SKIN

IN-DEPTH REVIEW

Pulmonary Manifestations in Pseudoxanthoma Elasticum: A Review of Current Literature

Noa Yassky[1], Nancy Wei[1], Mark Lebwohl, MD[1]

[1]The Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York

ABSTRACT

Background: Pseudoxanthoma elasticum is a hereditary disease characterized by calcification of elastic fibers that result in cutaneous, ophthalmologic, and cardiovascular complications. As the pulmonary system contains multiple cell types with abundant elastic fibers, pulmonary manifestations are expected, yet not often observed.

Objective: To review the current literature for clinical, radiologic, and histologic findings of pulmonary manifestations in patients with pseudoxanthoma elasticum.

Methods: A search of the PubMed computerized database limited to English language case reports and cross-sectional cohort studies as of December 2020 was performed using the key words “pseudoxanthoma elasticum”, “PXE”, “pulm*”, and “lung”.

Results: A total of 15 patients with clinical, radiologic, or histologic pulmonary manifestations of PXE were identified across four case reports and one cohort study. Progressive exertional dyspnea was the only symptom reported.

Discussion: Histologic and/or radiologic investigation of PXE patients who presented with progressive exertional dyspnea revealed calcification and irregularity of the elastic laminae in the pulmonary vasculature, the alveolar septa, or both. Additionally, spirometry and diffusion studies in PXE patients revealed a restrictive pattern of lung disease with significantly decreased perfusion compared to controls.

Conclusions: PXE patients with pulmonary symptoms severe enough to have clinical impact are extremely rare, and thus investigative workup is not recommended. Further research is needed to elucidate the clinical impact of lung calcification in PXE patients.

INTRODUCTION

Pseudoxanthoma Elasticum (PXE) is an autosomal recessive disease involving the calcification of elastic fibers resulting in ophthalmic, cutaneous, and cardiovascular clinical symptoms and has an estimated prevalence of 1:160,000.[1] The disorder is caused by an ABCC6 gene mutation that causes loss of function of the MRP6 protein, resulting in dysregulated tissue mineralization.[2] Characteristic traits of the disease include the presence of angioid streaks on funduscopic examination, cutaneous yellow xanthomatous papules in

flexural regions, and various cardiovascular manifestations. Serious complications of the disease secondary to elastic calcification of the tunica media layer of both peripheral and central arteries include permanent loss of vision, early onset myocardial infarction, valvular abnormalities such as mitral valve prolapse, intermittent claudication, and gastrointestinal hemorrhage. In the lung, elastin is expressed by pleural mesothelial cells, smooth muscle cells in airways and blood vessels, endothelial cells, and interstitial fibroblasts.[3] As the lungs contain extensive networks of elastic laminae, calcification of this system with some clinical manifestations is expected, yet not often reported clinically or in the literature. The purpose of this review is to identify clinical, radiologic, and histologic pulmonary findings of PXE.

METHODS

A PubMed search was conducted with the following terms, “PXE”, “pulm*” and “lung”, and investigation was limited to adult case reports and cohort studies appearing in the English-language literature as of December 2020. Articles wherein the full text was not available or of an irrelevant publication type such as literature reviews, conference abstracts, posters, and editorials were excluded. There was a total of four case studies and one cohort study included in this review of pulmonary manifestations in PXE patients.

RESULTS

The literature search yielded four case reports and one cohort study from four countries with a total of 15 cases of pulmonary manifestations of PXE. Publication years spanned from 1980-2020. A summary of the patient characteristics and clinical manifestations from each report is provided in Table 1.

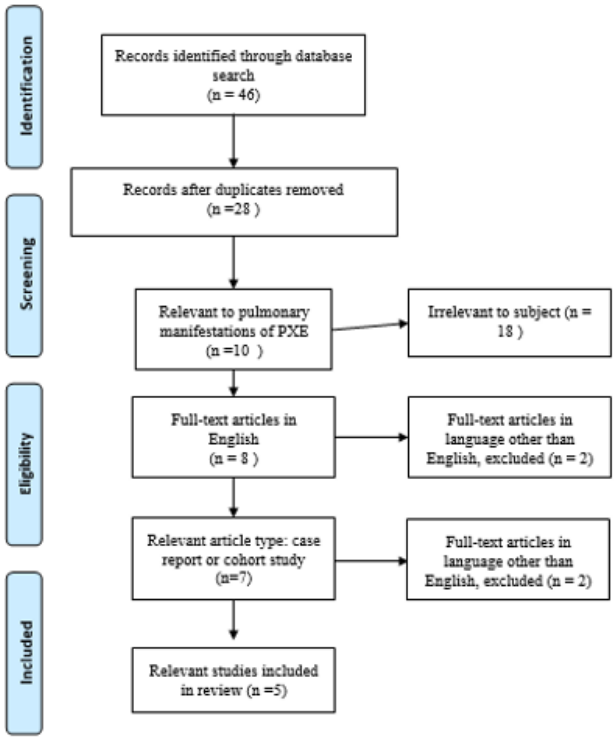

Figure 1. PRISMA Diagram

All four case reports featured PXE patients who complained of progressive dyspnea on exertion and underwent investigative workup that revealed elastic fiber irregularity in two discrete locations: the pulmonary arteries and the alveolar septum. Histologic vascular changes included fragmentation of elastic laminae in the tunica medica along with intimal and perivascular fibrosis.[4] Radiologic lung findings in one patient were limited to calcification and stenosis of the pulmonary artery that led to pulmonary hypertension.[5] One patient was found to only have discrete calcified nodules scattered diffusely across the alveolar septum without vascular changes.[6] A lung biopsy in a patient with severe dyspnea revealed calcified deposits within thickened alveolar lumina and septa, widespread irregularities in elastic laminae,

Table 1 Characteristics of PXE patients with pulmonary manifestations

Case report	Year published	Age (years)	Patients	Country	Diagnostic findings	Pulmonary Symptoms
Miki et al[4]	2007	68	1	Japan	Calcification of muscular arterial walls only	Exertional dyspnea*
Montani D et al[5]	2020	39	1	France	Pulmonary stenosis	Exertional dyspnea
Yamamoto N et al[6]	1996	74	1	Japan	Small, calcified nodules scattered in the alveolar septa only	Exertional dyspnea
Jackson A et al[7]	1980	51	1	Malaysia	Calcification and elastic fiber irregularities in pulmonary arteries, arterioles, venules and alveolar lumina and septa.	Exertional dyspnea
Pingel S et al[8]	2016	52.0 ±9.0	11	Germany	11 patients with pathologically low DLCO% under 75% 1 patient with TLC <80%	No clinical symptoms

*Attributed to patient's diagnosis of mitral regurgitation secondary to chordae tendineae rupture, not pulmonary pathology
± denotes standard deviation

and intimal fibrosis of arterial, arteriole and venous walls.[7] These biopsy findings in addition to xathomatous papules in the axilla led to the diagnosis of PXE during admission.

Pingel et al measured spirometry results in a cohort of 35 PXE patients and found significantly lower absolute and predicted carbon monoxide diffusing capacity (DLCO, DLCO%) when compared to controls.[8] Eleven of these patients (31.5%) had pathologically decreased DLCO values. Absolute total lung capacity (TLC) was significantly decreased in the PXE group; however, only one patient presented with a predicted TLC <80%. None of the patients were found to have abnormalities in predicted vital capacity (VC%) or forced expiration in 1 second (FEV1%).

DISCUSSION

This literature review demonstrates that elastic fiber calcification of the pulmonary arteries and alveolar septa can be a rare manifestation of PXE. All four patients who complained of progressive exertional dyspnea had radiologic and/or histologic evidence of pulmonary calcification. Theoretically, the significantly decreased TLC and DLCO values in PXE patients is consistent with decreased perfusion and a restrictive pattern of lung disease. One possible explanation for this is how PXE induced calcification in pulmonary arteries can result in stenosis and thus perfusion defects without effect on ventilation. Calcification and decreased elasticity of in alveolar septum can manifest as subclinical interstitial lung disease with decreased TLC. Continual calcification of these two regions over time could explain the insidious onset of progressive exertional dyspnea reported. However, spirometry abnormalities in PXE patients did not correlate with the presence of pulmonary symptoms. Long term observation for the development of dyspnea in the PXE cohort could be helpful in determining whether spirometry could be used as a screening tool for asymptomatic patients. In addition, while calcification of small arteries in the ocular, gastrointestinal,

and rarely cerebrovascular systems can result in bleeding complications of these areas, there were no reported cases of pulmonary hemorrhage. [9]

CONCLUSION

Currently, there is no standard of care for PXE or its pulmonary manifestations. Due to the exceedingly rare nature of clinically significant symptoms, screening and referral to pulmonary specialists for monitoring is not recommended. Even in the presence of progressive exertional dyspnea, the impact of diagnostic imaging on overall management in PXE patients is minimal. Although uncommon, physicians might consider PXE as a diagnosis of exclusion for unexplained progressive exertional dyspnea if found in conjunction with classic cutaneous lesions or ocular findings. Further research must be conducted to evaluate the long-term clinical impact of pulmonary manifestations on PXE patients and possible response to experimental systemic therapies currently in development.

Conflict of Interest Disclosures: Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen Research & Development, LLC, Leo Pharmaceuticals, Ortho Dermatologics, Pfizer, and UCB, Inc.and is a consultant for Aditum Bio, Allergan, Almirall, Arcutis Inc., Avotres Therapeutics, BirchBioMed Inc., BMD skincare, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Facilitate International Dermatologic Education, Foundation for Research and Education in Dermatology, Inozyme Pharma, Kyowa Kirin, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, Neuroderm, Pfizer, Promius/Dr. Reddy's Laboratories, Serono, Theravance, and Verrica.

Funding: None

Corresponding Author:
Nancy Wei
Icahn School of Medicine at Mount Sinai Hospital
The Kimberly and Eric J. Waldman Department of Dermatology
5 East 98th Street, 5th floor
New York, NY 10029
Phone: 212-241-6758
Email: nancy.wei@mountsinai.org

References:

1. Bergen, Arthur A. B., et al. "ABCC6 And Pseudoxanthoma Elasticum." *Pflügers Archiv - European Journal of Physiology*, vol. 453, no. 5, 2006, pp. 685–691., doi:10.1007/s00424-005-0039-0.
2. Ringpfeil F, McGuigan K, Fuchsel L, et al. Pseudoxanthoma elasticum is a recessive disease characterized by compound heterozygosity. *J Invest Dermatol*. 2006;126(4):782-786. doi:10.1038/sj.jid.5700115
3. Mecham RP. Elastin in lung development and disease pathogenesis. Matrix Biol. 2018 Nov;73:6-20. doi: 10.1016/j.matbio.2018.01.005. Epub 2018 Jan 11. PMID: 29331337; PMCID: PMC6041195.
4. Miki K, Yuri T, Takeda N, Takehana K, Iwasaka T, Tsubura A. An autopsy case of pseudoxanthoma elasticum: histochemical characteristics. Med Mol Morphol. 2007 Sep;40(3):172-7. doi: 10.1007/s00795-007-0368-5. Epub 2007 Sep 18. PMID: 17874051.
5. Montani D, Jaïs X, Humbert M, Sitbon O. Pulmonary Hypertension Complicating Pulmonary Artery Involvement in Pseudoxanthoma Elasticum. Am J Respir Crit Care Med. 2020 Sep 1;202(5):e90-e91. doi: 10.1164/rccm.202002-0248IM. PMID: 32413269.
6. Yamamoto N, Hasegawa H, Sakamoto H, Numata H, Fukuda T, Komatsu S, Kido Y. [Pseudoxanthoma elasticum with pulmonary calcification]. Nihon Kyobu Shikkan Gakkai Zasshi. 1996 Jun;34(6):716-20. Japanese translated to English. PMID: 8741541.
7. Jackson A, Loh CL. Pulmonary calcification and elastic tissue damage in pseudoxanthoma elasticum. Histopathology. 1980 Nov;4(6):607-11. doi: 10.1111/j.1365-2559.1980.tb02956.x. PMID: 7439889.
8. Pingel S, Passon SG, Pausewang KS, Blatzheim AK, Pizarro C, Tuleta I, Gliem M, Charbel Issa P, Schahab N, Nickenig G, Skowasch D, Schaefer CA. Pseudoxanthoma Elasticum - Also a Lung Disease? The Respiratory Affection of Patients with Pseudoxanthoma Elasticum. PLoS One. 2016 Sep 13;11(9):e0162337. doi: 10.1371/journal.pone.0162337. PMID: 27622520; PMCID: PMC5021259.
9. Liaqat M, Heymann WR. Anticoagulation in Patients with Pseudoxanthoma Elasticum. *Skinmed*. 2017;15(4):319-320. Published 2017 Aug 1.