

Pulmonary hypertension and multiple myeloma

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Abstract: The relationships between pulmonary hypertension multiple myeloma, monoclonal protein and finally drug treatment of plasma cell diseases are complex and not fully elucidated. Pulmonary hypertension has been reported as a rare complication of multiple myeloma (MM), more frequently in patients with POEMS syndrome. More recently pulmonary hypertension has been described during thalidomide treatment for refractory MM. We report a case of severe pulmonary hypertension associated with MM, pleural and cardiac amyloidosis. A revision of literature follows.

Keywords: Multiple Myeloma, Pulmonary Hypertension, Thalidomide

1. Introduction

Pulmonary hypertension comprise a group of diseases characterized by an increase in pulmonary vascular resistance leading to right ventricular failure. The relationships between pulmonary hypertension multiple myeloma, monoclonal protein and finally drug treatment of plasma cell diseases are complex and not fully elucidated. Pulmonary hypertension has been reported as a rare complication of multiple myeloma (MM) (1-3) , more frequently in patients with monoclonal plasma cell dyscrasia and a rare syndrome characterized by peripheral neuropathy, edema, skin changes (mainly hyper pigmentation) , hepatomegaly and endocrinopathy (POEMS syndrome) (4-6) . More recently pulmonary hypertension has been described during thalidomide treatment for refractory MM (7-8). We report a case of severe pulmonary hypertension associated with MM, pleural and cardiac amyloidosis . A revision of literature follows.

2. Case Report

65 years old man, heavy smoker for 30 years. In the two years preceding referral to our Department he began treatment with ramipril for arterial hypertension. In march 2008 he had an episode of exertion dyspnea with diaphoresis after an heavy effort (he had to walk rapidly with weights to catch a train). Exercise stress test and thallium 201 exercise scintigraphy did not disclose inducible myocardial ischemia. In the following months he began to complain worsening exertion dyspnea and he came to our observation in January

2010. At physical examination the patient was tachypnoic (22 breaths/min) . Cardiac physical examination did not disclose significant abnormalities. Jugular vein were distended. Liver was enlarged. Diffuse percussory hyperphonusis was found at chest examination. ECG showed sinus rhythm 92 beats/min, normal AV conduction and negative t waves V1-V4. The echocardiogram showed a mild hypertrophic left ventricle (septum and posterior wall thickness 11.5 mm) without segmental wall motion abnormalities and preserved E/A ratio. The right ventricle was dilated (36mm). An high velocity tricuspid regurgitation jet was detected with an estimated systolic pulmonary pressure of 80 mmHg Inferior vena cava was dilated (24 mm) without breathing related changes. Leg vein thrombosis was ruled out by Doppler examination. Chest X ray and lung TC showed mild emphysema and interstitial thickening. Blood gas analysis showed an isolated hypoxemia (pO₂ 62 mmHg). At laboratory examination was found a mild polyglobulia (Hb= 15.2 g/dl, MCV= 90 μm³) . Functional respiratory tests were compatible with a mixed obstructive –restrictive ventilatory impairment. Due to history of heavy smoking, chest X ray and TC abnormalities, hypoxemia and obstructive – restrictive ventilatory impairment in absence of other detectable causes for pulmonary hypertension a tentative diagnosis of cor pulmonale was made with prescription of long term oxygen treatment and bronchodilators.

A clinical control three months later showed a mild improvement of functional capacity and a decrease of pulmonary pressure (estimated systolic pulmonary pressure at Doppler echocardiography 50 mmHg).

In August 2010, despite ongoing oxygen therapy, he noticed a worsening of exertion dyspnea which finally developed after walking less than one hundred meters. Patient was tachycardic, tachypnoic. At chest examination basal right percussory dullness with abolition of respiratory murmur was appreciable. Patient was hospitalized. Echocardiography confirmed a right ventricular pressure overload with systolic pulmonary pressure > 80 mmHg. LV examination showed a diastolic pattern of abnormal relaxation. LVEF was preserved. At gross examination pleural fluid was limpid, citrine. Fluid examination did not disclose cytological abnormalities, protein and LDH concentrations were elevated. Chest CT scan was inconclusive. Diuretics were added to treatment with mild clinical improvement. A mild IgG lambda monoclonal peak was detected at serum immune electrophoresis with traces of lambda Bence Jones proteinuria.

In the first months of 2011 repeated thoracentesis were needed for recurrence of right pleural effusion until in April a pig-tail was positioned to drain fluid. An average daily removal of 150-200 ml was recorded in the following months.

In August 2011 a new ecocardiographic examination showed an increase of left ventricular wall thickness with increased echogenicity of septal myocardium and spotted "granular sparkling" appearance. A progression of LV diastolic impairment was demonstrated by a Doppler restrictive pattern. Pulmonary artery pressure was not significantly changed. Cardiac amyloidosis was suspected.

Right heart catheterization confirmed the existence of a mixed pre- post capillary pulmonary hypertension (pulmonary artery pressure 75/35 mmHg, mean 48 mmHg, PWP 21 mmHg) with increase of end-diastolic right ventricular and atrial pressure. Cardiac index was decreased (2.8 l/min/m²).

Patient was hospitalized for further clinical evaluation. Laboratory examination was unremarkable with exception of a mild hypoproteinemia and increased NT-pro BNP levels. Serum immunoelectrophoresis confirmed an IgGλ monoclonal and urine electrophoresis a Bence-Jones λ proteinuria. B2 microglobulin (3.3 mg/dl) and uric acid (8 mg/dl) were increased. Bone marrow biopsy revealed 30% monoclonal plasma cells (CD138+, k-, λ+). with perivascular amyloid deposition. Periumbelical fat biopsy with examination at polarized light after red congo staining showed a deposition of amyloid. Immunohistochemical examination was λ+, RC+, A protein (-). component was identical to serum light chain.

Treatment with VAD (vincristine 0,4 mg plus adriamycin 9 mg/m² and dexamethasone 40 mg i.v. days 1-4, 9-12, 17-20) was started.

Clinical conditions initially improved after chemotherapy, however in the winter of 2011 a refractory heart failure developed and the patient died a few days later.

3. Discussion

3.1. Multiple myeloma and Pulmonary Hypertension

At present few cases of pulmonary hypertension associated with MM have been reported in literature (1-2). We had previously described a case of a young male in whom transient severe pulmonary hypertension has been the symptom of onset of MM (9). The early and impressive response to the treatment with steroids and chemotherapy agents inducing a substantial decrease of circulating plasma cells, associated with a sudden decrease of pulmonary artery pressure (about 40 mmHg in systolic pulmonary artery pressure in 10 days), suggests that vasoactive mediators released by neoplastic cells, other than increase plasma viscosity, may have played a role in the pathogenesis of transient pulmonary hypertension. Pulmonary arterial hypertension secondary to vascular deposition of amyloid in the lungs is exceptional and is related to severe diffuse vascular deposition of amyloid with mild involvement of the alveolar septa (10). Shiue and McNally (1) described severe pulmonary hypertension in one patient with myeloma who had a diffuse lung lesion. Open lung biopsy revealed severe diffuse vascular deposition of amyloid with mild involvement of the alveolar septa. In the case discussed above at first examination a severe pulmonary hypertension was detected in absence of significant abnormalities of left ventricular function. An IgG lambda multiple myeloma was diagnosed eighteen months later with demonstration of cardiac, pleural and pulmonary vessel amyloidosis. We cannot rule out that abnormalities of diastolic function due to cardiac amyloid deposition may have contributed to increased pulmonary artery pressure in our patient however pulmonary wedge pressure was only slightly increased at right heart catheterization.

Deep venous thrombosis (DVT) and pulmonary embolism are not a rare complication of neoplastic diseases leading sometimes to severe thromboembolic pulmonary hypertension (11-12). Clinical presentation of chronic thromboembolic hypertension follow two main patterns: the first include progressive dyspnea on exertion, hemoptysis, and/or signs of right heart dysfunction including fatigue, palpitations, syncope, or edema after a single episode or recurrent episodes of overt pulmonary embolism. The development of clinical signs may last from a few months to many years. Three fourth of patients however have no history of acute pulmonary embolism. The clinical course is often indistinguishable from other forms of severe pulmonary hypertension, especially idiopathic pulmonary arterial hypertension. An hypercoagulable state has been described in patients with multiple myeloma; recently Zangari et al (13) showed a resistance to activated protein C in absence of factor V Leiden mutation in patients with myeloma. This resistance is associated with a four folds increase of DVT and pulmonary embolism. Interference of immune globulins with on fibrin structure, pro-coagulant antibodies, endothelial damage due to the effects of inflammatory cytokines released by neoplastic cells are

additional pro coagulant factors in multiple myeloma (14).

3.2. POEMS Syndrome and Pulmonary Hypertension

Monoclonal plasma cell dyscrasia has been associated with pulmonary hypertension in patients with a rare syndrome characterized by peripheral neuropathy, edema, skin changes (mainly hyperpigmentation), hepatomegaly and endocrinopathy. For this clinical condition the acronym POEMS was suggested by Bardwick in 1980 (15).

Twenty five percent of patients with POEMS followed up during a 10-year period developed pulmonary hypertension (4). A recent review suggested that the incidence of pulmonary hypertension in POEMS syndrome may be estimated between 5 and 10% of affected patients (16). Severe transient pulmonary hypertension has been reported in a patient with monoclonal gammopathy and dermatomyositis (17). Dramatic clinical improvement and decrease of pulmonary pressure was found after treatment with cyclophosphamide and prostacyclin. Abnormal release of vasoactive cytokines have been implicated in the pathogenesis of the disease (18-20). POEMS appears to be mediated by an abnormal release of pro-inflammatory cytokines. Interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α have been reported to be increased in association with the syndrome. Preliminary data suggest that vascular endothelial growth factor may play a role in the pathogenesis in POEMS (21-23); it induces a rapid and reversible increase in vascular permeability, is a growth factor for endothelial cells, and is considered important in angiogenesis.

3.3. Pulmonary Hypertension Associated with Thalidomide Treatment of Multiple Myeloma

Thalidomide induced pulmonary hypertension has been described during treatment for refractory MM (24). Thromboembolic events are one of the most important side effects of treatment with thalidomide. The pathogenic mechanisms of DVT associated with thalidomide have not been clearly established. Acquired activated protein C resistance and a reduction in thrombomodulin level have been associated with an increased risk of DVT.

However pre-capillary pulmonary hypertension not related to chronic thromboembolism have been reported during MM treatment with thalidomide. Younis (7) reported a 51-year-old man with relapsed IgA kappa MM who developed severe pulmonary hypertension (pulmonary artery pressure 70 mmHg) with normal mitral valve and left ventricular function. Bilateral lower extremity Doppler ultrasound and computerized tomography pulmonary angiogram were negative for deep venous thrombosis and pulmonary embolism respectively. Thalidomide withdrawal was associated with a decrease of pulmonary artery pressure, re challenging with a recurrence of pulmonary hypertension.

Similarly a 63-year-old woman with IIA IgG kappa MM refractory to multiple therapeutic regimens developed severe pulmonary hypertension (pulmonary artery pressure 90 mmHg) after few months of thalidomide. Left ventricular

function was normal and she has no evidence of cardiac amyloidosis and of thromboembolic disease. (8) Thalidomide was withdrawn. In the following months pulmonary artery pressure decreased progressively however she died for advanced myeloma state. Other case reports have been reported in literature (25-26).

A pilot prospective study in patients with MM treated with thalidomide showed the development of PH in four out of 82 patients, (4.87%) (27). Non imaging and imaging diagnostic methods excluded thromboembolic PH. Statistical analysis demonstrated significant correlation between structural heart disease and PH.

Patho-physiological mechanisms leading to PH in patients treated with Thalidomide are unknown. A 'functional' effect of thalidomide on pulmonary vascular tone has been hypothesized (27) with a vasodilator and vasoconstriction imbalance which may cause abnormal pulmonary vascular response interfering to a vicious circle perpetuating PH (28-29). An irreversible drug effect on endothelial and muscle vessel cells may occur and histopathological features of primary hypertension has been described at necroscopy (27).

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