A Case of Pulmonary Hypertension Associated with Idiopathic Hypereosinophilic Syndrome

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Summary
Hypereosinophilic syndrome (HES) is characterized by multi-organ damage that is associated with tissue hypereosinophilia. A persistently elevated eosinophilic count is also required for the diagnosis of HES. Although HES affects various organs, damage to pulmonary artery is rarely reported. We present a case of a 39-year-old man who was diagnosed with pulmonary hypertension (PH) associated with idiopathic HES. Although the pulmonary arterial hypertension specific drugs including intravenous epoprostenol could not control his PH, corticosteroid was effective for both hypereosinophilia and PH. Our case suggests the importance of steroid therapy as well as specific drugs for pulmonary arterial hypertension in the treatment of PH associated with HES.

(int Heart J Advance Publication)

Key words: Pulmonary arterial hypertension, Hypereosinophilia, Steroid therapy, Corticosteroid

Hypereosinophilic syndrome (HES) is characterized by multi-organ damage and/or dysfunction that are attributable to tissue hypereosinophilia with peripheral blood hypereosinophilia. Exclusion of other disorders or conditions as a major reason for multi-organ damage is necessary for the diagnosis of HES. Although various symptoms and organ damages such as eosinophilic myocarditis have been identified as HES, there are few reports regarding pulmonary hypertension (PH) caused by HES. Inflammation by eosinophil-derived effector molecules may play a role in the development of PH caused by HES. We report a case of PH associated with idiopathic HES, which was successfully treated by corticosteroid therapy.

Case Report
A 39-year-old man who had been diagnosed with pulmonary arterial hypertension was referred to our institute for the introduction of intravenous epoprostenol therapy. He had been identified as having hypereosinophilia at 26 years old. Secondary causes of hypereosinophilia, such as allergic diseases including bronchial asthma and drug-allergy; autoimmune diseases including eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis, parasite diseases, leukemia, and lymphoma; and cancer had been excluded after careful examination including bone marrow biopsy. Under the diagnosis of hypereosinophilia of undetermined significance, he had been prescribed corticosteroid (prednisolone 5 mg per day for maintenance dose). At 36 years old, exertional shortness of breath and pitting edema in lower limbs appeared and gradually became worse (World Health Organization functional class (WHO-FC) 3). Echocardiogram showed dilated right atrium and right ventricle and elevation of estimated right ventricular systolic pressure. Right heart catheterization showed 75/37 (49) mmHg (systole, diastole, and mean) for pulmonary arterial pressure (PAP), 9 mmHg for mean pulmonary artery wedge pressure, suggesting pre-capillary PH. After exclusion of other causes such as connective tissue diseases, congenital heart diseases, lung diseases, and chronic thromboembolic PH, he was diagnosed as idiopathic pulmonary arterial hypertension. Although ambrisentan 5 mg, sildenafil 60 mg, and beraprost 120 μg were prescribed for 1 year at the previous hospital, those medications did not improve his PH. PAP was 63/26 (43) mmHg, and pulmonary vascular resistance (PVR) remained high (5.3 Wood units). He was referred to our hospital for the introduction of intravenous epoprostenol.

When he came to our hospital, his clinical symptoms remained WHO-FC 3, and 6-minute walk distance (6 MWD) was 260 m. Laboratory data showed elevated brain natriuretic peptide (BNP) level (307.6 pg/mL). Chest X-ray showed bilateral pulmonary artery dilatation and cardiac dilatation (Figure 1), and electrocardiogram showed right ventricular hypertrophy and high voltage of R wave in V1, suggesting right ventricular overload (Figure 2). We
introduced intravenous epoprostenol and gradually increased the dose up to 25 ng/kg/minute. Although right heart catheterization showed slight improvement of PH (PAP for 49/26 (35) mmHg, PVR for 3.0 Wood units), his PH was not sufficiently controlled by specific pulmonary arterial hypertension medications including intravenous epoprostenol. The peripheral blood eosinophils under 5 mg of prednisolone remained high before and after intravenous epoprostenol therapy (5772 cells/μL and 4383 cells/μL, respectively). We hypothesized that hypereosinophilia might play an important role for the development of PH, which indicates that PH was caused by idiopathic HES. Then we increased the dose of prednisolone to 60 mg/day and tapered to 10 mg as maintenance dose in the following 3 months to control hypereosinophilia. Immediately after increasing prednisolone, PH as well as eosinophilic count significantly improved (PAP for 40/17 (29) mmHg, PVR for 1.9 Wood units) (Figure 3). WHO-FC also improved from 3 to 2, and 6MWD reached 500 m. The BNP level returned to normal range (4.7 pg/mL). Echocardiographic findings showed additional right ventricular reverse remodeling (Figure 4). His PH has been stable by pulmonary arterial hypertension specific medications and steroid therapy.

Discussion

We described a case of PH associated with idiopathic HES. Sufficient steroid therapy as well as specific combination therapy for pulmonary arterial hypertension including intravenous epoprostenol were necessary to control PH with idiopathic HES, indicating that the main mechanism of the PH was inflammation caused by hypereosinophilia. Recently, various mechanisms for the development of PH have been identified. There are some evidence that inflammation plays a pivotal role in the pathogenesis of PH. An animal study showed that mice developed prominent pulmonary vascular remodeling in the case of pulmonary eosinophilic infiltration. Another animal study revealed that the deficiency of adiponectin exacerbated PH by increasing eosinophil recruitment into the lung and suggested that eosinophils could play an important role in pathogenesis on inflammation-induced PH in mouse model. Furthermore, autopsy of pulmonary arterial hypertension patients with marked elevated peripheral blood eosinophils showed thickened intima and media in pulmonary artery with eosinophil infiltration, which suggests the association between eosinophils infiltration and pulmonary vascular remodeling. In this case, it was considered that the main mechanism for PH was inflammation caused by eosinophils. Hyper permeability of vessels by hypereosinophilia also might contribute to PH because he had been in a hyperdynamic state.

Because there are few reports regarding PH associated with HES in human, the therapeutic strategy has not

Figure 1. Chest X-ray on admission. Chest X-ray showed bilateral pulmonary artery dilatation and cardiac dilatation.

Figure 2. Electrocardiogram on admission. Right ventricular hypertrophy and high voltage of R wave in V1 suggesting right ventricular overload existed.
PULMONARY HYPERTENSION ASSOCIATED WITH HES

Figure 3. Clinical course after referral to our hospital. CO indicates cardiac output; PVR, pulmonary vascular resistance; WU, Wood units; 6MWD, 6-minute walking distance; and BNP, brain natriuretic peptide.

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<th>On admission</th>
<th>After PAH specific therapy</th>
<th>After sufficient steroid therapy</th>
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<tr>
<td>Sildenafil</td>
<td>60 mg/day</td>
<td>60 mg/day</td>
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<td>Ambrisantan</td>
<td>5 mg/day</td>
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<td>Epoprostenol</td>
<td>250 ng/kg/minute</td>
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<td>Prednisolone</td>
<td>5 mg/day</td>
<td>60 mg/day</td>
<td>10 mg/day</td>
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<tr>
<td>Eosinophil</td>
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<td>PVR (Wood units)</td>
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<tr>
<td>CO</td>
<td>7.33 L/minute</td>
<td>7.07 L/minute</td>
<td>8.20 L/minute</td>
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<tr>
<td>PVR</td>
<td>4.9 WU</td>
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<tr>
<td>6MWD</td>
<td>260 m</td>
<td>410 m</td>
<td>500 m</td>
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<tr>
<td>Eosinophils</td>
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<td>4629/μL</td>
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<td>BNP</td>
<td>331.4 pg/mL</td>
<td>192.0 pg/mL</td>
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Figure 4. Echocardiographic findings on admission, after pulmonary artery hypertension specific therapy, and sufficient steroid therapy. PAH indicates pulmonary arterial hypertension and TAPSE, tricuspid annular plane systolic excursion.
been well established. First, we added the pulmonary arterial hypertension specific medications,\textsuperscript{7} which could not sufficiently control his PH. Then we increased the dose of steroid therapy to control the peripheral eosinophilic count, while the patient already had steroid therapy. Our case suggests the importance of sufficient dose of steroid therapy and the possibility of peripheral eosinophilic count as therapeutic target for PH associated with HES.

In conclusion, we reported a rare case of PH associated with idiopathic HES. Sufficient steroid therapy as well as pulmonary arterial hypertension specific combination therapy were necessary to control PH. This case advocates the close relationship between inflammation and PH and the importance of suppressing inflammation for the treatment of PH with HES.

Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

References