment, due

to the history of recurrent pulmonary embolism. Six months ago, the patient achieved complete remission of thrombocythemia (platelet count at a level lower than 300 000/ml) and treatment with busulfan was temporarily discontinued. Pulmonary hypertension specific therapy with bosentan continues, as it is well tolerated and diagnosis of untreated CTEPH is well established.

In conclusion, the diagnosis of CTEPH should be suspected in case of a non-massive pulmonary embolism associated with increased systolic pulmonary arterial pressure. Evaluation concluding pulmonary angiography in case of persistent pulmonary hypertension represents the gold standard for the diagnosis of CTEPH [3]. Adequate anticoagulation therapy and evaluation for pulmonary endarterectomy from specialized centers are indicated [10]. In cases of massive pulmonary embolism, mobile right atrial thrombi should be immediately treated [6], but in other cases ther-

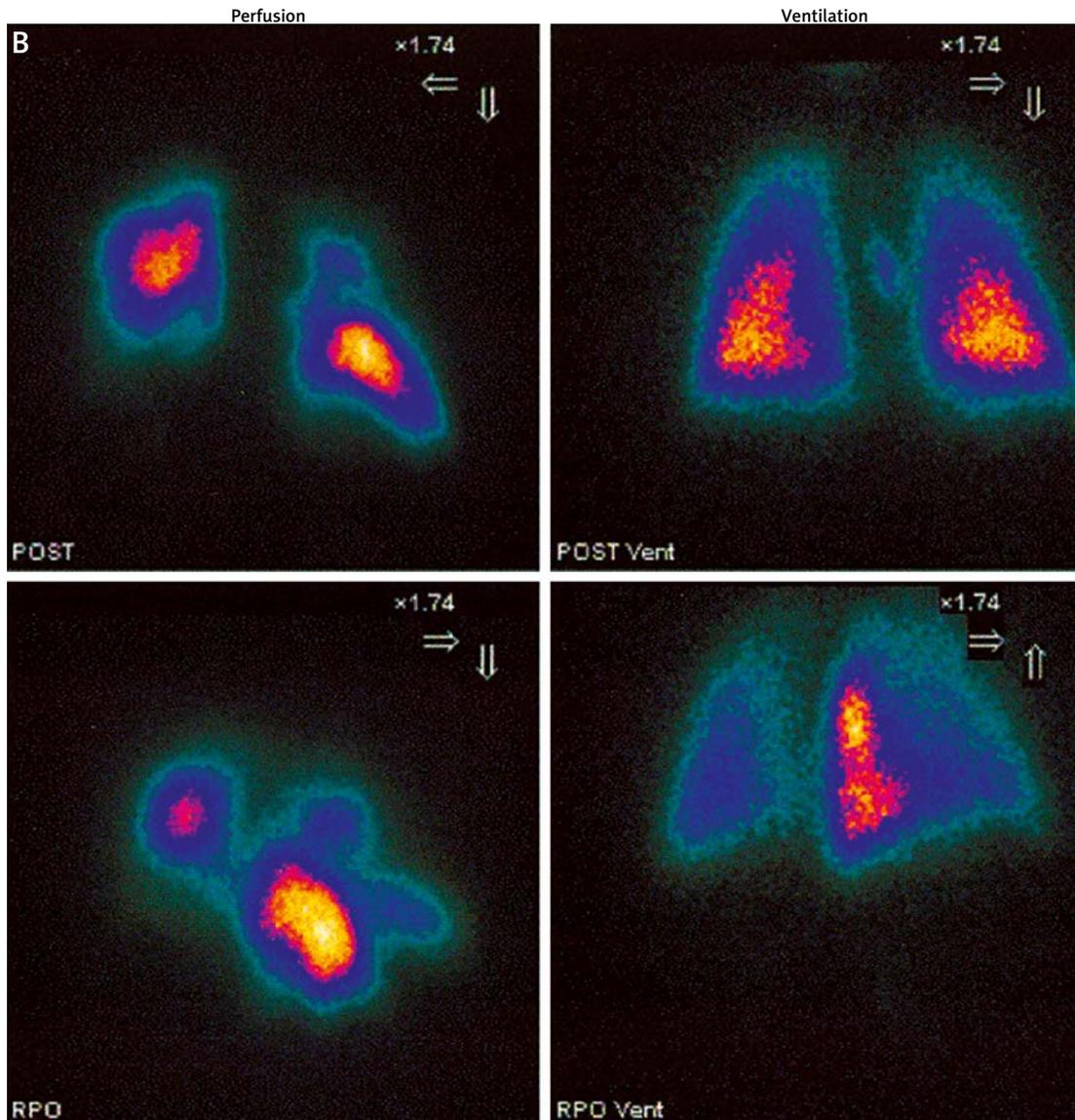


Figure 2. B – Lung V/Q scan

apeutic approaches have to be individualized and a multidisciplinary approach is necessary when comorbidities are present.

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