Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Human Pathology Reports 29 (2022) 300666

Contents lists available at ScienceDirect

Human Pathology Reports

journal homepage: www.journals.elsevier.com/human-pathology-reports

Active pulmonary interstitial fibrosis in a COVID-19 survivor diagnosed by transbronchial lung cryobiopsy six months after onset

Yutaka Muto [a,b], Koji Okudela [c,*], Atsuhito Nakazawa [a], Kakeru Hisakane [d], Mai Matsumura [c], Tamiko Takemura [e], Tae Iwasawa [f], Takashi Ogura [a]

[a] Division of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama 236-0051, Japan
[b] Department of Respiratory Medicine, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8953, Japan
[c] Department of Pathology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
[d] Department of Pulmonary Medicine and Oncology, Nippon Medical School Tama Nagayama Hospital, 1-7-1 Nagayama, Tama-city, Tokyo 206-8512, Japan
[e] Division of Pathology, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama 236-0051, Japan
[f] Division of Radiology, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama 236-0051, Japan

ARTICLE INFO

Keywords:
Post-COVID-19
Subclinical interstitial lung abnormalities
Progressive interstitial fibrosis

ABSTRACT

We present a 76-year-old man who visited our center because of persistent dyspnea with hypoxia on exertion 6 months after onset of coronavirus disease 2019. Chest computed tomography showed bilateral extensive subpleural reticulation with traction bronchiectasis predominantly in the lower lung lobes. Transbronchial lung cryobiopsy revealed spatially and temporally intermittent interstitial fibrosis with mild lymphoid cell infiltration. Not only were there membranous fibrotic scars on the alveolar septa, but there were scattered foci of alveolar collapse with young fibroblastic proliferations, suggesting progressive interstitial fibrotic lesions. In addition to fibrotic phase of diffuse alveolar damage, the acceleration of subclinical preexisting interstitial lung abnormalities might have affected his respiratory condition.

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occasionally leads to respiratory failure. Diffuse alveolar damage (DAD) and thrombosis were common pathological features of pulmonary involvement in COVID-19 [1]. Clinically, they lead to acute respiratory distress syndrome.

Even after recovering from the acute phase of COVID-19, many survivors still suffer from its long-term effects. An ambidirectional cohort study in China revealed that 76% of COVID-19 survivors had at least one lingering symptom as late as six months after the disease onset [2]. Several recent reports have suggested that persistent interstitial pneumonia is one of the important post-COVID-19 sequelae [3]. Radiologically, more than a third of COVID-19 survivors had fibrotic-like changes on chest CT scan [4].

The accurate mechanism of interstitial pneumonia in COVID-19 survivors remains unclear. Various components are considered as candidates associated with the pathogenesis of interstitial pneumonia after COVID-19 infection; they include viral infection itself, the secondary cytokine cascade, and mechanical ventilation [5]. In addition, little is known about how long pathological progression of pulmonary fibrosis lasts after COVID-19 infection. Herein, we present a case of active pulmonary interstitial fibrosis diagnosed by transbronchial lung cryobiopsy 6 months after onset of COVID-19.

Case presentation

A 76-year-old Japanese man was admitted to a hospital with acute respiratory failure. He had a medical history of angina pectoris, type 2 diabetes, and hypertension. He had smoked 20 cigarettes per day for 35 years from 20 to 55 years old. Chest computed tomography (CT) of the lungs showed bilateral diffuse ground-glass opacities with slight subpleural reticulation, which implied preexisting subclinical interstitial

Abbreviations: COVID-19, coronavirus disease 2019, CT, computed tomography; DAD, diffuse alveolar damage; DL_{CO}, diffuse capacity for carbon monoxide; KL-6, Krebs von den Lungen-6; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, percutaneous oxygen saturation; VC, vital capacity.

* Corresponding author.
E-mail address: kojixok@yokohama-cu.ac.jp (K. Okudela).

https://doi.org/10.1016/j.hpr.2022.300666
Received 26 April 2022; Accepted 23 June 2022
Available online 27 June 2022

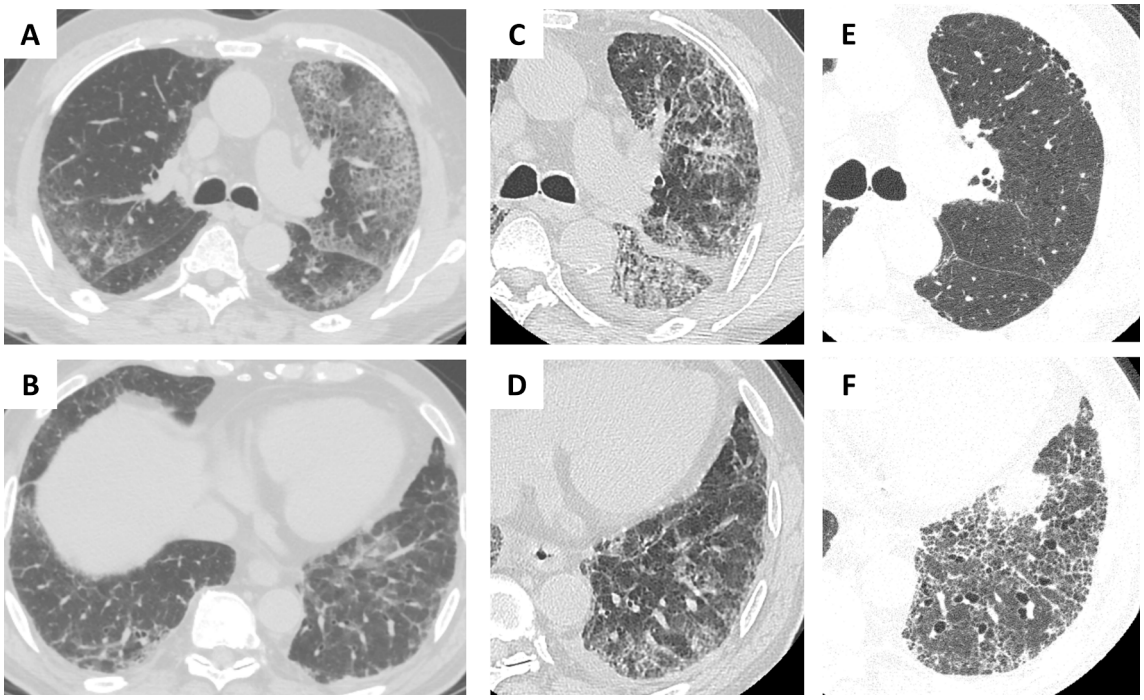

Fig. 1. Radiological findings of the patient The left panels (A, B) are chest CT scans upon diagnosis of COVID-19 that show bilateral diffuse ground-glass opacities in the lungs and slight subpleural reticulation with bronchiectasis. The middle panels (C, D) are chest CT scans 2 months after onset that show that ground-glass opacities remained, and that slight pleural effusion appeared. The right panels (E, F) are chest CT scans 6 months after onset that show extensive subpleural reticulation with traction bronchiectasis distributed predominantly in the lower lung lobes. Ground-glass opacities which had been observed at onset had disappeared. COVID-19, coronavirus disease 2019; CT, computed tomography.

lung abnormalities (Fig. 1A, 1B). The patient was diagnosed with COVID-19 based on SARS-CoV-2 positivity using reverse transcription-PCR. Remdesivir, corticosteroids, and antibiotics were administered, and noninvasive positive pressure ventilation was required for 20 days. After 2 months of treatment, the patient was discharged with long-term oxygen therapy (the flow rates of 2 L/min at rest and 5 L/min with exertion) (Fig. 1C, 1D). However, his dyspnea with hypoxia on exertion had remained unresolved throughout the course of treatment. Then, he was referred to our hospital for further investigation 6 months after onset of COVID-19. A physical examination revealed a height of 155.0 cm, body weight of 60.0 kg, a respiratory rate of 18/min, and percutaneous oxygen saturation (SpO_2) of 94% (ambient room air). Fine crackles were heard on inhalation at the bilateral lower back areas. Laboratory data showed elevation of Krebs von den Lungen-6 (KL-6) (1158 U/mL) and surfactant protein D (213.7 ng/mL), while serum C-reactive protein (0.12 mg/dL) was within the normal range. Chest X-ray revealed bilaterally diffuse granular shadow predominantly in the lower lung zones. Chest CT revealed bilaterally extensive subpleural reticulation with traction bronchiectasis distributed predominantly in the lower lung lobes, while the ground-glass opacities that had been observed at onset of COVID-19 had disappeared (Fig. 1E, 1F). Pulmonary function test results showed vital capacity (VC) of 2.43 L (82.9% of predicted value), forced expiratory volume in the first second of 1.88 L (83.6% of predicted value), and diffuse capacity for carbon monoxide (DL_{CO}) of 8.19 mL/min/mmHg (62.0% of predicted value). Transthoracic echocardiography showed no elevation of peak tricuspid regurgitation velocity (2.69 m/s). Six-minute walk test results revealed the distance of 455 m and minimum SpO_2 of 78% in ambient room air. Bronchoalveolar lavage fluid revealed inflammatory changes with a cell differential count of 64.0% macrophages, 25.1% lymphocytes, and 10.5% neutrophils, and the CD4/CD8 ratio was 0.7. Transbronchial lung cryobiopsy was performed from the left lower lobe via the B8a and B9a bronchi. Histological examination revealed spatially and temporally intermittent interstitial fibrosis with mild lymphoid cell infiltration. Not only were there membranous fibrotic scars on the alveolar septa, but there were also scattered foci of alveolar collapse with young fibroblastic proliferation (fibroblastic foci) (Fig. 2). These findings suggested that there could be active and potentially progressive interstitial fibrosis, which is similar to usual interstitial pneumonia. Multidisciplinary discussion was conducted, and we concluded that his condition was fibrotic phase of DAD complicated with progression of preexisting interstitial lung abnormalities. He started daily oral nintedanib. After 4 months of antifibrotic therapy, VC improved to 2.88 L (97.0% of predicted value). DL_{CO} was 8.86 mL/min/mmHg (66.7% of predicted value) and serum KL-6 level was 1210 U/mL.

Discussion

It is now well known that severe COVID-19 is DAD pathologically. DAD is divided into exudative, proliferative, and fibrotic phases. The exudative phase is characterized by alveolar septal edema, hyaline membranes, and leukocytes infiltration, whereas the organizing phase is characterized by young fibroblastic proliferation and type II pneumocyte hyperplasia. The fibrotic phase follows about three weeks after onset of COVID-19 [1,6,7]. In the present case, the membranous fibrosis on the alveolar septa was observed. Lymphoid cell infiltration was mild. They were consistent with the scar of DAD. In addition to the membranous fibrotic scars, fibroblastic foci were formed; it indicated the pulmonary interstitial fibrosis was progressive even 6 months after onset of COVID-19 [8].

To date, some reports have described the pathological features of the lungs of COVID-19 survivors several months after onset. Two patients who had been treated using veno-venous extracorporeal membrane oxygenation underwent lung transplantation more than 4 months and 6 months after diagnosis of COVID-19, respectively [9,10]. The explanted lungs showed diffuse interstitial fibrosis with mild lymphocytic infiltrates. Another study showed that usual interstitial pneumonia was the most common pathological finding in 18 patients who had

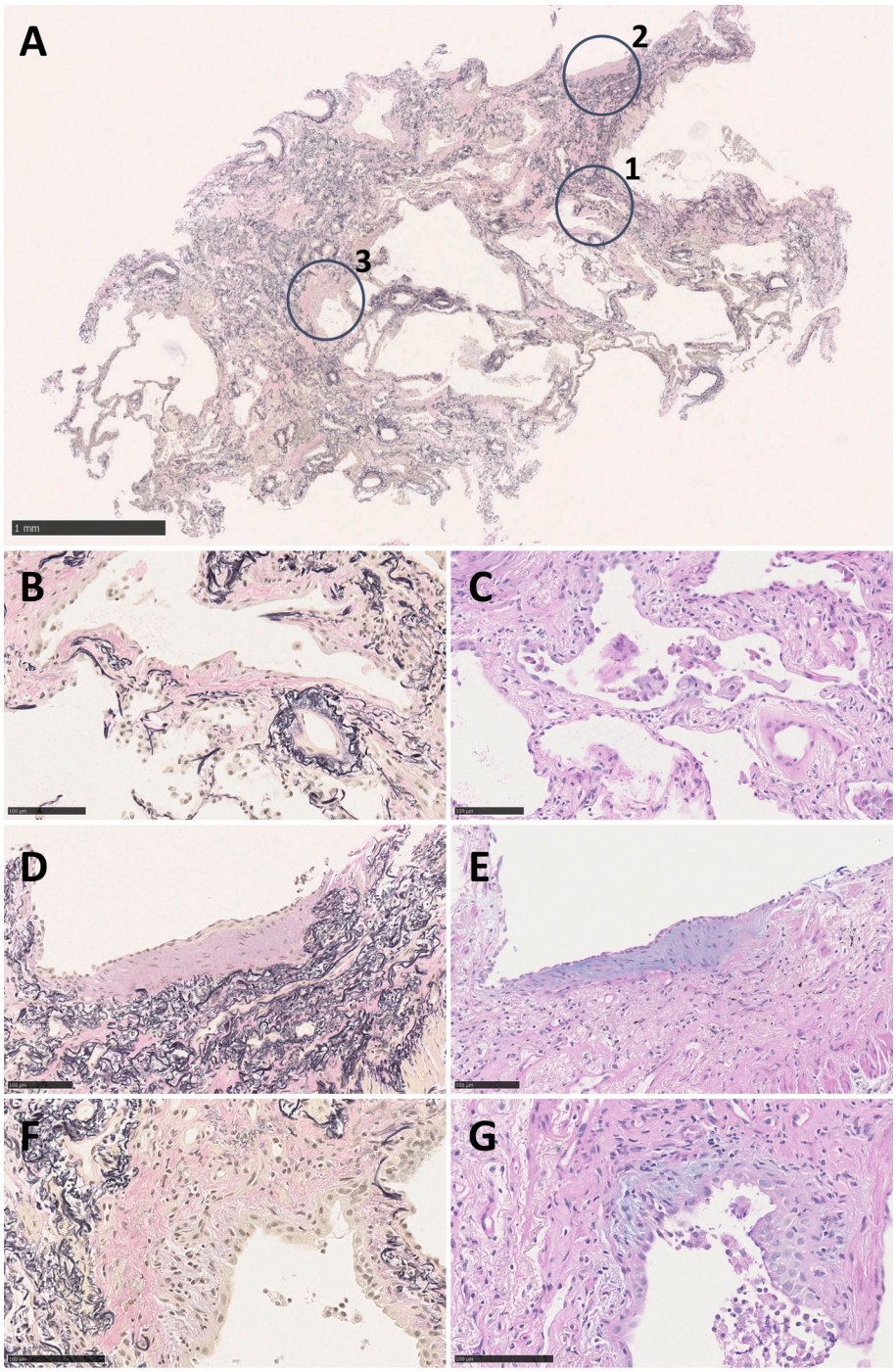

Fig. 2. Histological findings of specimens from transbronchial lung cryobiopsy Histological appearances of the transbronchial lung cryobiopsy specimen are shown. The scanning view reveals spatially intermittent alveolar collapse and interstitial fibrosis (A). Membranous fibrotic scars can be observed on alveolar septa (A circle 1, B, and C), along with foci of alveolar collapse with young fibroblastic proliferation (fibroblastic foci) (A circle 2, D and E), and also zonal/layered fibrosis consisting of different temporal phase fibrosis (A circle 3, F and G). Very mild lymphoid cell infiltration in fibrotic interstitium is seen (C, E, and G). Images B/C, D/E, and E/G are closed up views from circles 1, 2, and 3 in A, respectively. Elastica van Gieson was used for A, B, D, and F. Alcian Blue Periodic Acid Schiff was used for C, E, and G.

undergone surgical lung biopsy an average of 142 days after diagnosis of COVID-19 [11]. The findings from those cases and ours support the notion that persistent interstitial pneumonia can be one of the important post-COVID-19 sequelae.

The progression period of pulmonary interstitial fibrosis after COVID-19 infection remains unclear. Since 6 months was too long for young fibroblastic cells to proliferate as simple scars of COVID-19, other pathogenesis might have affected the activity of fibrosis. Several recent reports have suggested that COVID-19 can progress or exacerbate preexisting interstitial pneumonia [12,13]. In the present case, the patient was ex-smoker and slight subpleural reticulation and bronchiectasis were present on chest CT scan at onset of COVID-19. They were consistent with preexisting subclinical interstitial lung abnormalities despite the absence of imaging data before onset of COVID-19 [14]. One possibility we suppose is that the preexisting interstitial lung abnormalities were accelerated by COVID-19 infection.

As for treatment, nintedanib was administrated based on the determination at multidisciplinary discussion including pulmonologists, radiologists, and pathologists. Nintedanib is effective in retardation of the progression of interstitial lung diseases [15]. A case report has shown a significant improvement of COVID-19-related pulmonary fibrosis by nintedanib administrated about 2 months after onset of COVID-19 [16]. In the present case, after 4 months of nintedanib therapy, VC in pulmonary function test improved despite the high level of serum KL-6. DL_{CO} remained low level; it could have been affected by his smoking history. Careful follow-up is necessary to monitor the progression of

interstitial fibrosis.

Conclusion

Transbronchial lung cryobiopsy revealed active pulmonary interstitial fibrosis 6 months after onset of COVID-19. Based on the pathological findings, acceleration of preexisting subclinical interstitial lung abnormalities might have affected his respiratory condition in addition to the scars of DAD. Accumulation of studies on COVID-19 survivors is needed to understand the potential pathological bases of post-COVID-19 condition and to establish efficient therapeutic strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

We thank the technicians at the Division of Pathology of Kanagawa Cardiovascular and Respiratory Center for their technical assistance.

Patient consent statement

The investigation was conducted in accordance with the Declaration of Helsinki of 1975. The content of this paper is a clinical case report. Our institutions don't require ethical approval for case report publications.

References

[1] T. Mauad, A.N. Duarte-Neto, L.F.F. da Silva, E.P. de Oliveira, J.M. de Brito, E.C. T. do Nascimento, R.A. de Almeida Monteiro, J.C. Ferreira, C.R.R. de Carvalho, P. H. do Nascimento Saldiva, M. Dolhnikoff, Tracking the time course of pathological patterns of lung injury in severe COVID-19, Respir. Res. 22 (1) (2021), https://doi.org/10.1186/s12931-021-01628-9.

[2] C. Huang, L. Huang, Y. Wang, X. Li, L. Ren, X. Gu, L. Kang, L.i. Guo, M. Liu, X. Zhou, J. Luo, Z. Huang, S. Tu, Y. Zhao, L.i. Chen, D. Xu, Y. Li, C. Li, L.u. Peng, Y. Li, W. Xie, D. Cui, L. Shang, G. Fan, J. Xu, G. Wang, Y. Wang, J. Zhong, C. Wang, J. Wang, D. Zhang, B. Cao, 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (10270) (2021) 220–232.

[3] C. Valenzuela, G. Waterer, G. Raghu, Interstitial lung disease before and after COVID-19: a double threat? Eur. Respir. J. 58 (2021) 2101956, https://doi.org/10.1183/13993003.01956-2021.

[4] X. Han, Y. Fan, O. Alwalid, et al., Fibrotic Interstitial Lung Abnormalities at 1-year Follow-up CT after Severe COVID-19, Radiology 301 (2021) E438–E440, https://doi.org/10.1148/radiol.2021210972.

[5] S.R. Ambardar, S.L. Hightower, N.A. Huprikar, K.K. Chung, A. Singhal, J.F. Collen, Post-COVID-19 pulmonary fibrosis: novel sequelae of the current pandemic, J. Clin. Med. 10 (11) (2021) 2452.

[6] A. Nalbandian, K. Sehgal, A. Gupta, M.V. Madhavan, C. McGroder, J.S. Stevens, J. R. Cook, A.S. Nordvig, D. Shalev, T.S. Sehrawat, N. Ahluwalia, B. Bikdeli, D. Dietz, C. Der-Nigoghossian, N. Liyanage-Don, G.F. Rosner, E.J. Bernstein, S. Mohan, A. A. Beckley, D.S. Seres, T.K. Choueiri, N. Uriel, J.C. Ausiello, D. Accili, D. E. Freedberg, M. Baldwin, A. Schwartz, D. Brodie, C.K. Garcia, M.S.V. Elkind, J. M. Connors, J.P. Bilezikian, D.W. Landry, E.Y. Wan, Post-acute COVID-19 syndrome, Nat. Med. 27 (4) (2021) 601–615.

[7] L.V.S. Carvalho, C.S. Souza, J.L.M. Fontes, et al., COVID-19 beyond DAD: Persisting microcirculation thrombosis, hidden infections, and early pulmonary fibrosis as remaining challenges of the disease, Hum. Pathol. Rep. 27 (2022), 300607.

[8] T.E. King Jr, M.I. Schwarz, K. Brown, et al., Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality, Am. J. Respir. Crit. Care Med. 164 (6) (2001) 1025–1032.

[9] S.W. Aesif, A.C. Bribriesco, R. Yadav, et al., Pulmonary Pathology of COVID-19 Following 8 Weeks to 4 Months of Severe Disease: A Report of Three Cases, Including One With Bilateral Lung Transplantation, Am. J. Clin. Pathol. 155 (2021) 506–514, https://doi.org/10.1093/ajcp/aqaa264.

[10] S. Lindstedt, E. Grins, H. Larsson, et al., Lung transplant after 6 months on ECMO support for SARS-CoV-2-induced ARDS complicated by severe antibody-mediated rejection, BMJ Open Respir. Res. 8 (2021) e001036, https://doi.org/10.1136/bmjresp-2021-001036.

[11] K.E. Konopka, W. Perry, T. Huang, et al., Usual Interstitial Pneumonia is the Most Common Finding in Surgical Lung Biopsies from Patients with Persistent Interstitial Lung Disease Following Infection with SARS-CoV-2, EClinicalMedicine 42 (2021) 101209, https://doi.org/10.1016/j.eclinm.2021.101209.

[12] G. Aftab, M. Ahmad, K.A. Hamid, Progression of Hypersensitivity Pneumonitis Due to COVID-19, Am. J. Respir. Crit. Care Med. 203 (2021) A2005, https://doi.org/10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A2005.

[13] Y.H. Lee, C.H. Kim, J. Lee, Coronavirus disease 2019 pneumonia may present as an acute exacerbation of idiopathic pulmonary fibrosis, J. Thorac. Dis. 12 (2020) 3902–3904, https://doi.org/10.21037/jtd-20-1658.

[14] G.R. Washko, G.M. Hunninghake, I.E. Fernandez, M. Nishino, Y. Okajima, T. Yamashiro, J.C. Ross, R.S.J. Estépar, D.A. Lynch, J.M. Brehm, K.P. Andriole, A. A. Diaz, R. Khorasani, K. D'Aco, F.C. Sciurba, E.K. Silverman, H. Hatabu, I. O. Rosas, Lung volumes and emphysema in smokers with interstitial lung abnormalities, N Engl. J. Med. 364 (10) (2011) 897–906.

[15] K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, K.K. Brown, Nintedanib in Progressive Fibrosing Interstitial Lung Diseases, N Engl J Med 381 (18) (2019) 1718–1727.

[16] H. Ogata, T. Nakagawa, S. Sakoda, A. Ishimatsu, K. Taguchi, M. Kadowaki, A. Moriwaki, M. Yoshida, Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019, Respirol. Case Rep. 9 (5) (2021) e00744, https://doi.org/10.1002/rcr2.744.