DOI: 10.1002/pul2.12098

CASE REPORT

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Precapillary pulmonary arterial hypertension in a patient with Proteus syndrome

Akash Mathavan[1] | **Akshay Mathavan**[1] | **Cyrus Vahdatpour**[2] | **Christina Eagan**[2] | **Saminder Singh Kalra**[2] | **Ali Ataya**[2]

[1]College of Medicine, University of Florida, Gainesville, Florida, USA

[2]Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, Gainesville, Florida, USA

Correspondence
Ali Ataya, Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, 1600 SW Archer Rd, Gainesville, FL 32610, USA.
Email: ali.ataya@medicine.ufl.edu

Funding information
None

Abstract

Proteus syndrome is a rare progressive multisystem disorder characterized by asymmetric, disproportionate overgrowth of bone, skin, and other tissue types. Molecular pathogenesis has been identified as somatic activating mutations of the AKT1 gene. The presentation of Proteus syndrome is exceptionally variable. Respiratory complications include emphysematous lung disease and predisposition to pulmonary emboli, the latter of which is a significant source of mortality. Pulmonary hypertension due to longstanding hypoxic lung disease as well as chronic thromboembolic events has been observed in this population. In contrast, precapillary pulmonary arterial hypertension in the absence of chronic pulmonary emboli and parenchymal lung disease has not been described in the literature on patients with Proteus syndrome. We report such a case in a young patient with Proteus syndrome, reviewing subsequent management and emphasizing the need for a detailed investigation of dyspnea.

KEYWORDS

dyspnea, Proteus syndrome, pulmonary arterial hypertension, pulmonary embolism

INTRODUCTION

Proteus syndrome is a complex multisystem disorder characterized by mosaic postnatal malformations and asymmetric, disproportionate overgrowth of multiple tissue types.[1,2] The syndrome is exceptionally rare, with an incidence of less than one in one million people worldwide. Somatic activating mutations of the oncogene AKT1 have been identified as the principal driver of pathogenesis for clinical overgrowth and tumor susceptibility.[3] Although phenotypic expression can be remarkably variable, common manifestations include unrelenting, distorting overgrowth, unique bony abnormalities including hyperostosis of the skull, dysregulated adipose distribution, vascular malformations, and cutaneous findings such as cerebriform connective tissue nevi.[4,5] Due to the wide spectrum of presentation, there is considerable overlap with other asymmetric overgrowth syndromes that makes diagnosis challenging. In Proteus syndrome, pulmonary manifestations are of particular importance as pulmonary emboli are one of the most common causes of mortality; other respiratory complications include emphysematous bullous changes, pulmonary nodules, and restrictive asymmetric thoracic overgrowth.[6,7] Although data are very limited, studies have also

demonstrated Group 3 pulmonary hypertension secondary to diffuse parenchymal lung disease as well as Group 4 chronic thromboembolic pulmonary hypertension (CTEPH).[8,9] We present a novel case of precapillary pulmonary arterial hypertension in a patient with Proteus syndrome without evidence of underlying parenchymal lung disease or chronic pulmonary embolism.

CASE PRESENTATION

A 23-year-old woman with known Proteus syndrome presented to the clinic for over 6 years of progressively worsening shortness of breath. She was dyspneic with moderate exertion (World Health Organization functional class 3), requiring nasal cannula oxygen therapy at 2–3 L/min. She denied worsening of shortness of breath upon supine or upright position, cough, wheezing, fevers, or chills. Of note, she demonstrated rapidly progressive, asymmetric, disproportionate limb overgrowth beginning at 7 months of age, leading to a diagnosis of Proteus syndrome via clinical criteria at an outside institution. Complications included a lipoma of the right forearm removed at the age of two, progressively enlarging cutaneous venous malformations of the lower extremities requiring excision, and diffuse joint pain with mild kyphoscoliosis. Her history was relevant for a pulmonary embolism 5 years before encounter, which was managed with anticoagulant therapy. A computed tomography (CT) of the chest at that time demonstrated multiple small filling defects within pulmonary arterial branches consistent with pulmonary emboli and an enlarged main pulmonary artery measuring 3.8 cm in diameter.

Previous workup for her shortness of breath included a transthoracic echocardiogram (TTE) 3 years before presentation, which estimated a moderately elevated right ventricular systolic pressure (RVSP) of 56 mmHg. Unfortunately, the patient was lost to follow-up at that time. On presentation to the clinic, she was afebrile with a heart rate of 112 beats per minute and blood pressure of 152/90 mmHg. Her oxygen saturation was 94% on the nasal cannula at 3 L/min. Pertinent physical examination showed a nondistressed woman with a loud P2 and a 3/6 nonradiating holosystolic murmur in the left lower sternal border. Musculoskeletal presentation included asymmetrically enlarged left upper extremity and right foot with hypertrophic, maligned digits.

Based on the patient's history of pulmonary emboli, the initial consideration for her shortness of breath was

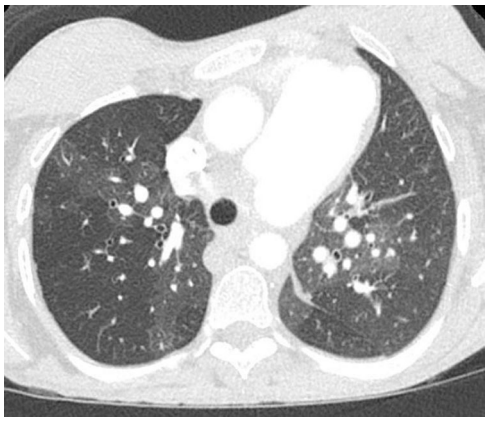

FIGURE 1 Contrasted computed tomography angiography of the chest in the transverse plane and lung window demonstrating enlarged main pulmonary artery measuring up to 41 mm in transverse diameter with no evidence of acute or chronic pulmonary emboli and no parenchymal lung disease with mosaic attenuation.

CTEPH. Pulmonary function tests demonstrated a decreased forced vital capacity (FVC) of 51.4% and forced expiratory volume in 1 s (FEV1) of 53.3% with a preserved FEV1/FVC of 103.4%. An elevated total lung capacity (TLC) of 117.2% and mildly reduced diffusing capacity for carbon monoxide of 72.9% were also observed. These results indicated an extrinsic restrictive process; however, her kyphoscoliosis was mild in nature. A CT angiography of the chest indicated no evidence of acute or chronic pulmonary emboli throughout the proximal subsegmental arterial branches but did visualize an enlarged main pulmonary artery up to 4.1 cm. Normal lung parenchyma was noted; however, there was also evidence of mosaic attenuation throughout both lungs (Figure 1). A ventilation–perfusion scan did not show any evidence of unmatched perfusion deficits throughout the lungs; these findings failed to meet established diagnostic criteria for and effectively ruled out CTEPH.[10] Subsequent TTE demonstrated an ejection fraction of 55%–60%, severely dilated right atrium, RVSP of 75–80 mmHg, and depressed right ventricular function with tricuspid annular plane systolic excursion (TAPSE) of 16 mm (Figure 2). Right-heart catheterization, reported in Table 1, revealed precapillary pulmonary hypertension with no high-risk features. The patient was initiated on dual oral therapy with tadalafil 40 mg daily and macitentan 10 mg daily and reported subjective improvement in dyspnea at a 3-month follow-up. At this time, repeat TTE demonstrated stable ejection fraction and improving right ventricular function with an RVSP of 65–70 mmHg and TAPSE of 18 mm.

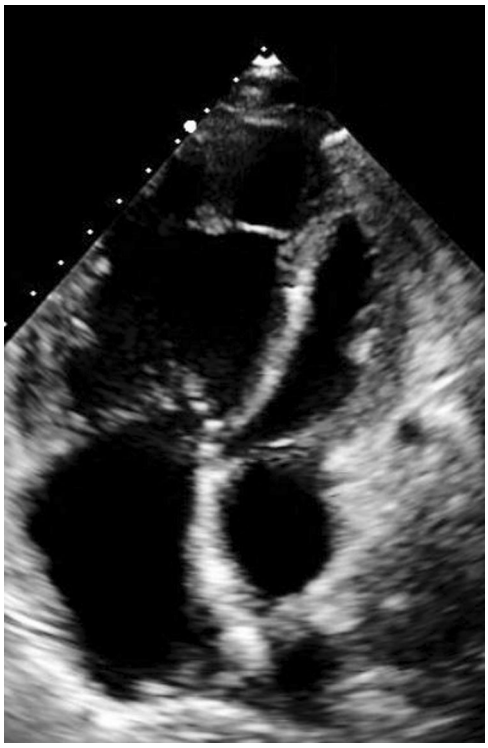

FIGURE 2 Transthoracic echocardiogram apical four-chamber view demonstrating dilated right atrium and right ventricle with interventricular bowing.

TABLE 1 Right heart catheterization

RAP (mmHg)	15
sRV/dRV (mmHg)	105/15
sPA/dPA (mmHg)	105/48
mPAP (mmHg)	72
PAOP (mmHg)	14
CO (TD) (L/min)[a]	4.2
CI (TD) (L/min/m^2)	2.5
PVR (Wood units)	13.8
PVRi (Wood units m^2)	23.2
SvO_2 (%)	69

Abbreviations: CI, cardiac index; CO, cardiac output; dPA, diastolic pulmonary artery pressure; dRV, diastolic right ventricular pressure; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance; PVRi, indexed pulmonary vascular resistance; RAP, right atrial pressure; sPA, systolic pulmonary artery pressure; sRV, systolic right ventricular pressure; SvO_2, venous oxygen saturation; TD, thermodilution.

[a]Measured using the thermodilution method.

DISCUSSION

Due to the rarity and variable presentation of Proteus syndrome, a timely and accurate diagnosis can be challenging. Before the identification of somatic mutations of the AKT1 gene as the underlying molecular basis of Proteus syndrome, stringent clinical criteria were devised to diagnose the disorder. Proper application of the criteria has proven to be reliable in the identification of Proteus syndrome and remains effective due to prohibitive factors that may impede genetic testing. Patient presentations must fulfill all general criteria (mosaic distribution, sporadic occurrence, and progressive course) as well as select features from categorical criteria (classified into categories A, B, and C).[1,4,5] The reported patient's course satisfied all general criteria as well as four specific criteria, two of which were from category B: linear epidermal nevi, asymmetric and disproportionate overgrowth of limbs, lipomas, and vascular malformations.

Among complications apparent in Proteus syndrome, susceptibility to deep vein thromboses and pulmonary emboli is a significant source of premature mortality and morbidity.[6,11,12] The predisposition to thromboembolic events is multifactorial. The presence of vascular anomalies likely contributes to malformed vessels with hemostasis and inflammatory endothelial dysfunction, leading to a pro-thrombotic environment. This is supported by the higher frequency of observed thromboembolic events in patients with other overgrowth syndromes associated with vascular malformations, such as Klippel–Trenaunay syndrome, as well as in patients with isolated congenital vascular defects.[13,14] Furthermore, gene products of AKT1 are involved in the PI3K/AKT/mTOR pathway and regulate various proliferative and metabolic processes. Studies indicate a significant role of the AKT1 kinase in vascular tone and angiogenesis; activating mutations may contribute to endothelial dysfunction that further predisposes patients with Proteus syndrome to thromboembolic events.[15] Thus, a high degree of clinical suspicion and active surveillance is vital in this patient population. The use of anticoagulant therapy, even in young patients, has been endorsed to prevent associated complications and premature death.

CTEPH has been observed in a patient with Proteus syndrome who notably presented with lung cavitations as well as in patients with other overgrowth syndromes.[9,16] Treatment is pulmonary thromboendarterectomy for those who are surgical candidates. Given our patient's history of pulmonary emboli, CTEPH was among the initial principal considerations for her longstanding, progressive dyspnea. However, a ventilation–perfusion scan failed to demonstrate significant unmatched perfusion defects. Pulmonary hypertension secondary to chronic hypoxic lung disease has also been observed. Precapillary pulmonary hypertension in the absence of underlying lung disease or chronic thromboembolic disease has not been described before in Proteus syndrome. We present the first known case of precapillary pulmonary arterial hypertension in a patient with Proteus syndrome with a positive response to pulmonary arterial hypertension-directed dual oral

therapy. This case emphasizes the necessity of a complete investigation of pulmonary hypertension in patients with Proteus syndrome.

AUTHOR CONTRIBUTIONS

Substantial contributions to the concept or design of the work or the acquisition, analysis, or interpretation of the data: Akash Mathavan, Akshay Mathavan, Ali Ataya. Drafting of the work or revising it critically for important intellectual content: Akash Mathavan, Akshay Mathavan, Christina Eagan, Saminder Singh Kalra, Ali Ataya. All authors contributed and approved the final version of the article.

ACKNOWLEDGMENT

The authors declare that there is no funding to disclose.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

Patient consent was obtained for the publication of this article.

ORCID

Akash Mathavan http://orcid.org/0000-0003-3496-2542
Ali Ataya http://orcid.org/0000-0001-8505-1680

REFERENCES

1. Biesecker LG, Happle R, Mulliken JB, Weksberg R, Graham JM Jr, Viljoen DL, Cohen MM Jr. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet. 1999;84:389–95.
2. Cohen Jr., MM. Proteus syndrome review: molecular, clinical, and pathologic features. Clin Genet. 2014;85:111–9.
3. Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, Turner J, Cannons JL, Bick D, Blakemore L, Blumhorst C, Brockmann K, Calder P, Cherman N, Deardorff MA, Everman DB, Golas G, Greenstein RM, Kato BM, Keppler-Noreuil KM, Kuznetsov SA, Miyamoto RT, Newman K, Ng D, O'Brien K, Rothenberg S, Schwartzentruber DJ, Singhal V, Tirabosco R, Upton J, Wientroub S, Zackai EH, Hoag K, Whitewood-Neal T, Robey PG, Schwartzberg PL, Darling TN, Tosi LL, Mullikin JC, Biesecker LG. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011;365:611–9.
4. Turner JT, Cohen Jr., MM, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. Am J Med Genet A. 2004;130A:111–22.
5. Biesecker LG. The challenges of Proteus syndrome: diagnosis and management. Eur J Hum Genet. 2006;14:1151–7.
6. Slavotinek AM, Vacha SJ, Peters KF, Biesecker LG. Sudden death caused by pulmonary thromboembolism in Proteus syndrome. Clin Genet. 2000;58:386–9.
7. Mirmomen SM, Arai AE, Turkbey EB, Bradley AJ, Sapp JC, Biesecker LG, Sirajuddin A. Cardiothoracic imaging findings of Proteus syndrome. Sci Rep. 2021;11:6577.
8. Dannunzio S, Dweck E, Bashar M. Cystic lung disease in a patient with Proteus syndrome. Chest. 2015;148:383A.
9. Fernandes CJCDS, de Oliveira EP, Salibe-Filho W, Terra-Filho M, Jardim C, Kato-Morinaga LT, Hoette S, de Souza R. Lung cavities in chronic thromboembolic pulmonary hypertension. Clinics (Sao Paulo). 2020;75:e1373.
10. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26:143.
11. Cohen Jr., MM. Causes of premature death in Proteus syndrome. Am J Med Genet. 2001;101:1–3.
12. Keppler-Noreuil KM, Lozier JN, Sapp JC. Characterization of thrombosis in patients with Proteus syndrome. Am J Med Genet A. 2017;173:2359–65.
13. Douma RA, Oduber CE, Gerdes VE, van Delden OM, van Eck-Smit BL, Meijers JC, van Beers EJ, Bouma BJ, van der Horst CM, Bresser P. Chronic pulmonary embolism in Klippel-Trenaunay syndrome. J Am Acad Dermatol. 2012;66:71–7.
14. Nakano TA, Zeinati C. Venous thromboembolism in pediatric vascular anomalies. Front Pediatr. 2017;5:158.
15. Lee MY, Luciano AK, Ackah E, Rodriguez-Vita J, Bancroft TA, Eichmann A, Simons M, Kyriakides TR, Morales-Ruiz M, Sessa WC. Endothelial Akt1 mediates angiogenesis by phosphorylating multiple angiogenic substrates. Proc Natl Acad Sci USA. 2014;111:12865–70.
16. Seferian A, Jaïs X, Savale L, Jevnikar M, Ghigna MR, Weatherald J, Assoun S, Fadel E, Simonneau G, Sitbon O, Humbert M, Montani D. Klippel-Trenaunay syndrome as a rare cause of chronic thromboemboembolic pulmonary hypertension. Respir Med. 2019;76:48–53.

How to cite this article: Mathavan A, Mathavan A, Vahdatpour C, Eagan C, Kalra SS, Ataya A. Precapillary pulmonary arterial hypertension in a patient with Proteus syndrome. Pulm Circ. 2022;12:e12098. https://doi.org/10.1002/pul2.12098