Case report • DOI: 10.2478/pneum-2023-0020 • 71 • 2022 • 54-59

sciendo

Pneumologia

Interstitial lung disease with genetic susceptibility: case report

Aleksandra Ana[1], Adriana Ana Trușculescu[2,3,*]

[1] Department of Pulmonology, Clinical Hospital for Infectious Diseases and Pneumophthisiology "Dr. Victor Babeș", Timișoara, Romania
[2]Pulmonology Department, 'Victor Babes' University of Medicine and Pharmacy, Timișoara, Romania
[3] Victor Babes University of Medicine and Pharmacy, Center for Research and Innovation in Precision Medicine of Respiratory Diseases (CRIPMRD), 'Victor Babes', Timisoara,Romania

Abstract

English:

Introduction: *Interstitial lung disease (ILD) includes more than 200 progressive conditions classified based on common clinical, imaging or pathophysiological factors.*
Case presentation: *A 37-year-old male, former smoker, with unknown exposure and a family history of incompletely identified ILD, underwent functional and imaging investigations that raise the suspicion of an ILD with a pattern of non-specific interstitial pneumonia (NSIP). High-resolution computer tomography (HRCT) imaging detects the progression of lesions. The severely altered functional status does not allow a lung biopsy to be performed to elucidate the aetiology and establish the optimal therapeutic approach. Bronchoscopy with bronchial aspirate sampling and bronchoalveolar lavage does not suggest a specific ILD aetiology. A diagnosis of diffuse fibrosing and progressive ILD – an unclassifiable phenotype – was established, and after a multidisciplinary discussion, antifibrotic treatment was initiated. A genetic test was performed for a possible familial ILD with a genetic component. The test identified the presence of an autosomal recessive combined immunodeficiency due to NF-κB inducing kinase (NIK) deficiency associated with the MAP3K14 gene leading to the suspicion of a familial ILD.*
Discussion: *Genetic testing is essential for diagnosis of ILD, especially in young patients with a family history. Antifibrotics are the only available option for such cases; if immunosuppressive therapy should be initiated still remains a question. Is a lung transplant a realistic solution in such cases?*
Conclusions: *Familial aggregation and genetic changes should be sought for in diffuse ILD diagnosis.*

Keywords

ILD • NSIP • familial aggregation • young patient • genetic evaluation

Pneumopatie interstițială difuză cu caractere genetice: prezentare de caz

Rezumat

Romanian:

Indroducere: *Pneumopatiile interstitiale difuze acoperă mai mult de 200 de afecțiuni cu caracter progresiv clasificate pe baza caracteristicilor clinice, imagistice sau fiziopatologice comune.*
Prezentarea cazului: *Propunem cazul clinic al unui bărbat de 37 de ani, fost fumător, fără expunere profesională și domestică cunoscuta, cu antecedente familiale de boli pulmonare interstițiale incomplet identificate care efectuează investigații funcționale și imagistice care ridică suspiciunea de pneumopatie interstitiala difuza (PID) cu un pattern pneumopatie interstițială nespecifică (NSIP). Imagistica tomografie computerizată de înaltă rezoluție (HRCT) detectează progresia leziunilor. Starea funcțională sever alterată nu permite efectuarea unei biopsii pulmonare pentru a elucida etiologia și a stabili abordarea terapeutică optimă. Bronhoscopia cu prelevare de aspirat bronșic și lavaj bronhoalveolar nu sugerează o etiologie specifică. S-a stabilit diagnosticul de pneumopatie interstițială difuza forma fibrozanta de tip progresivă – fenotip neclasabil iar în urma unei discuții multidisciplinare a fost inițiat tratamentul antifibrotic. S-a ridicat suspiciunea unei pneumopatii interstitiale cu o componentă genetică familiala motiv pentru care s-a efectuat testare genetica. Testul a identificat prezența unei imunodeficiențe combinate autosomal recesive datorate deficienței kinazei inductoare de NF-κB (NIK) asociată cu gena MAP3K14, ceea ce a crescut suspiciunea de ILD familială.*
Discuții: *Testele genetice sunt importante pentru stabilirea unui diagnostic, mai ales în astfel de cazuri. Antifibroticele sunt singura abordare disponibilă pentru astfel de cazuri sau ar trebui inițiată terapia imunosupresivă? Este transplantul pulmonar o soluție reală în astfel de cazuri?*
Concluzii: *Agregarea familială și componentele genetice sunt esențiale în boala pulmonară interstițială difuză.*

Cuvinte-cheie

PID • NSIP • pacient tanar • agregare familiala • evaluare genetica • antifibrotice

*Corresponding author: Trușculescu Ana Adriana
E-mail: ana.trusculescu@umft.ro

Open Access. © 2022 Ana and Trusculescu, published by Sciendo
This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License.

Introduction

The interstitial lung disease (ILD) group includes more than 200 conditions classified based on common clinical, imaging or pathophysiological factors (1). While some entities may be linked to specific causes, in many individuals, no exposure can be specifically identified; therefore, ILDs can be divided into two types: ILDs with a known cause and ILDs without a known cause, including the idiopathic interstitial pneumonias (2). Risk factors for ILD progression are male sex, older age, lower baseline pulmonary function and a radiological or pathological pattern of usual interstitial pneumonia (3).

Family history is one of the risk factors for idiopathic ILD (4). Although there is no consensus definition, familial ILD is usually defined as a case of ILD in which the patient also has a family history of two or more relatives with ILD. There is growing evidence that genetic factors contribute to the development of ILD, notably in the context of familial aggregation (5).

Case description

We present the case of a 37-year-old male, former smoker (20 PA, abstinent for 18 months), with no occupational or domestic exposure to smoke, with a family history of incompletely identified ILD (mother diagnosed with sarcoidosis, deceased at 45 years, and the father diagnosed with an unknown lung disease with progressive evolution towards chronic respiratory failure, deceased at 36 years).

The patient had moderate obstructive sleep apnea syndrome and mild SARS-COV-2 viral infection. The patient did not follow-up with any chronic treatment.

He was admitted to our hospital with complaints of recurrent episodes of dry cough, progressive dyspnoea (mMRC3), asthenia and fatigue. The symptomatology started approximately 2 years before (2020), but it intensified in January 2021 when the patient was diagnosed with a mild SARS-COV-2 viral infection. In January 2021, the patient underwent a native chest computer tomography (CT) scan showing diffuse centrilobular emphysema, multiple thin-walled air cysts predominantly in the upper lobes and associated bibasilar ground glass areas with a mosaic appearance (Figure 1A). At that time, the suspicion of diffuse ILD was raised, but it was decided that the patient would be followed-up without other investigations.

During 2021, the patient was evaluated functionally and immunologically. Lung function tests showed a moderate restriction (forced vital capacity, FVC = 57%, forced expiratory volume, FEV1 = 61%, FEV1/FVC = 89%) and a severe decrease in the diffusing capacity of the lung for carbon monoxide (DLCO = 26%). The 6 min walking test (6MWT) showed a significant decrease in exercise tolerance and revealed latent respiratory failure (walked distance = 74% of predicted, oxygen saturation (SpO_2) decreased from 95% to 71%).

The patient was also investigated from an immunological point of view; a broad panel of antibody tests were performed cyclic citrullinated peptide (anti-CCP-negative), antineutrophil cytoplasmic antibodies (anti-cANCA, pANCA-negative), antinuclear antibody (ANA profile-negative), with a weakly positive rheumatoid factor (RF) (14.4 IU/mL) and positive proliferating cell nuclear antigen (anti-PCNA antibodies). Alpha1 antitrypsin deficiency and thyroid dysfunction were also ruled out.

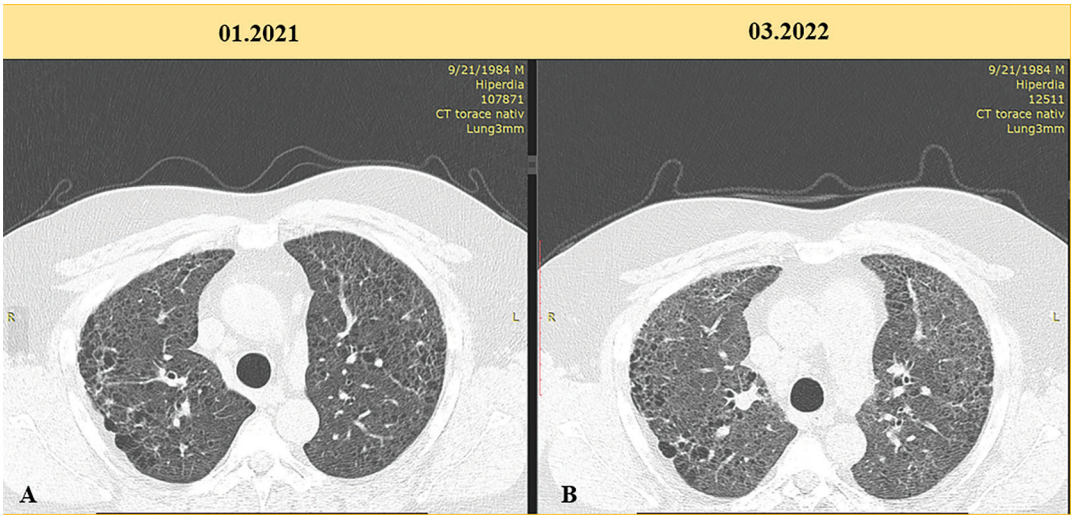


Figure 1. CT scan of the chest showing diffuse centrilobular emphysema, multiple thin-walled air cysts predominantly in the upper lobes and bibasilar ground glass areas with a mosaic appearance: (A) initial CT scan (January 2021). (B) Follow-up CT scan (March 2022). CT, computer tomography.

In March 2022, the CT scan was repeated on the patient, which showed the same type of lesions as the previous one, but with a moderate progression of air cysts and ground glass areas (Figure 1B).

In April 2022, DLCO was repeated for him, which showed a 2% impairment compared with the previous one (DLCO = 24%). The 6MWT was performed on the patient, and a critical impairment of exercise tolerance was observed. The patient walked 54% of the predicted walking distance, and his oxygen saturation dropped to 50%. The patient did not follow any corticosteroid or chronic treatment later on.

On admission to our clinic (May 2022), physical examination revealed good general condition, moon face, obesity (BMI = 33.56 kg/m^2), finger clubbing, SpO_2 = 85% after exercise and 96% at rest. Normally shaped thorax, symmetrical respiratory expansions. Lung auscultation reveals bibasilar velcro crackles. Examination results of other systems were normal.

The usual laboratory tests were performed but no significant changes were observed. We noticed mild hepatocytolysis (ALT = 47.9 U/L), mild hyponatraemia (Na = 127 mmol/L) and the presence of a weakly positive RF (RF = 16I U).

Taking into account the patient's physical appearance (obesity, moon face) and the possibility of initiating corticotherapy, we raised the suspicion of Cushing's syndrome, for which we dosed the nocturnal salivary cortisol and the adrenocorticotropic hormone, both within normal limits.

Considering the immunological history, we also raised the suspicion of possible connective tissue disorder. With this aim, we completed the antibody panel tests with circulating immune complexes and the C3 complement fragment values, within normal parameters.

During the hospitalisation period, we reevaluated the patient's functional status. Spirometry did not show significant changes compared with the previous one (FVC = 57%, FEV1 = 61%, FEV1/FVC = 80.55%), but a significant decline of DLCO was observed within 1 month, decreasing from 24 % to 19%. The severely altered functional status did not allow a lung biopsy to be performed to elucidate the aetiology and establish the optimal therapeutic approach. Bronchoscopy with bronchial aspirate sampling and bronchoalveolar lavage (BAL) was performed but without suggestive results for a specific ILD pattern (mild lymphocytic alveolitis).

For a better qualitative and quantitative assessment of the radiological lesions, we performed high-resolution computer tomography (HRCT) in our clinic, which brought us new suggestive characteristics to support a nonspecific interstitial pneumonia (NSIP) pattern, namely the sparing of the subpleural space without an obvious progression of lesions from an imaging point of view (Figure 2).

We performed interdisciplinary evaluations. During the rheumatological evaluation, the capillaroscopy revealed a normal capillary pattern.

An echocardiography exam was performed, which did not show suggestive characteristics of pulmonary hypertension, but in the context of ILD, a right heart catheterisation was recommended.

Diagnosis

After corroborating all these data, the established diagnosis was diffuse fibrosing progressive ILD – unclassifiable phenotype. The patient meets three of the four progression criteria, namely progression of fibrotic type lesions in the last 3–24 months associated with worsening of respiratory symptoms, FVC decrease ≥5% of the predicted value in

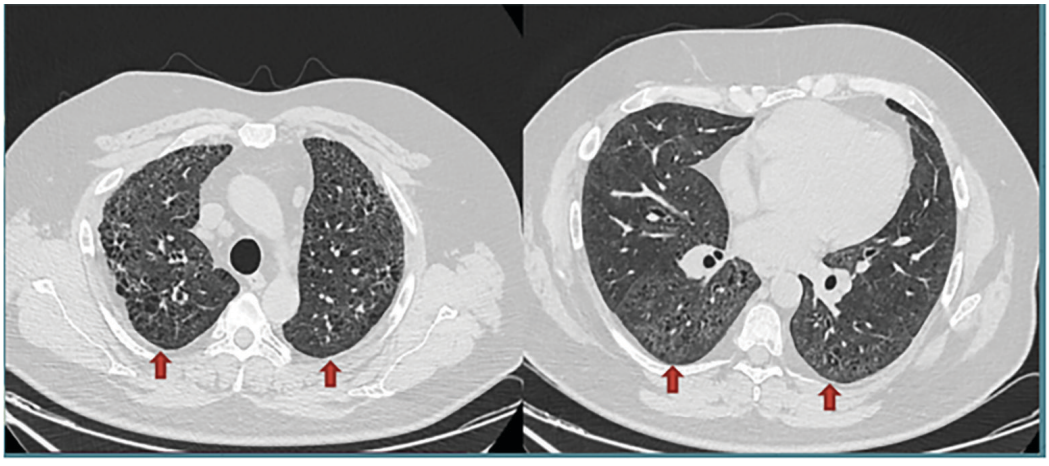


Figure 2. Diffuse centrilobular emphysema, multiple thin-walled air cysts predominantly in the upper lobes and bibasilar ground glass areas and the sparing of the subpleural spare (red arrows).

association with symptomatology worsening in the last 3–24 months and 6MWT with a decrease in the distance traveled by >50 m in the last 3–24 months or significant desaturation (minimum 4%).

Treatment

The case was discussed in the periodic multidisciplinary discussion in our center, and the initiation of antifibrotic treatment with nintedanibum 300 mg/day (150 mg twice a day) was decided.

At the 3-month follow-up, a slight dyspnoea improvement was observed, with a subjective increase in effort tolerance. We also observed a slight improvement in lung function (FVC = 59%, FEV1 = 61%, FEV1/FVC = 85%, DLCO = 21%).

The patient has had no side effects associated with the antifibrotic medication during follow-up.

Considering the family history of the patient, with both parents suffering from severe and lethal ILDs, the next logical step was performing a genetic test for a possible familial ILD with a genetic component. In October 2022, the patient underwent a panel tests with a total of 523 genes, including a surfactant metabolism panel, primary immunodeficiency panel and common variable immunodeficiency panel. The genetic test concluded that the patient had an autosomal recessive combined immunodeficiency due to NF-κB inducing kinase (NIK) deficiency associated with the *MAP3K14* (mitogen-activated protein kinase kinase kinase 14) gene. Following this result, we recommended immunophenotyping, which is currently in progress.

In order to exclude a potential immune deficiency, immunoglobulin levels and antibodies were administered with results within normal limits.

Discussion

ILD is an umbrella term for the assembly of disorders that cause lung scarring or fibrosis. Lung scarring causes stiffness in the lungs resulting in breathing difficulty. Lung injury from ILD is often irreversible and worsens over time (6).

ILD can be idiopathic, and this variant is the most common type of ILD. Other aetiologies that lead to ILD include autoimmune disease, chemotherapy, radiation, drugs, environmental and occupational exposure and genetic causes (7). The prevalence of ILD is 20% higher in men (80.9 per 100,000) than that in women (4).

The incidence of familial aggregation in unclassifiable ILDs in closely related family members is between 2% and 20%. These cases remain classified as unclassifiable despite the genetic predisposition.

Surfactant protein C (SFTPC) (~1%), surfactant protein A2 (SFTPA2) (~1%), telomerase reverse transcriptase (TERT) (~15%) and telomerase RNA component (TERC) (~1%) gene mutations are responsible for approximately 20% of all familial ILDs, but most responsible genes have not yet been identified. TERT mutation was also observed in more than 50 types of cancers.

Eighty percent of familial ILDs have evidence of vertical transmission, suggesting a single autosomal dominant mechanism (8).

NIK deficiency associated with the *MAP3K14* gene is the most remarkable feature of this case. NIK is best known for its' regulation of immune system development and function. It plays a critical role in developing lymphoid organs' appropriate function of different immune cells, including macrophages, T cells, B cells, dendritic cells and hematopoietic stem cells. NIK is a central mediator of immune responses, and therefore, aberrant NIK activation or expression has been linked to several immune, inflammatory and metabolic diseases such as lupus erythematosus, rheumatoid arthritis, osteoporosis, lung cancer, leukemias and lymphomas (9). After conducting a comprehensive examination of existing literature, we couldn't find any evidence of a relationship between NIK deficiency caused by the MAP3K14 gene and ILDs, indicating the necessity for further research.

While much remains to be learned about the full spectrum of NIK functions, it is clear that NIK and NF-κB signaling are essential for many diverse functions of immune cells, inflammatory disease pathogenesis and malignancies (10).

BAL is useful not only in diagnosing a variety of specific ILDs but also in narrowing the differential diagnosis. Investigations into the function of pulmonary lymphocytes in the body's defence mechanisms have mainly been based by the examination of cells taken from the lung through BAL. New tools that use the genomic characterisation of BAL cells can make an accurate ILD diagnosis, monitor disease activity and choose novel therapies for specific forms of ILD (11).

Is the initiation of immunosuppressive treatment recommended? Immunosuppression is still the mainstay of therapy in ILDs other than idiopathic pulmonary fibrosis (IPF). Therapies include administration of corticosteroids, mycophenolate mofetil, methotrexate, azathioprine, rituximab and cyclophosphamide (12).

There is a considerable amount of compelling data in the literature to support using immunosuppressive drugs to treat progressive interstitial pneumonia. Combinations of antifibrotic drugs with immsunosuppressive agents may enhance efficacy and prevent the progression of forms of ILDs characterised by extensive and progressive fibrosis (13).

Can lung transplantation be a viable solution in this case?

The survival rate varies significantly among patients with non-IPF ILD and exceeds that of IPF by many years, especially in cases of sarcoidosis, connective tissue disease, NSIP and occupational ILD (14).
According to the International Society of Heart and Lung Transplantation, the median survival rate after a lung transplant is 5.2 years for patients with idiopathic interstitial lungs and almost 7 years for ILDs that are not idiopathic (15).
In this case, depending on the follow-up, if the progression is maintained, lung transplantation should be considered as an viable option.

Conclusions

It is already demonstrated that bloodline relatives of familial ILD patients are at markedly elevated risk for ILD as compared with the general population (16).
Family history is recognised as one of the most potent risk factors for idiopathic ILD, and cases that run in families comprise a syndrome termed “familial interstitial lung disease” (17,18);
Diverse ILD clinical phenotypes can be seen within a family, and available evidence suggests that underlying genetic risk is the primary determinant of disease outcomes (19).
In terms of understanding the genetic basis of ILDs, although tremendous progress has been made in recent years, research in this area is still needed.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

Authors contributions

Patient care, data collection and interpretation, analysis and evaluation of CT images were taken care of by AA and AT. AA and AT wrote and edited the manuscript.

Institutional review board statement

Not applicable.

Data availability statement

All data used to support the findings of this study are available from the corresponding author upon reasonable request.

Informed consent statement

Informed consent was obtained from all subjects involved in this study.

References

1. Jakubczyc A, Neurohr C. Diagnostik und therapie bei interstitiellen lungenerkrankungen. *Deutsche Medizinische Wochenschrift*. 2018;143(24): 1774–1777. doi:10.1055/a-0622-9299.
2. Crystal RG, Bitterman PB, Rennard SI, Hance AJ, Keogh BA. Interstitial lung diseases of unknown cause. Disorders characterized by chronic inflammation of the lower respiratory tract (first of two parts). *The New England Journal of Medicine*. 1984;310(3): 154–166. doi:10.1056/NEJM198401193100304.
3. Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. *Respiratory Research*. 2020;21(1): 32. doi:10.1186/s12931-020-1296-3.
4. Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. *European Respiratory Review*. 2018;27(150): 180077. doi:10.1183/16000617.0077-2018.
5. Borie R, Le Guen P, Ghanem M, Taillé C, Dupin C, Dieudé P, et al. The genetics of interstitial lung diseases. *European Respiratory Review*. 2019;28(153): 190053. doi:10.1183/16000617.0053-2019.
6. Montesi SB, Fisher JH, Martinez FJ, Selman M, Pardo A, Johannson KA. Update in interstitial lung disease 2019. *American Journal of Respiratory and Critical Care Medicine*. 2020;202(4): 500–507. doi:10.1164/rccm.202002-0360UP.
7. Demedts M, Wells AU, Antó JM, Costabel U, Hubbard R, Cullinan P, et al. Interstitial lung diseases: an epidemiological overview. *The European Respiratory Journal Supplement*. 2001;32: 2s–16s.
8. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*. 2013;188(8): e13–e64. doi:10.1164/rccm.201309-1634ST.
9. Paciolla M, Pescatore A, Conte MI, Esposito E, Incoronato M, Lioi MB, et al. Rare mendelian primary immunodeficiency diseases associated to impaired NF-κB signaling. *Genes and Immunity*. 2015;16(4): 239–246. doi:10.1038/gene.2015.3.

10. Saitoh Y, Martínez Bruyn VJ, Uota S, Hasegawa A, Yamamoto N, Imoto I, et al. Overexpression of NF-κB inducing kinase underlies constitutive NF-κB activation in lung cancer cells. *Lung Cancer*. 2010;70(3): 263–270. doi:10.1016/j.lungcan.2010.03.001.
11. Meyer KC, Raghu G. Bronchoalveolar lavage for the evaluation of interstitial lung disease: is it clinically useful? *The European Respiratory Journal*. 2011;38(4): 761–769. doi:10.1183/09031936.00069509.
12. van den Bosch L, Luppi F, Ferrara G, Mura M. Immunomodulatory treatment of interstitial lung disease. *Therapeutic Advances in Respiratory Disease*. 2022;16: 17534666221117002. doi:10.1177/17534666221117002.
13. Meyer KC. Immunosuppressive agents and interstitial lung disease: what are the risks? *Expert Review of Respiratory Medicine*. 2014;8(3): 263–266. doi:10.1586/17476348.2014.880054.
14. Kapnadak SG, Raghu G. Lung transplantation for interstitial lung disease. *European Respiratory Review*. 2021;30(161): 210017. doi:10.1183/16000617.0017-2021.
15. Stącel T, Nęcki M, Antończyk R, Latos M, Urlik M, Kościołek J, et al. Effectiveness of lung transplantation in patients with interstitial lung diseases. *Transplantation Proceedings*. 2020;52(7): 2143–2148. doi:10.1016/j.transproceed.2020.03.050.
16. Mathai SK, Schwartz DA, Warg LA. Genetic susceptibility and pulmonary fibrosis. *Current Opinion in Pulmonary Medicine*. 2014;20(5): 429–435. doi:10.1097/MCP.0000000000000074.
17. Kropski JA. Familial interstitial lung disease. *Seminars in Respiratory and Critical Care Medicine*. 2020;41(2): 229–237. doi:10.1055/s-0040-1708054.
18. Mikolasch TA, Garthwaite HS, Porter JC. Update in diagnosis and management of interstitial lung disease. *Clinical Medicine (London, England)*. 2017;17(2): 146–153. doi:10.7861/clinmedicine.17-2-146.
19. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. *European Respiratory Review*. 2019;28(151): 180100. doi:10.1183/16000617.0100-2018.