



Case report

A fatal case of diffuse alveolar hemorrhage complicated by rheumatoid arthritis

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ABSTRACT

We describe a fatal case of diffuse alveolar hemorrhage (DAH) complicated by rheumatoid arthritis (RA). A female patient was diagnosed with RA two months earlier and was treated with prednisolone and tacrolimus due to abnormalities in chest images. The patient was admitted to Hamanomachi Hospital for exertional dyspnea and was treated for exacerbation of chronic heart failure. Even after treatment for heart failure, exertional dyspnea remained. Chest CT imaging revealed contractile, patchy consolidations and ground-glass opacities (GGO) with a peribronchial distribution, suggesting an organizing pneumonia (OP) pattern. She was then treated with an additional 25 mg/day of prednisolone following a clinical diagnosis of OP. When the prednisolone dose was tapered, chest imaging showed worsening infiltration. A bronchoscopy was conducted, and bronchoalveolar lavage fluid was sanguineous, indicating DAH. Given that additional workup for the other etiology of DAH was negative, DAH was thought to be related to RA. Intensive treatment, including pulse dose methylprednisolone, failed to halt progression of respiratory failure, leading to a fatal outcome. The clinical presentation proved challenging due to its rarity. DAH might be a differential diagnosis in RA patients with consolidations and GGO in chest CT images. We review past cases of RA-associated DAH and assess potential treatment choices for future cases.

1. Introduction

Rheumatoid arthritis (RA) is a common, systemic, autoimmune disease that primarily affects the joints, often leading to significant morbidity and mortality [1]. Extra-articular manifestations can occur in the skin, eyes, kidneys, heart, gastrointestinal tract, and lungs. Clinically, lung involvement can present several patterns of interstitial lung diseases, rheumatoid nodules, pleural disease, and upper/lower airway diseases (bronchiectasis, follicular bronchiolitis, etc.) [2]. Rarely, diffuse alveolar hemorrhage (DAH) may occur as a pulmonary vascular involvement of RA, which has been described in a few case reports.

DAH is a disease state characterized by pulmonary hemorrhage due to disruption of the alveolar-capillary basement membrane [3,4]. Hemoptysis and progressive exertional dyspnea are the usual presenting symptoms, although these are not always manifest.

In this report, we describe a case of a patient with DAH, complicated by RA, but without any signs of systemic vasculitis. The clinical

presentation proved challenging, resulting in a fatal outcome. We review past cases of RA-associated DAH and assess potential treatment choices for future cases.

2. Case report

An 89-year-old Japanese woman was referred to the Department of Respiratory Medicine for mild exertional dyspnea with abnormal chest imaging.

She had been diagnosed with seropositive RA two months earlier for multiple arthralgias involving knees, shoulders, elbows, wrists, and hands, along with significant morning stiffness over five months. She was a housewife and a life-long non-smoker, with no family history of autoimmune diseases. A blood test at the time of her RA diagnosis revealed elevated C-reactive protein (CRP) (5.61 mg/dL) and anti-citrullinated protein antibodies (ACPA) (211 U/mL). Anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), and

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rheumatoid factor (RF) were negative. Ultrasonography of the wrist joints showed the presence of synovitis. Based on these findings, she was diagnosed with RA. Chest CT imaging showed slight subpleural reticular shadows in both lower lobes and subpleural consolidations (Fig. 2A). Treatment was initiated with 10 mg/day of prednisolone and tacrolimus due to abnormalities in her chest images, but tacrolimus was discontinued later because of concerns about drug-induced interstitial pneumonia.

She was admitted to Hamanomachi Hospital due to progressive exertional dyspnea that had continued more than one month. She was diagnosed with exacerbation of chronic heart failure, based on findings of pitting edema in her legs, cardiac enlargement with right pleural effusion in chest images, and an elevated NT-proBNP level in a blood test. Additionally, chest CT showed patchy consolidations and ground-glass opacities (GGO) with a peribronchial distribution, predominantly in the right lobes, suggesting a radiologic pattern of organizing pneumonia (OP) (Fig. 2B). These CT findings suggested that pulmonary edema was aggravating the interstitial pneumonia.

First, she was treated with furosemide and spironolactone for the heart failure from admission day 1. She responded well to these diuretics, and symptoms of heart failure improved, but exertional dyspnea remained. She underwent coronary angiography on day 3, which confirmed the absence of significant stenotic lesions. Since her exertional dyspnea did not improve much even after treatment for heart failure, pulmonary disease was suspected.

The patient was then referred to the Department of Respiratory Medicine on day 8. She had a temperature of 36.5 °C, blood pressure of 108/68 mmHg, a heart rate of 76 beats per minute, oxygen saturation of 98% under room air. Her RA-associated joint symptoms were well controlled. Physical examination revealed slight late inspiratory crackles in her right chest with no peripheral edema. Sputum cultures

showed no evidence of bacterial or fungal infections. Given her advanced age, a bronchoscopy examination was not performed at that time. She was treated with additional PSL doses (25 mg/day) for clinical diagnosis of OP from day 9 (Fig. 4).

The PSL dose was tapered to 20 mg/day on day 23. Chest imaging showed worsening of infiltration (Fig. 1D, Fig. 2C) on day 26. Her oxygen saturation (SpO₂) dropped to <90%, and oxygen therapy was initiated with nasal cannula at 1 L/min on day 27. Repeated physical examination revealed no peripheral edema. Her level of NT-proBNP was decreased compared to that on admission. Echocardiography showed preserved left ventricular function with no dilation of the inferior vena cava. These findings indicated little contribution of chronic heart failure to the worsening lung infiltration. To enable a diagnosis, bronchoscopy was performed on day 28. Bronchoscopy showed hemoptysis from the right main bronchus to the trachea. (Fig. 3B). Bronchoalveolar lavage fluid from the right B3 bronchus was sanguineous, indicating DAH. Cytology of the lavage showed neutrophil predominance (neutrophils 85%, lymphocytes 2%, macrophages 13%). Infectious workup was negative, including *Aspergillus* antigen and *Pneumocystis jirovecii* DNA PCR. We ordered additional serological examinations to evaluate the etiology of DAH: repeated ANCA and ANA, anti-double-stranded DNA, anti-glomerular basement membrane (GBM), anti-Ro, anti-La, anti-RNP, and anti-phospholipid antibodies were all negative. Urinary analysis revealed no hematuria, proteinuria, or erythrocyte casts through the course. A thorough review of patient medications was performed, and edoxaban for chronic atrial fibrillation was discontinued.

Despite treatment with pulsed-dose methylprednisolone and levofloxacin, respiratory failure and anemia continued to progress. Hemoptysis appeared from day 32. The patient received additional treatment with red blood cell transfusions, intravenous immunoglobulin (IVIG), and sivelestat, which were unable to halt the progression of DAH.

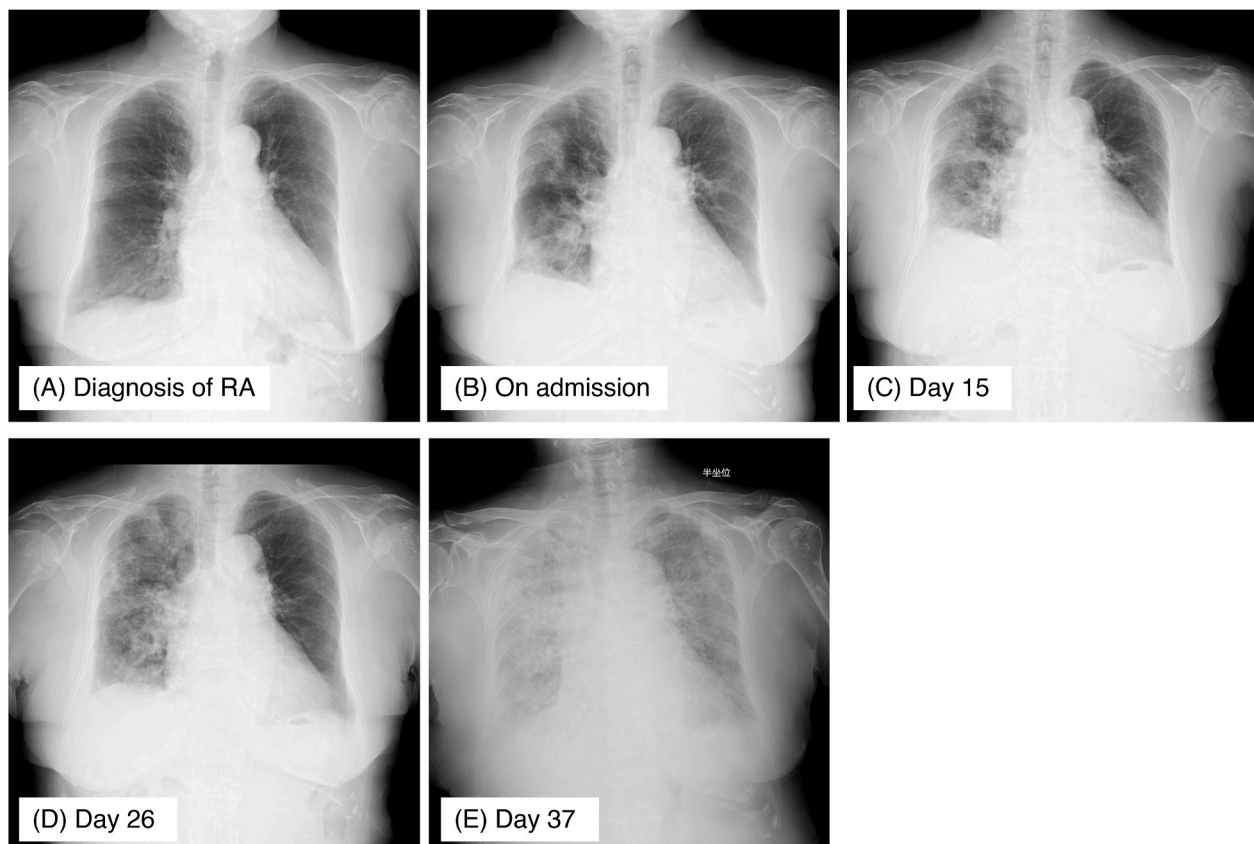


Fig. 1. Chest X-ray images of the patient.

Chest X-ray images (A) upon diagnosis of rheumatoid arthritis, (B) on admission, (C) on day 15, (D) on day 26, and (E) on day 37.

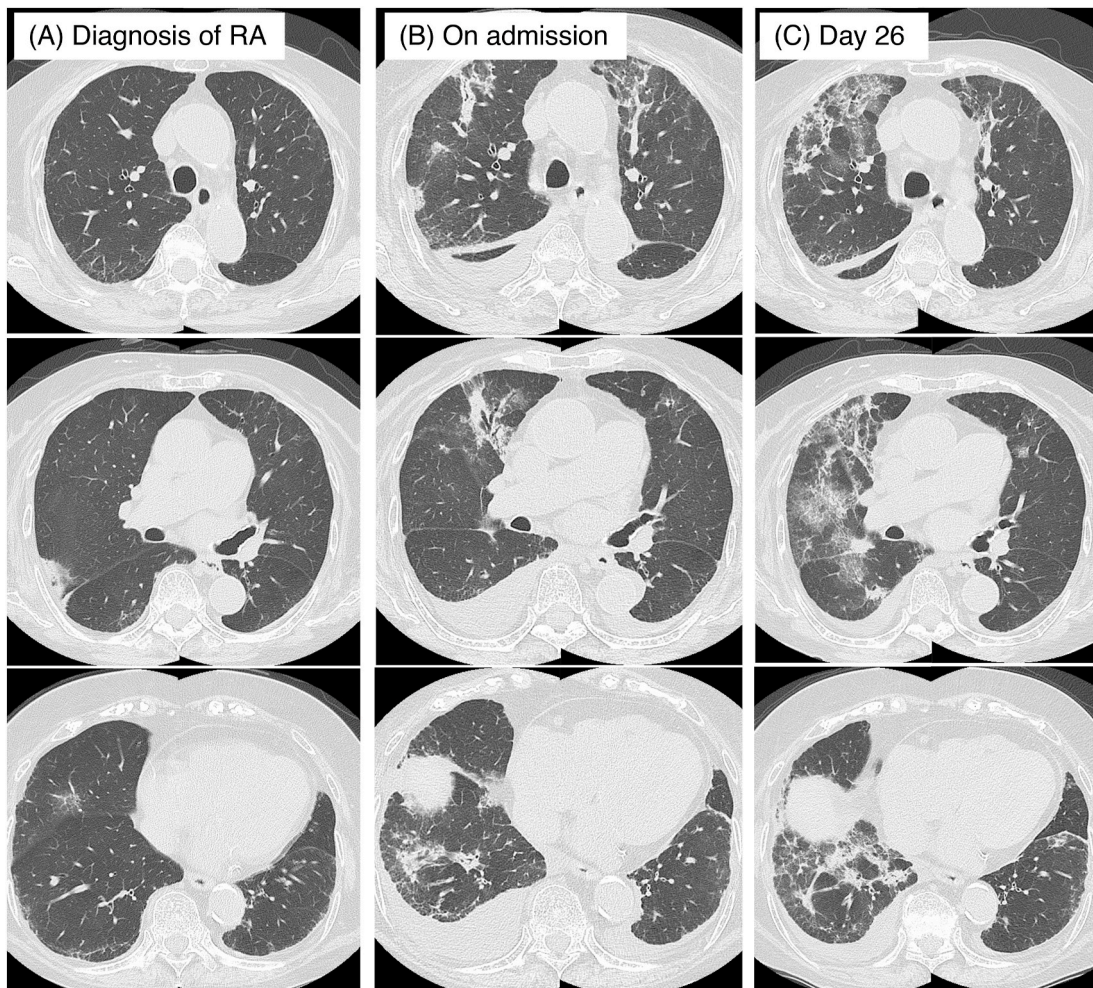


Fig. 2. Chest CT images of the patient.

(A) Chest CT images at the initial diagnosis of rheumatoid arthritis. Slight subpleural reticular shadows in both lower lobes and subpleural consolidations are manifest. (B) On admission to Hamanomachi Hospital (day 1). Chest CT images showed patchy consolidations and ground-glass opacities (GGO) with peribronchial distribution predominantly in the right lobes, suggesting a radiologic pattern of organizing pneumonia (OP). Right pleural effusion was also noted. (C) On day 26, chest CT images showed worsening GGO and consolidations. Pleural effusion was reduced compared to that on admission.

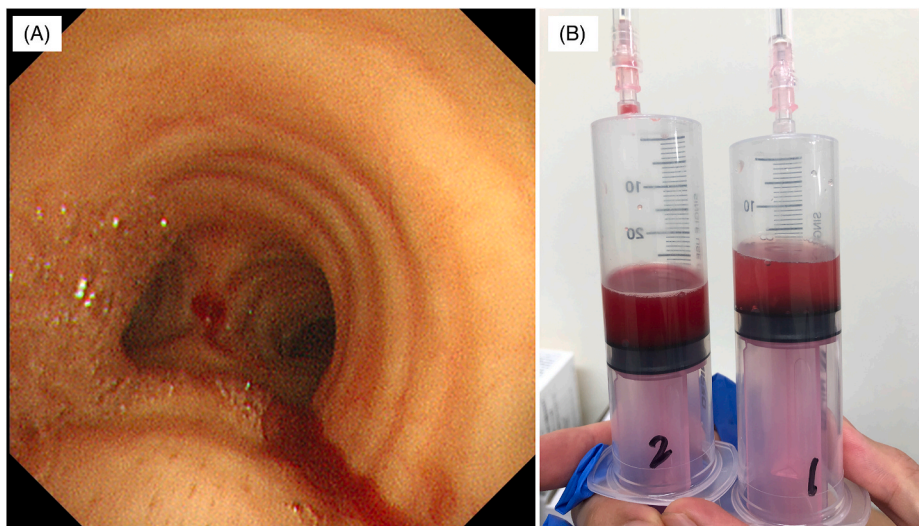


Fig. 3. Bronchoscopic findings showing diffuse alveolar hemorrhage.

(A) Bronchoscopy shows hemoptysis from the right main bronchus to the trachea. (B) Bronchoalveolar lavage fluid from the right B3 bronchus shows significant alveolar hemorrhage.

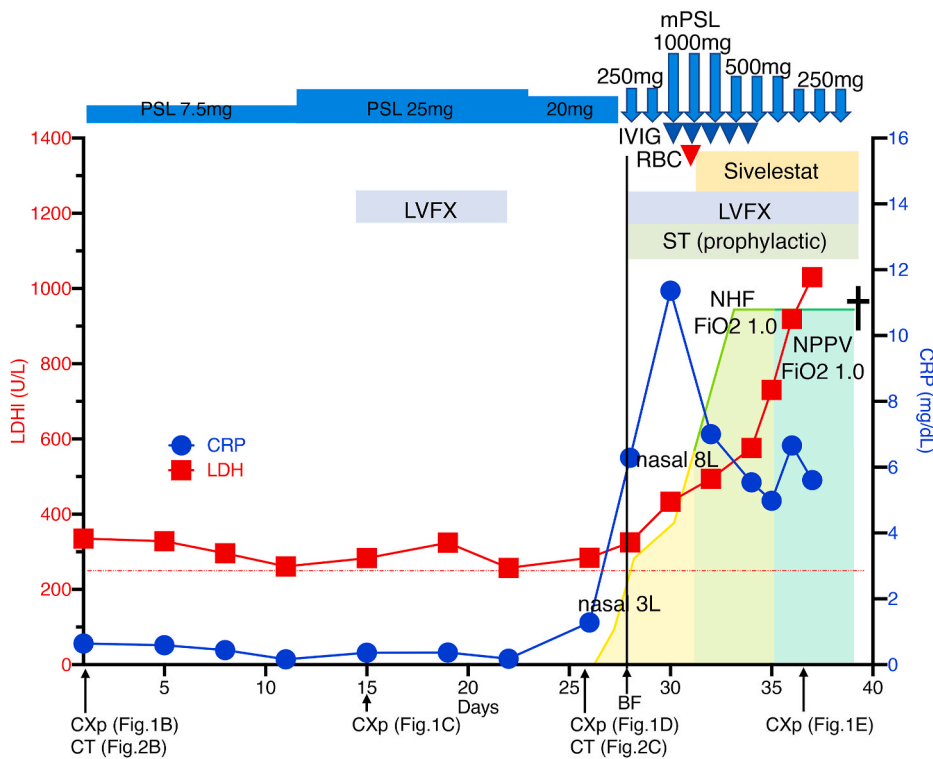


Fig. 4. A clinical course of the case.

The patient was referred to the Department of Respiratory Medicine on admission day 8. Diffuse alveolar hemorrhage was diagnosed by bronchoscopy on day 28. Despite treatment, including pulsed-dose methylprednisolone, respiratory failure progressed, leading to a fatal outcome on day 39. mPSL: methylprednisolone, PSL: prednisolone, IVIG: intravenous immunoglobulin, RBC: red blood cell transfusion, LVFX: levofloxacin, ST: sulfamethoxazole-trimethoprim, CRP: C-reactive protein, LDH: lactate dehydrogenase, BF: bronchoscopy, NHF: nasal high flow, FiO2: fraction of inspiratory oxygen, NPPV: non-invasive positive pressure ventilation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The patient died on day 39.

3. Discussion

DAH is one of the rarer presentations of RA and it is a diagnostic challenge for the physician. DAH can occur in a large variety of clinical conditions: granulomatosis with polyangiitis, microscopic polyangiitis, anti-GBM disease, systemic lupus erythematosus, Sjogren syndrome, bland hemorrhages in patients with mitral valve disease, excessive anticoagulation, and drug-related [3,4]. DAH associated with RA is considered to be pulmonary capillaritis, and most reported cases complicate the systemic vasculitis, especially those with serum ANCA activity [5] or a high RF titer [6,7], called rheumatoid vasculitis [8]. This patient had a low RF titer and normal complement titers, atypical for rheumatoid vasculitis.

We excluded other etiologies of DAH. ANA, anti-ds-DNA antibodies, anti-Ro, anti-La, anti-GBM antibodies, anti-phospholipid antibodies, and anti-RNP antibodies were all negative, with no evidence of hematuria, proteinuria, or erythrocyte casts in the urine. These findings excluded SLE, anti-GBM disease, and ANCA-related vasculitis. There was no evidence of mitral abnormalities in the echocardiogram. Anticoagulation therapy with edoxaban could have contributed to worsening DAH, but it could not have been the main cause, since it continued to progress, even after discontinuation of edoxaban. Therefore, we concluded that DAH was related to RA without other etiologies.

To date, only five cases of RA-associated DAH without systemic vasculitis have been reported (Table 1) [9–11]. Four cases had DAH with a known diagnosis of RA [9,11]. In the fifth case, DAH was the initial presentation of RA [10]. The patient in this report is the sixth case of RA-associated DAH without systemic vasculitis. There could be unknown, autoimmune pathogenesis underlying RA-associated DAH without systemic vasculitis in these cases.

The clinical presentation of the patient in this report was challenging since radiologic features presented an OP pattern without hemoptysis or desaturation. In general, DAH shows similar CT findings, regardless of its cause [12]. Chest CT findings include GGO or consolidation in the

Table 1

Clinical characteristics of patients with rheumatoid arthritis-associated diffuse alveolar hemorrhage in the absence of systemic vasculitis.

Age	Sex	ACPA	RF	Treatment	Outcome	Reference
56	M	n.a.	1:1280	Glucocorticoid, cyclophosphamide	Improved	[9]
64	M	n.a.	1:1280	Glucocorticoid	Fatal (cardiac)	[9]
25	F	n.a.	1:2560	Glucocorticoid, cyclophosphamide	Improved	[9]
45	F	n.a.	70 IU/mL	Glucocorticoid	Improved	[10]
36	F	n.a.	n.a.	Glucocorticoid, rituximab, AZA	Improved	[11]
89	F	211 U/mL	3.0 IU/mL	Glucocorticoids, IVIG, sivelestat	Fatal	This case

n.a.: not available, ACPA: anticitrullinated peptide antibodies, RF: rheumatoid factor, AZA: azathioprine, IVIG: intravenous immunoglobulin.

presence of acute hemorrhage [12]. Ill-defined centrilobular nodules may predominate in some DAH cases [12]. Within days of an acute episode of hemorrhage, the presence of interlobular septal thickening may be seen in association with GGO [12]. In later stages, an interstitial abnormality and fibrosis may sometimes occur [12]. In this case, there were two possibilities: DAH might have occurred coincidentally with OP, or DAH might just have resembled an OP pattern in chest CT images.

Although evidence of treatment for DAH is limited, corticosteroids and immunosuppressive agents remain the standard treatment [13]. High-dose glucocorticoids are usually initiated while waiting for test results to confirm a specific cause of capillaritis, which then guides the selection of additional immunosuppressive therapies. As reported, cyclophosphamide, rituximab, azathioprine, and IVIG, in addition to glucocorticoids, are generally the options to treat DAH associated with RA [9–11]. This patient’s advanced age made us hesitant to administer an aggressive therapy, such as cyclophosphamide or rituximab. We chose IVIG in combination with pulsed glucocorticoids for safer medication; however, the possible efficacy of IVIG in patients with DAH is

unknown. We also used sivelestat, a neutrophil elastase inhibitor that is approved for acute respiratory distress syndrome (ARDS) in Japan [14] on the assumption of neutrophil inflammation in conjunction with DAH. Again, the therapeutic potential of sivelestat on DAH is unknown.

The limitation of this case is the lack of tissue biopsy, but we were concerned about biopsy-related complications at the patient's very advanced age. From the clinical course and laboratory values, such as LDH, it was assumed that the patient had pulmonary vasculitis, but this could not be verified directly.

In summary, we witnessed a fatal case of DAH complicated with RA in an elderly patient. Despite its rarity, this case emphasizes consideration of DAH in RA patients who present a radiographic appearance of GGO and consolidation.

Patient consent for publication

Written, informed consent was obtained from the patient and her family.

Declaration of competing interest

All authors of the manuscript declare that there are no conflicts of interest.

References

- [1] D. Aletaha, J.S. Smolen, Diagnosis and management of rheumatoid arthritis: a review, *JAMA, J. Am. Med. Assoc.* 320 (2018) 1360–1372, <https://doi.org/10.1001/jama.2018.13103>.
- [2] D. Wang, J. Zhang, J. Lau, S. Wang, V. Taneja, E.L. Matteson, R. Vassallo, Mechanisms of lung disease development in rheumatoid arthritis, *Nat. Rev. Rheumatol.* 15 (2019) 581–596, <https://doi.org/10.1038/s41584-019-0275-x>.
- [3] M.L. Krause, R. Cartin-Ceba, U. Specks, T. Peikert, Update on diffuse alveolar hemorrhage and pulmonary vasculitis, *Immunol. Allergy Clin.* 32 (2012) 587–600, <https://doi.org/10.1016/j.jiac.2012.08.001>.
- [4] A.R. Lara, M.I. Schwarz, Diffuse alveolar hemorrhage, *Chest* 137 (2010) 1164–1171, <https://doi.org/10.1378/chest.08-2084>.
- [5] W.D. Travis, T. V Colby, C. Lombard, H.A. Carpenter, A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation, *Am. J. Surg. Pathol.* 14 (1990) 1112–1125. <http://www.ncbi.nlm.nih.gov/pubmed/2252102>.
- [6] A.E. Voskuyl, A.H. Zwinderman, M.L. Westedt, J.P. Vandenbroucke, F. C. Breedveld, J.M.W. Hazes, Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study, *Ann. Rheum. Dis.* 55 (1996) 190–192, <https://doi.org/10.1136/ard.55.3.190>.
- [7] E. Myasoedova, C.S. Crowson, C. Turesson, S.E. Gabriel, E.L. Matteson, Incidence of extraarticular rheumatoid arthritis in olmsted county, Minnesota, in 1995–2007 versus 1985–1994: a population-based study, *J. Rheumatol.* 38 (2011) 983–989, <https://doi.org/10.3899/jrheum.101133>.
- [8] S. Kishore, L. Maher, V. Majithia, Rheumatoid vasculitis: a diminishing yet devastating menace, *Curr. Rheumatol. Rep.* 19 (2017) 39, <https://doi.org/10.1007/s11926-017-0667-3>.
- [9] M.I. Schwarz, M.R. Zamora, T.N. Hodges, E.D. Chan, R.P. Bowler, R.M. Tuder, Isolated pulmonary capillaritis and diffuse alveolar hemorrhage in rheumatoid arthritis and mixed connective tissue disease, *Chest* 113 (1998) 1609–1615, <https://doi.org/10.1378/chest.113.6.1609>.
- [10] R. Dua, J. Rawat, Diffuse alveolar hemorrhage in a patient of rheumatoid arthritis, *Lung India* 31 (2014) 194, <https://doi.org/10.4103/0970-2113.129899>.
- [11] A. Osman, P. Galiatsatos, S. Bose, S. Danoff, Rheumatoid arthritis causing diffuse alveolar haemorrhage: a novel therapeutic approach, *BMJ Case Rep.* (2017) (2017) 2–6, <https://doi.org/10.1136/bcr-2017-220509>.
- [12] Wayne Richard Webb, Nestor L. Muller, David P. Naidich, *High-Resolution CT of the Lung*, fifth ed., Lippincott Williams & Wilkins, 2014.
- [13] O.C. Ioachimescu, J.K. Stoller, Diffuse alveolar hemorrhage: diagnosing it and finding the cause, *Cleve. Clin. J. Med.* 75 (2008) 258–280, <https://doi.org/10.3949/ccjm.75.4.258>.
- [14] T. Kido, K. Muramatsu, K. Yatera, T. Asakawa, H. Otsubo, T. Kubo, Y. Fujino, S. Matsuda, T. Mayumi, H. Mukae, Efficacy of early sivelestat administration on acute lung injury and acute respiratory distress syndrome, *Respirology* 22 (2017) 708–713, <https://doi.org/10.1111/resp.12969>.