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CASE REPORT

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Pulmonary hypertension during high-dose GM-CSF therapy of autoimmune pulmonary alveolar proteinosis

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To the editor,

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by alveolar surfactant accumulation, progressive dyspnea, and hypoxemic respiratory insufficiency, and in some patients, secondary infections, pulmonary fibrosis, respiratory failure, and death.[1] GM-CSF (granulocyte/macrophage colony-stimulating factor) autoantibodies cause aPAP by blocking GM-CSF signaling, which impairs alveolar macrophage functions including surfactant clearance.[2]

Inhaled GM-CSF is a pharmacologic approach in development as therapy of aPAP that restores GM-CSF-dependent macrophage functions including surfactant clearance. Several studies, including two controlled clinical trials, reported that inhaled recombinant GM-CSF (rGM-CSF) is effective and safe as therapy of aPAP when administered at daily doses of 250–300 μg.[3–5] Clinical experience and small studies suggest the existence of a dose–response relationship for inhaled rGM-CSF therapy of aPAP.[6] Notwithstanding, no controlled studies have identified a treatment dose, frequency, or duration needed to achieve maximum therapeutic benefit or studied the safety of higher doses.

We describe an aPAP patient who developed transient pulmonary hypertension while receiving "high-dose" inhaled rGM-CSF (sargramostim).

CASE PRESENTATION

A 42-year-old man presented with clinical, radiographic, and laboratory evidence of aPAP. Physical examination was significant only for mild respiratory distress; the rest of the pulmonary and cardiac physical examination was unremarkable. The peripheral blood oxygen saturation (SpO_2) at rest on room air was 92%. He received bilateral

whole lung lavage (WLL) and inhaled sargramostim (Figure 1). A serum GM-CSF autoantibody test was increased (137 μg/mL; normal <3.1 μg/mL) and blocked GM-CSF signaling, confirming the diagnosis of aPAP (Figure 1a). Bilateral WLL was required repeatedly, and the sargramostim dose was increased sequentially from 500 μg once daily, to 500 μg twice daily, and finally 750 μg twice daily. In total, seven bilateral WLLs and 1416 mg of sargramostim were administered over approximately 2 years and were associated with improvement in the symptoms, signs, and radiographic manifestations of aPAP and reduction in the requirement for WLL therapy (Figure 1).

The patient re-presented 8 months later with new onset fatigue of several months duration and worsening dyspnea. Physical examination revealed mild bilateral pitting edema of the lower extremities to the level of the ankles but was otherwise unremarkable. The lungs were clear to auscultation and the SpO_2 at rest while breathing room air was 97%. Pulmonary function testing revealed normal spirometry and lung volumes and a diffusing capacity of the lungs for carbon monoxide (DLco) at 84.1% of the predicted value. An echocardiogram revealed a mildly dilated right atrium and moderately dilated right ventricle, minimal tricuspid regurgitation, tricuspid annular plane systolic excursion (TAPSE) of

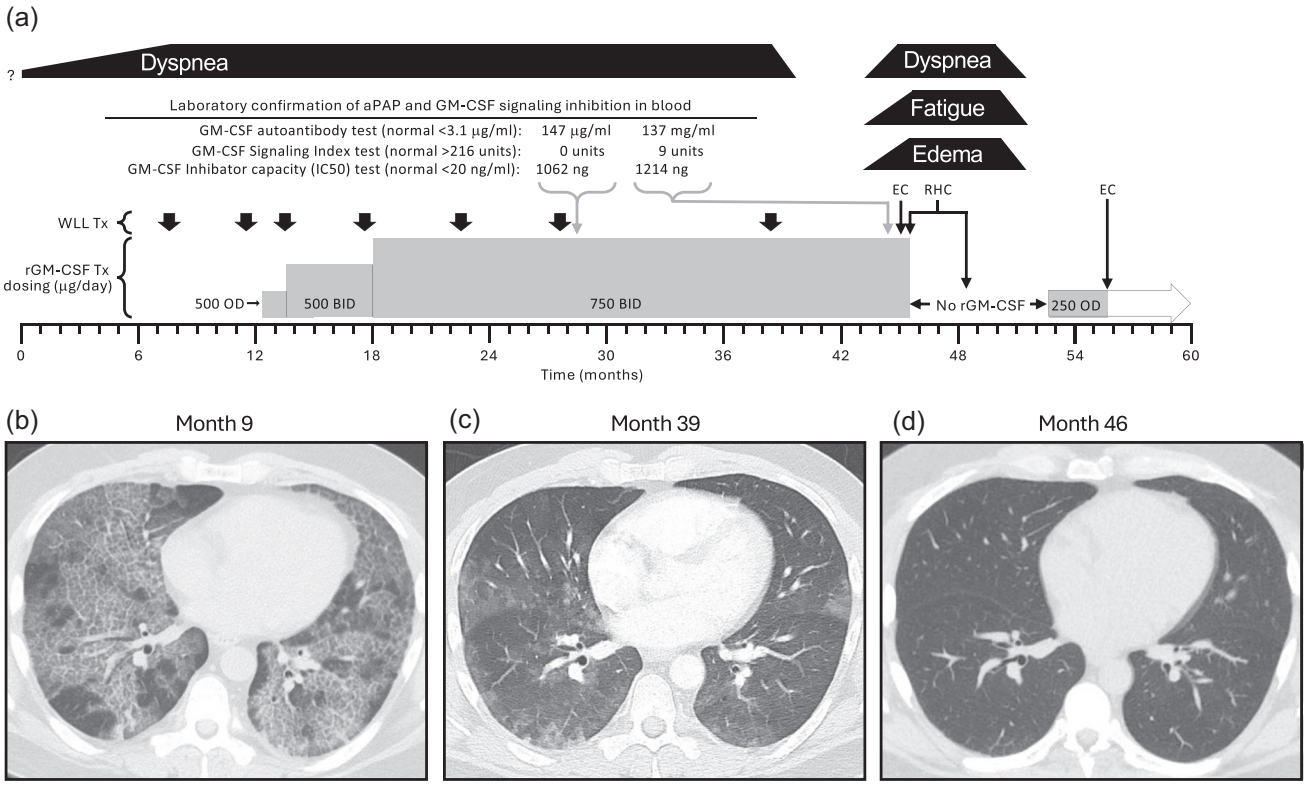

FIGURE 1 (a) Timeline of the patient's clinical course. At age 42 (month 0), he first presented with progressive dyspnea of insidious onset. He received whole lung lavage (WLL) repeatedly (thick arrows) and was started on inhaled rGM-CSF (sargramostim) therapy. The diagnosis of autoimmune pulmonary alveolar proteinosis (aPAP) was confirmed by measuring serum GM-CSF autoantibody concentration, GM-CSF signaling in whole blood (GM-CSF Signaling Index test), and rGM-CSF signaling inhibition in whole blood (GM-CSF IC50 test)—all performed at the Translational Pulmonary Science Center laboratory in Cincinnati. As the dose of rGM-CSF was escalated from 500 μg once daily (OD) to 750 twice daily (BID) (gray boxes), the interval between repeated WLL procedures increased; WLL was no longer required 28 months after starting "high-dose" rGM-CSF therapy. Six months later (month 46), he re-presented with dyspnea, fatigue, and lower extremity edema. An echocardiogram (EC) identified right atrial and right ventricular enlargement, and right heart catheterization (RHC) identified pulmonary arterial hypertension (PAH), and rGM-CSF was discontinued on suspicion of involvement. Three months later, a repeat RHC showed a resolution of PAH. Seven months after discontinuance, rGM-CSF was restarted at a lower "maintenance" dose. Three months later, a repeat echocardiogram (EC) was normal. Inhaled sargramostim was prescribed to continue at the lower "maintenance" dose (open gray arrow) with periodic future ECs (not shown) to monitor for the potential development of PAH. (b) At initial presentation, a chest computed tomography (CT) scan revealed significant ground glass opacification with superimposed septal thickening ("crazy paving") characteristic of aPAP. (c) After repeated WLL and prolonged inhaled sargramostim therapy including "high-dose" (750 μg twice daily) administration for more than 2 years, the crazy paving was markedly reduced. (d) After prolonged therapy with "high-dose" inhaled sargramostim, representation with symptoms, signs, and RHC evidence of PAH, the chest CT showed no evidence of aPAP lung disease.

17 mm, and normal left ventricular size and ejection fraction (55%–60%). A right heart catheterization (RHC) identified mild pre-capillary pulmonary hypertension with a mean pulmonary arterial pressure 25 mmHg (normal < 20 mmHg), pulmonary vascular resistance of 3.52 Wood units (normal < 2.0 Wood units), and preserved cardiac output and index with no other high-risk features (Table 1).

On suspicion of potential involvement, high-dose inhaled sargramostim was discontinued. Computed tomography pulmonary angiogram did not reveal any pulmonary emboli. Three months later, a RHC was normal (Table 1). Seven months after discontinuance, inhaled sargramostim was restarted at a lower dose (250 μg/day) (Figure 1a). Three months later, a repeat echocardiogram returned to baseline with normal right atrial size, normal right ventricular size, and a TAPSE of 21 mm.

TABLE 1 Results of right heart catheterization while receiving and after discontinuing "high-dose" inhaled sargramostim therapy.[a]

Parameter	While receiving "high-dose" sargramostim (750 μg twice daily)	Three months after discontinuing sargramostim therapy
RA pressure, mmHg	8	8
RV systolic pressure, mmHg	34	28
RV diastolic pressure, mmHg	8	8
PASP, mmHg	34	28
PADP, mmHg	18	14
mPAP, mmHg	25	20
PAOP, mmHg	9	12
Cardiac output (TD), L/min	4.5	4.8
Cardiac output (Fick), L/min	5.99	6.2
Cardiac index (TD), L/min/m^2	2.0	2.1
Cardiac index (Fick), L/min/m^2	2.6	2.7
PVR, WU	3.55	1.67
SVI, mL/m^2	35.7	38.6
PAC, mL/mmHg	4.89	5.8
Arterial oxygen saturation, %	94	92
Central Venous oxygen saturation, %	67	70
Hemoglobin, g/dL	14	15

Abbreviations: mmHg, millimeters of mercury; mPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PADP, pulmonary artery diastolic pressure; PAOP, pulmonary artery occlusion pressure; PASP, pulmonary artery systolic pressure; PVR, peripheral vascular resistance; RA, right atrial; RV, right ventricular; SVI, stroke volume index; TD, thermodilutions; WU, woods units.

[a]Performed with the patient in a supine position using a routine clinical Swan-Ganz catheter (Edwards LifeScience). See Figure 1 for the time during the clinical course that each procedure was performed.

DISCUSSION

We report the occurrence of transient precapillary pulmonary arterial hypertension during "high-dose" (750 μg twice daily) inhaled sargramostim therapy in a patient with aPAP that resolved upon treatment discontinuance.

The observation of clinical and radiographic improvement and reduced WLL use during "high-dose" inhaled sargramostim therapy in this aPAP patient is an important finding. WLL achieves a rapid partial treatment effect on aPAP lung disease by physically "washing" excess surfactant out of the lungs, but it does not correct the underlying cellular defect or stop the abnormal surfactant accumulation and is typically required repeatedly.[7] In contrast, inhaled rGM-CSF pharmacotherapy acts more slowly but is capable of restoring GM-CSF-dependent alveolar macrophage functions including surfactant clearance and can stop the pathologic accumulation of surfactant.[3,8] Thus, aPAP patients with severe lung impairment may require therapy with WLL for its "debulking" effect but can also benefit from rGM-CSF pharmacotherapy aimed at correcting the underlying pathophysiological defect and reducing or eliminating the abnormal surfactant accumulation and the need for repeated WLL. These results add to a growing number of reports indicating some aPAP patients achieve therapeutic benefit from "high-dose" rGM-CSF therapy[6] while others (approximately half to two-thirds) appear to respond to "low-dose" (i.e., 250 μg/day) therapy.[3–5] Further studies are needed to confirm and define the dose–response effects of inhaled rGM-CSF therapy of aPAP.

The observation that our patient developed clinical signs, symptoms, and RHC documentation of PAH while receiving "high-dose" sargramostim, which resolved upon discontinuance of the "high-dose" treatment, is also important. The temporal relationship between the onset of PAH after initiating and resolution after discontinuance of "high-dose" sargramostim therapy suggests but does not prove a causal relationship. None of the approximately 360 aPAP patients receiving 'low-dose'

inhaled rGM-CSF in controlled trials (PAGE, IMPALA, IMPALA2) were reported to have developed PAH despite close observation[4,5] (NCT02702180). Nor did any of the 12 aPAP patients receiving escalating doses (up to 500 μg daily on alternating weeks) develop PAH during a small retrospective study.[6] To our knowledge, the occurrence of PAH in association with inhaled rGM-CSF administration has not been reported. Since GM-CSF receptors are present on a range of immune and other cells and GM-CSF can stimulate vascular endothelial growth factor (VEGF) expression,[9] it is tempting to speculate that GM-CSF may indirectly alter vascular tone by promoting vascular remodeling through VEGF or stimulating immune cell proliferation. Alternatively, GM-CSF might increase vascular tone directly by reducing nitric oxide production resulting in vasoconstriction.[10] Notwithstanding, given the increasingly widespread therapeutic use of inhaled rGM-CSF in men, women, and children with aPAP, it will be useful to observe the potential development of PAH in such individuals to determine if a causal relation exists and, if so, define the mechanism.

In conclusion, the identification of transient mild PAH in an aPAP patient receiving high-dose inhaled rGM-CSF therapy may be a rare but important complication of a rare disease that highlights the need to closely monitor such individuals during therapy.

AUTHOR CONTRIBUTIONS

Ali Ataya wrote the first draft of the manuscript. Bruce Trapnell and Brenna Carey analyzed the data and generated the figures and table. All authors contributed ideas for analyses. All authors provided input and edited the manuscript. Ali Ataya is the guarantor of this work and affirms the integrity, accuracy, and completeness of the data and analysis presented in this manuscript.

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CONFLICT OF INTEREST STATEMENT

AA consults for Partners Therapeutics and Savara. CM consults for Partners Therapeutics and serves on the scientific advisory board of Savara. All other authors declare no conflicts of interest.

ETHICS STATEMENT

Patient consent was obtained.

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