



Editorial: Advances and Updates in Diffuse Cystic Lung Diseases

Bruno Guedes Baldi^{1*}, Souheil El-Chemaly² and Kai-Feng Xu³

¹ Pulmonary Division, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil, ² Division of Pulmonary and Critical Care Medicine, Brigham's and Women's Hospital, Harvard Medical School, Boston, MA, United States, ³ State Key Laboratory of Complex Severe and Rare Diseases, Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Keywords: diagnostic imaging, genetics, diffuse cystic lung disease, pathogenesis, treatment

Editorial on the Research Topic

Advances and Updates in Diffuse Cystic Lung Diseases

This Frontiers Research Topic aimed to update relevant information, to publish advances and to determine future research directions regarding diffuse cystic lung diseases (DCLDs), such as lymphangiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and Birt-Hogg-Dubé (BHD) syndrome.

Diffuse cystic lung diseases are a variety group of diseases characterized by the presence of multiple cysts in more than one lung lobe, usually bilateral (1). Chest high-resolution computed tomography (HRCT) is the main tool and a multidisciplinary discussion is desirable in the approach to DCLDs. The main etiologies of DCLDs include LAM, PLCH, and other smoking-related diseases, BHD syndrome, lymphocytic interstitial pneumonia, pulmonary amyloidosis, bronchiolitis, metastatic neoplasms, and light-chain deposition disease, etc. (2, 3). New disorders are continuously included in the differential diagnosis of DCLDs, and based on the fact that management and prognosis vary according to the etiology, it is important to try to narrow such differential and, if possible, to confirm the cause, which might require a lung biopsy (1, 4).

Several advances were obtained in the understanding of DCLDs in the last decades, especially in the pathogenesis, genetics, and in the diagnostic approach of LAM and PLCH, and, additionally, in the treatment of LAM (5–7). Despite improvements in such issues, there is still no curative treatment for LAM and PLCH (5, 7). Furthermore, the pathophysiology and natural history of several DCLDs are still not fully understood.

Therefore, new studies addressing DCLDs are desired to expand knowledge in the area, and to improve the management of patients. Five studies were published in this Research Topic, two about LAM, two focusing on BHD syndrome and a review about PLCH, highlighting diverse topics.

Previous studies demonstrated that serum matrix metalloproteinases (MMP) –2 and –9 were higher in LAM compared to healthy controls (8, 9). However, doxycycline, a MMP inhibitor, had no effects on pulmonary function decline in a clinical trial in LAM (10). Serum vascular endothelial growth factor (VEGF) -D is a useful biomarker included in the diagnostic guidelines of LAM (5). Previous studies demonstrated that serum VEGF-D was greater in patients with LAM than in healthy controls and in those with other cystic lung diseases (11, 12). Terraneo et al. assessed the role of MMP-2, MMP-7, VEGF-C, and VEGF-D in women with LAM and TSC. The authors found that MMP-2 was greater in LAM compared to controls and TSC patients, and that MMP-7 was higher in TSC-LAM patients. The authors reinforced the importance of VEGF-D in the diagnosis of LAM, and demonstrated that VEGF-C seems to have no role in the diagnosis of LAM and TSC. The authors concluded that MMP-2 and MMP-7 are promising biomarkers in LAM, although further studies with larger populations and with other DCLDs are required to confirm their findings.

OPEN ACCESS

Edited and reviewed by:

Laurent Pierre Nicod,
University of Lausanne, Switzerland

*Correspondence:

Bruno Guedes Baldi
bruno.guedes2@terra.com.br

Specialty section:

This article was submitted to
Pulmonary Medicine,
a section of the journal
Frontiers in Medicine

Received: 06 April 2021

Accepted: 17 May 2021

Published: 07 June 2021

Citation:

Baldi BG, El-Chemaly S and Xu K-F
(2021) Editorial: Advances and
Updates in Diffuse Cystic Lung
Diseases. *Front. Med.* 8:691688.
doi: 10.3389/fmed.2021.691688

Song et al. provided a comprehensive review of the pathogenesis of LAM and discussed the role of the mTOR signaling pathway in cell growth and proliferation. Although the authors highlighted the role of mTOR inhibitors in attenuating the lung function decline in LAM, they reinforced that such drugs are not a curative therapy (6). Furthermore, other potential therapeutic targets for LAM were presented in this review, such as inhibition of autophagy, inhibition of receptor tyrosine kinases, including VEGF receptors, hormonal blockade, urokinase-type plasminogen activator, blockade of the mTORC2 pathway, and DNA damage checkpoint (13, 14). This review supports the idea that in the future the treatment of LAM will be based on the combination of drugs, acting on different pathogenic pathways.

Zong et al. presented a novel heterozygous variant (c.912delT/p.E305KfsX18) in exon 9 of the folliculin gene, a tumor suppressor, in seven patients with BHD syndrome from a Chinese family. All patients presented with bilateral pulmonary cysts on HRCT, three had primary spontaneous pneumothorax (PSP), and none had cutaneous or renal lesions. This case series strengthens the importance of screening for folliculin gene variants in patients with pulmonary cysts and PSP, and of trying to establish a correlation between genotype and phenotypic presentation, although it is not always clear in genetic disorders.

Muller et al. performed a meta-analysis of published epidemiological data using Bayes equation to determine for the first time the prevalence of BHD syndrome and, additionally, information regarding PSP. The main findings of this study were as follows: (1) The prevalence of BHD in the general population was 1.86 (95% confidence interval: 1.16–3.00) per million; (2) The probability of having BHD syndrome among patients with apparent PSP was 9%; (3) The incidence rate of PSP in the

general population was 8.69 (95% confidence interval: 6.58–11.46) per 100,000 person-years; (4) The prevalence of PSP was 0.77 (95% confidence interval: 0.52–1.02) per 100,000; (5) The overall probability of PSP in BHD syndrome was 43%. Therefore, this study reinforces that BHD syndrome is rare and has a high probability of developing PSP, and the recommendation to screen for BHD syndrome in patients with PSP.

Diverse topics about PLCH are discussed in this broad narrative review by Radzikowska. The author presented updated issues about PLCH, emphasizing definition, classification, epidemiology, pathogenesis, genetic features, clinical manifestations, radiological and histological presentations, and diagnostic approach. Moreover, potential therapeutic modalities are highlighted in such review, including smoking cessation, corticosteroids, chemotherapy and target drugs. Future perspectives in PLCH include to expand the understanding of the pathogenesis, the identification of biomarkers to support diagnosis, prognosis and therapeutic response, to define efficacy and enhance experience with target drugs, and to identify curative treatments.

In summary, the manuscripts included in this Research Topic highlighted diverse issues and added relevant data to improve knowledge in the area of DCLDs. Although several advances were obtained in the genetic characterization, pathogenesis and diagnostic approach regarding DCLDs in recent years, there is still a need to identify novel targets and therapeutic modalities with curative results, especially in LAM and PLCH.

AUTHOR CONTRIBUTIONS

All authors wrote, reviewed, and approved the final version of the manuscript.

REFERENCES

- Baldi BG, Carvalho CRR, Dias OM, Marchiori E, Hochhegger B. Diffuse cystic lung diseases: differential diagnosis. *J Bras Pneumol.* (2017) 43:140–9. doi: 10.1590/s1806-37562016000000341
- Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse cystic lung disease. Part I. *Am J Respir Crit Care Med.* (2015) 191:1354–66. doi: 10.1164/rccm.201411-2094CI
- Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse cystic lung disease. Part II. *Am J Respir Crit Care Med.* (2015) 192:17–29. doi: 10.1164/rccm.201411-2096CI
- Raoof S, Bondalapati P, Vidyula R, Ryu JH, Gupta N, Raoof S, et al. Cystic lung diseases: algorithmic approach. *Chest.* (2016) 150:945–65. doi: 10.1016/j.chest.2016.04.026
- McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, et al. Official American thoracic society/Japanese respiratory society clinical practice guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med.* (2016) 194:748–61. doi: 10.1164/rccm.201607-1384ST
- McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med.* (2011) 364:1595–606. doi: 10.1056/NEJMoa1100391
- Shaw B, Borchers M, Zander D, Gupta N. Pulmonary langerhans cell histiocytosis. *Semin Respir Crit Care Med.* (2020) 41:269–79. doi: 10.1093/med/9780198746690.003.0425
- Pimenta SP, Baldi BG, Acencio MMP, Kairalla RA, Carvalho CRR. Doxycycline use in patients with lymphangioleiomyomatosis: safety and efficacy in metalloproteinase blockade. *J Bras Pneumol.* (2013) 37:424–30. doi: 10.1590/S1806-37132011000400003
- Chang WYC, Cane JL, Blakey JD, Kumaran M, Pointon KS, Johnson SR. Clinical utility of diagnostic guidelines and putative biomarkers in lymphangioleiomyomatosis. *Respir Res.* (2012) 13:34. doi: 10.1186/1465-9921-13-34
- Chang WYC, Cane JL, Kumaran M, Lewis S, Tattersfield AE, Johnson SR. A 2-year randomised placebo-controlled trial of doxycycline for lymphangioleiomyomatosis. *Eur Respir J.* (2014) 43:1114–23. doi: 10.1183/09031936.00167413
- Young LR, Vandyke R, Gulleman PM, Inoue Y, Brown KK, Schmidt LS, et al. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. *Chest.* (2010) 138:674–81. doi: 10.1378/chest.10-0573
- Xu K-F, Zhang P, Tian X, Ma A, Li X, Zhou J, et al. The role of vascular endothelial growth factor-D in diagnosis of lymphangioleiomyomatosis (LAM). *Respir Med.* (2013) 107:263–8. doi: 10.1016/j.rmed.2012.10.006
- El-Chemaly S, Taveira-Dasilva A, Goldberg HJ, Peters E, Haughey M, Bienfang D, et al. Sirolimus and autophagy inhibition in lymphangioleiomyomatosis: results of a phase I clinical trial. *Chest.* (2017) 151:1302–10. doi: 10.1016/j.chest.2017.01.033
- Atochina-Vasserman EN, Abramova E, James ML, Rue R, Liu AY, Ersumo NT, et al. Pharmacological targeting of VEGFR signaling

with axitinib inhibits Tsc2-null lesion growth in the mouse model of lymphangiomyomatosis. *Am J Physiol Lung Cell Mol Physiol.* (2015) 309:L1447–54. doi: 10.1152/ajplung.00262.2015

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Baldi, El-Chemaly and Xu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.