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Case Report

Pulmonary Arterial Hypertension Associated With Idiopathic Hypereosinophilic Syndrome: Importance of Eosinophilia Control With Steroid Therapy

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Basic and autopsy-based studies suggest that eosinophilic infiltration causes the progression of pulmonary vascular lesions. Pulmonary arterial hypertension (PAH) associated with hypereosinophilia is rare. We report the case of a 48-year-old woman diagnosed with PAH and idiopathic hypereosinophilic syndrome (IHES) 12 and 11 years earlier, whose hypereosinophilia and pulmonary hypertension (PH) worsened and improved with prednisolone (PSL) dosage reduction and increase, respectively. Effective management of PAH associated with IHES should include eosinophilia control through appropriate steroid therapy, highlighting that eosinophilia-associated inflammation might be linked to a subset of pulmonary vascular diseases.

Case

We present the case of a young woman admitted to our hospital with dyspnea (World Health Organization functional class IV), cough, prominent jugular vein distention, and impaired oxygenation (rest oxygen saturation 90%). Her medical history was significant for IHES diagnosed at the age of 36 years, subsequently complicated by right heart failure and PAH after the exclusion of connective tissue disease, chronic thromboembolic PH, and other systemic diseases as potential causes. At the age of 47 years, after the tapering of PSL doses to 1.25 mg (Fig. 1), there was a deterioration of pulmonary hemodynamics (mean pulmonary arterial pressure of 61 mm Hg, pulmonary vascular resistance of 13.4 Wood units, mean right atrial pressure of 12 mm Hg, and cardiac index of 3.8 L/min/m^2), and functional capacity (6-minute walking distance of 132 m).

One month before the index hospitalization, PSL was discontinued because of good eosinophilia control. The patient developed worsening PH and heart failure, necessitating urgent hospitalization. On index admission, laboratory tests again revealed an elevated eosinophil count (16,988/μL) and brain natriuretic peptide level (109.6 pg/mL). Echocardiography revealed right ventricular hypertrophy and pressure overload without left ventricular involvement (Fig. 2A). Chest computed tomography imaging showed mosaic ground-glass opacities around the bronchi consistent with eosinophilic lung disease associated with hypereosinophilic syndrome (HES; Fig. 2B). Because of the absence of an underlying cause of eosinophilia, we diagnosed worsening IHES and right heart failure. The furosemide dose was increased from 10 mg/d to 40 mg/d. Additionally, PSL treatment was restarted at 20 mg/d on day 1 of admission and increased to 40 mg/d on days 2 and 3. Eosinophilic lung disease and right heart failure improved and eosinophil count reduced to 81/μL on day 15. Despite no change in pulmonary vasodilator treatment, right heart catheterization on day 14 showed improved pulmonary hemodynamics with a mean pulmonary arterial pressure of 37 mm Hg, pulmonary vascular resistance of 6.7 Wood units, and mean right atrial pressure of 4 mm Hg (Fig. 1). Functional capacity also increased (6-minute walking distance on day 14, 343 m). The patient was discharged on day 17 with PSL 20 mg/d.

Discussion

Chusid et al.[1] established the 3 characteristic criteria of IHES: (1) persistently elevated eosinophil count ≥ 1500/μL for at least 6 months or death within 6 months; (2) no apparent underlying cause of eosinophilia; and (3) symptoms suggestive of organ involvement by eosinophilic infiltration. Eosinophilic activation associated with hypereosinophilia induces the release of cytotoxic substances through

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Novel Teaching Points

- Eosinophil infiltration drives the progression of pulmonary vascular lesions.
- PAH linked to idiopathic hypereosinophilia is rare.
- Control of eosinophilia is crucial for PAH management.
- Steroid therapy is effective in modulating the PAH that is associated with IHES.

degranulation, leading to tissue damage, fibrosis, and prothrombotic tendencies in multiple organ systems. Previous reports have linked cardiac dysfunction, thromboembolic phenomena, and vascular diseases to most HES-related deaths.[2] The coexistence of IHES and PAH is extremely rare, with steroid therapy for IHES exacerbation improving PAH symptoms in a few cases.[3,4] Recent research on IHES highlights the eosinophil-mediated release of cationic proteins, which promote vascular calcification and atherogenesis through bone morphogenetic protein receptor signalling pathways. Thickening of the arterial intima and media associated with eosinophilic infiltration was reported in autopsies of individuals with PAH.[5] Mouse research has shown that eosinophil granule extracts promote the proliferation of pulmonary artery smooth muscle cell proliferation,[6] which suggests that eosinophilic inflammation-induced pulmonary vascular remodelling could be the mechanism underlying PH exacerbations.

Immune-suppressive therapy, particularly interventions that incorporate PSL, has been documented as beneficial in the context of PH, which complicates connective tissue diseases.[7] Steroids inhibit pulmonary arterial smooth muscle cell proliferation, a pathological alteration observed in patients with PAH, by hindering nuclear factor κB nuclear translocation,[8] suggestive of a potential role for PSL as a regulatory factor in the pathogenic progression of PAH.

Previous reports on IHES and PAH have focused primarily on steroid therapy improvements in treatment-naive patients, with a short observational period (ie, < 2 years). However, in this case, approximately 10 years after the initiation of PSL treatment, IHES and PH were exacerbated after the steroid dosage was tapered, with subsequent improvement of PH with intensified steroid treatment without altering the oral pulmonary vasodilator therapy. This suggests that an increase or decrease in eosinophil count might influence pulmonary vascular lesions in patients with PAH and IHES. Individual discussions about discontinuing PSL and a cautious approach to dosage tapering are necessary, even long after PSL treatment initiation.

In this case, PH was refractory to treatment with 3 pulmonary vasodilators. In a previous case report, the use of therapeutic agents for PH, including intravenous epoprostenol, was insufficient to adequately control PH, which complicated HES.[4] These findings indicate that conventional PH treatments might not be effective for managing this pathological condition.

This case suggests that an effective management of PAH associated with IHES requires controlling eosinophilia

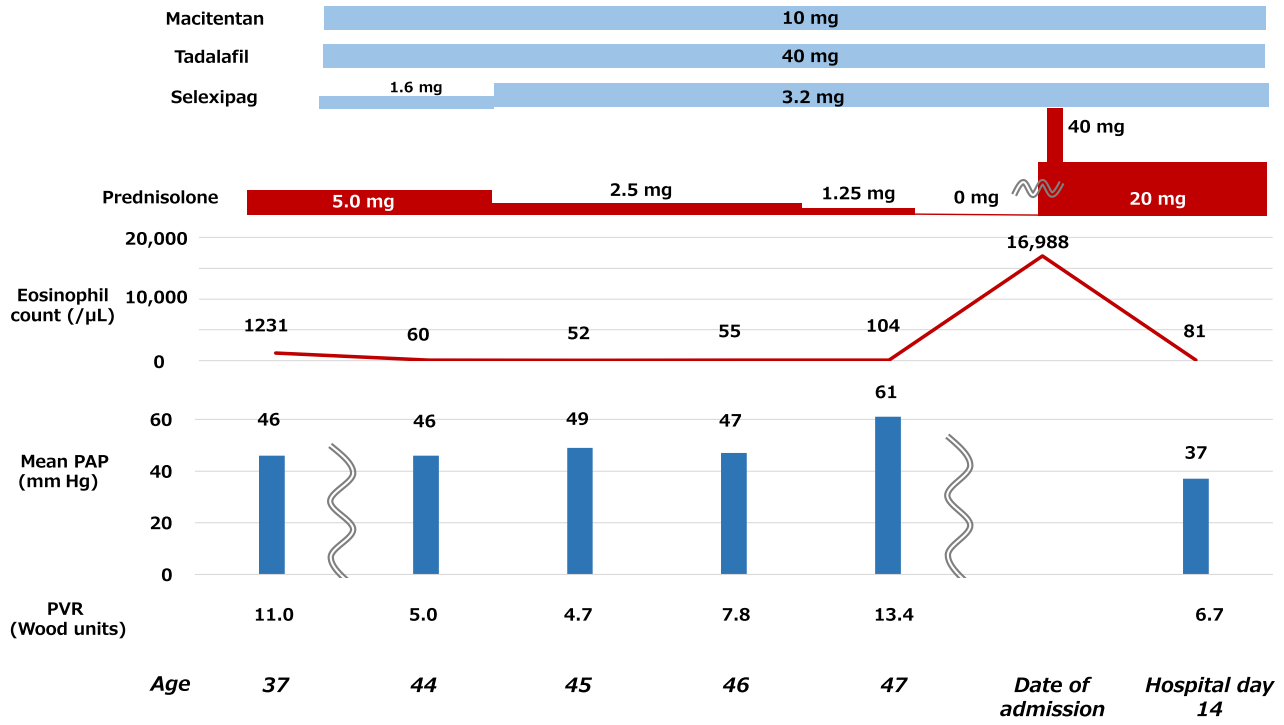

Figure 1. Clinical course. PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance.

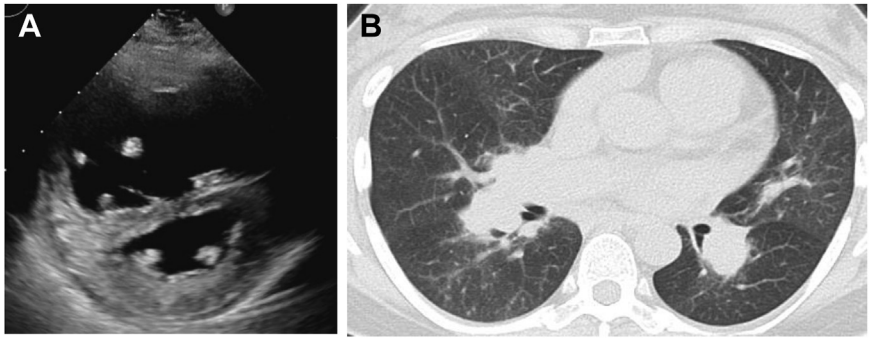

Figure 2. Imaging studies. (**A**) Transthoracic echocardiography image showing an enlarged right ventricle and a ventricular septum displaced toward the left ventricle. (**B**) Chest computed tomography scan showing mosaic ground-glass opacities around the bronchi, consistent with eosinophilic lung disease.

through adequate steroid therapy, highlighting the potential link between eosinophilia-associated inflammation and a specific subset of pulmonary vascular diseases.

Ethics Statement

This study was approved by the Committee for Clinical Studies and Ethics of Kyorin University School of Medicine, Tokyo, Japan (No. 1595).

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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