Pulmonary hypertension related to thalidomide therapy in refractory multiple myeloma

Thalidomide is an effective treatment both in advanced multiple myeloma (MM) and as first-line therapy in combination with dexamethasone or other cytotoxic chemotherapy [1, 2].

Two cases [3, 4] of pulmonary hypertension in the absence of thromboembolic events have been described in patients with MM during thalidomide treatment [5].

A 63-year-old woman was diagnosed in 1998 with IIA MM IgG kappa, evolved from monoclonal gammopathy of unknown significance (MGUS). She was refractory to melphalan and prednisone (MP) and then received eight monthly cycles of VED (teniposide, cyclophosphamide and dexamethasone), and achieved a partial response.

In December 2002, VAD (vincristine, doxorubicine and dexamethasone) chemotherapy was initiated for disease progression, but the patient received only two cycles as a result of intolerance. Thereafter, she refused further chemotherapy and autologous transplant.

In October 2003 the patient started thalidomide 100 mg daily with progressive increase to 200 mg daily and dexamethasone (40 mg daily, days 1–4) for 7 months without significant side-effects. She also received low-weight heparin as prophylaxis for thromboembolic complications.

In May 2004, while on thalidomide, she presented with dizziness, asthenia and breathlessness and was hospitalised.

Physical examination documented mild jugular turgor, mild oedema of lower extremities and 2/6 systolic murmur in mesocardium; cyanosis was not found. ECG showed right ventricle strain and hypertrophy. Chest X-ray revealed enlarged heart. Echocardiography documented severe pulmonary hypertension (pulmonary artery pressure 90 mmHg) with mild tricuspid insufficiency and paradoxic movement of ventricular septum with normal left ventricular function, without evidence of cardiac amyloidosis. A diagnosis of severe pulmonary hypertension was made.

Bilateral upper and lower extremities Doppler ultrasound, pulmonary computed tomography and ventilation-perfusion scan were negative for deep venous thrombosis and pulmonary embolism. Coagulation parameters, including C and S protein, were normal.

Blood gas analysis and O₂ saturation excluded hypoxemia; imaging and functional lung investigations were negative for respiratory system disorders and collagen vascular diseases. Familial anamnesis was negative for pulmonary hypertension.

With the hypothesis of a pharmacological pathogenesis, thalidomide was promptly interrupted. A cardiologic evaluation was carried out monthly; the echocardiograms revealed a progressive reduction of pulmonary artery pressure to 60 mmHg, while blood gas analysis showed a mild respiratory insufficiency. An echocardiographic control was subsequently carried out in September 2004 and the pulmonary artery pressure further decreased to 55 mmHg.

Because of progressive disease, the patient received bortezomib, without major side-effects, but 1 month later she was hospitalised again in advanced myeloma state with overt cardiac failure, and died.

The aetiology of pulmonary hypertension in these patients remains unclear; as in the reports by Younis [3] and Hattori et al. [4], we failed to detect any known causes of pulmonary hypertension.

As in the case reported by Younis [3], we suggest a possible direct correlation between thalidomide and pulmonary hypertension, since in both cases a rapid decrease of pulmonary artery pressure after thalidomide discontinuation was observed. Furthermore, the development of pulmonary hypertension might be dose-independent, since our patient received a lower dose of thalidomide compared with Younis’ case. This could possibly be due to a ‘functional’ effect of thalidomide on pulmonary vascular tone. On the other hand, it is noteworthy that pulmonary pressure value, while improving, did not recover up to the baseline value, possibly because of an irreversible drug effect on endothelial and muscle vessel cells. In fact, in Hattori et al.’s report [4] the autopsy revealed the histopathological features of primary hypertension.

Further investigations are required to understand whether pulmonary hypertension may be considered as an adverse effect of thalidomide and how the drug eventually affects vessel endothelial cells.
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