



Case report

Lymphocytic interstitial pneumonia in a patient with mixed connective tissue disease – A case report

Chin-Wei Kuo^a, Kung-Chao Chang^b, Han-Yu Chang^a, Tang-Hsiu Huang^{a,*}^a Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan^b Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ARTICLE INFO

Keywords:

Lymphocytic interstitial pneumonia
Mixed connective tissue disease

ABSTRACT

Lymphocytic interstitial pneumonia (LIP) is an uncommon interstitial lung disease that is characterized by an interstitial infiltrate of lymphoplasmacytic cells. While idiopathic LIP appears to be extremely rare, most reported cases of LIP have been associated with coexisting immune derangements, particularly autoimmune diseases such as Sjögren's syndrome. In this report, we describe the presentation of LIP in a patient with underlying mixed connective tissue disease.

1. Introduction

Lymphocytic interstitial pneumonia (LIP) is an uncommon lymphoproliferative disease of the lung. It is characterized by a dense interstitial infiltrate of lymphocytes, plasma cells, and some histiocytes [1]. Typical symptoms include progressive dyspnea, cough, and fatigue [2]. A plain chest radiograph frequently shows non-specific bibasilar reticulonodular infiltrates, whereas high-resolution computed tomography (CT) may reveal bilateral diffuse ground-glass opacities, centrilobular nodules, thickened septal lines, and scattered cystic lesions. Radiographic features of pulmonary hypertension and honeycombing are late-stage manifestations [3,4].

LIP is often associated with autoimmune diseases such as primary Sjögren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus. To the best of our knowledge, LIP as the predominant pulmonary manifestation of mixed connective tissue disease (MCTD) has not been reported before. In this case report, we describe a patient with longstanding MCTD who developed LIP years after the initial manifestation of her connective tissue disease.

1.1. Case report

The patient was a forty-six-year-old non-smoking female. She was

diagnosed with MCTD in 1998 based on the manifestations including tissue-proven scleroderma, myositis, Raynaud's phenomenon, sclerodactyly, and positive anti-U1 RNP antibodies. Later in 2005, she was found to have secondary Sjögren's syndrome presenting with sicca symptoms and a positive Schirmer test. A chest radiograph taken in 2008 was unremarkable (Fig. 1A). Over the next few years, she slowly but progressively developed increasing intolerance of exercise such that she experienced dyspnea when hurrying on level ground or walking up a slight hill. At the end of 2015, she was hospitalized for the treatment of pneumonia involving her left lower lung. The chest radiograph taken at that time showed, in addition to her left-lower-lobe consolidation, bilaterally diffuse linear and reticular infiltrations interspersed with finely-cystic lesions (Fig. 1B). The microbial culture of her sputum yielded *Chryseobacterium gleum*. Her acute symptoms of fever and cough soon subsided following treatment with combined ampicillin and sulbactam. However, her exertional dyspnea persisted. A follow-up chest radiography approximately one month later revealed significant resolution of the left-lower-lobe consolidation, but persistent cystic lesions and reticular infiltrates in the rest of her bilateral lung parenchyma (Fig. 1C). Subsequent comprehensive evaluations, including a repeated check of her autoantibodies, did not reveal evidence of macrocytic anemia, hypothyroidism, or a different autoimmune disease (Table 1). CT scan of the chest revealed thickened interlobular septa,

Abbreviations: CT, Computed tomography; LIP, Lymphocytic interstitial pneumonia; MCTD, Mixed connective tissue disease; NSIP, Nonspecific interstitial pneumonia; PCR, Polymerase chain reaction

* Corresponding author. Division of Chest Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, No. 138, Sheng-Li Rd. Tainan 704, Taiwan.

E-mail address: tangomycin0713@gmail.com (T.-H. Huang).

<https://doi.org/10.1016/j.rmcr.2018.06.003>

Received 19 February 2018; Accepted 4 June 2018

2213-0071/ © 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Fig. 1. Serial chest radiographs of the patient. The baseline chest radiograph from 2008 was unremarkable (A); a subsequent chest radiograph in December 2015 shows pneumonic consolidation in the left lower field and bilaterally diffuse linear, reticular, and cystic infiltrates (B); another chest radiograph in January 2016 shows resolution of the consolidation but persistence of the interstitial and cystic infiltrates (C).

Table 1
Relevant serologies of the patient.

Autoantibody	Serum level or titer	Normal range (Unit)
Antinuclear antibody (ANA)	1:1280	< 1:160
Anti-dsDNA Ab	1:10	≤1:10
Anti-U1-RNP Ab	64.7	< 10 (U/mL)
Anti-SS-A/Anti-Ro Ab	> 240	< 10 (U/mL)
Anti-SS-B/Anti-La Ab	6.0	< 7 (U/mL)
Anti-Sm Ab	4.1	< 7 (U/mL)
Anti-topoisomerase/Anti-Scl-70 Ab	1.0	< 7 (U/mL)
C3	85.5	58.0–147.0 (mg/dL)
C4	8.7	11.0–35.0 (mg/dL)
Creatinine kinase	179	26–192 (U/mL)
TSH	1.0	0.27–4.20 (μIU/mL)
HBsAg	Negative	Negative
HCV Ab	Negative	Negative

Ab, antibody; TSH, thyroid stimulating hormone, HBsAg, surface antigen of hepatitis B virus; HCV Ab, anti-hepatitis C virus antibody.

multiple centrilobular nodules, and discrete thin-walled cysts that were particularly predominant in her bilateral middle-to-lower lung fields (Fig. 2A–D). Her pulmonary function test reported a moderate degree of an obstructive ventilatory defect and severely impaired diffusion capacity (her forced expiratory volume in one second and diffusion capacity for carbon monoxide were 43% and 26% of the predicted values, respectively, Table 2).

A video-assisted thoracoscopic biopsy of the patient's right-middle-lobe lung (sampling a wedge-shaped piece of parenchyma measuring 6 × 4 × 0.8 cm) was then performed. During the operation, multiple cystic and nodular lesions were observed on the surface of her right lung under thoracoscopy (Fig. 3).

The most prominent histologic findings of the biopsied lung specimen were multiple foci of dense infiltration of many small to medium-sized lymphoid cells admixed with plasma cells and histiocytes (Fig. 4A and B). These infiltrating lymphoid cells were immunohistochemically negative for CD5, CD10 and bcl-2. They formed follicles in the interstitium both adjacent to and distant from the bronchioles, which were mainly composed of CD20-positive B cells forming germinal centers and CD3-positive T cells at the periphery (Fig. 4C and D). The multiplex polymerase chain reaction (PCR) with heteroduplex analysis revealed the polyclonality of these lymphoid cells (Supplementary Fig. 1). Microbial cultures of the biopsied lung did not yield the growth of any bacteria, mycobacteria, or fungus. No coexisting feature of non-specific interstitial pneumonia (NSIP) was found (Fig. 4E). Localized fibrinoid vasculitis was discerned but only in one small focus (Fig. 4F). The diagnosis of lymphocytic interstitial pneumonia was made based on a summation of her clinical, radiographic, and pathological manifestations.

Following the diagnosis, we treated the patient with systemic corticosteroid starting with a dose of 40 mg of methylprednisolone per day that was gradually tapered to a daily maintenance dose of 10 mg of prednisolone. Serial pulmonary function tests between December 2015 and July 2017 showed an initial increase in all her spirometric parameters, which was followed by a relative stable trend (Table 2). A follow-up CT of the chest about seven months later showed no interval change in the reticular and cystic lesions (Fig. 2E–H).

2. Discussion

LIP was first described by Liebow and Carrington in 1969 [5]. In contrast to lymphoma, it is generally considered a benign pulmonary lymphoproliferative disorder with dense interstitial infiltration of polyclonal B and T cells [6]. The definite diagnosis of LIP is generally made based on histopathological findings. The radiographic and

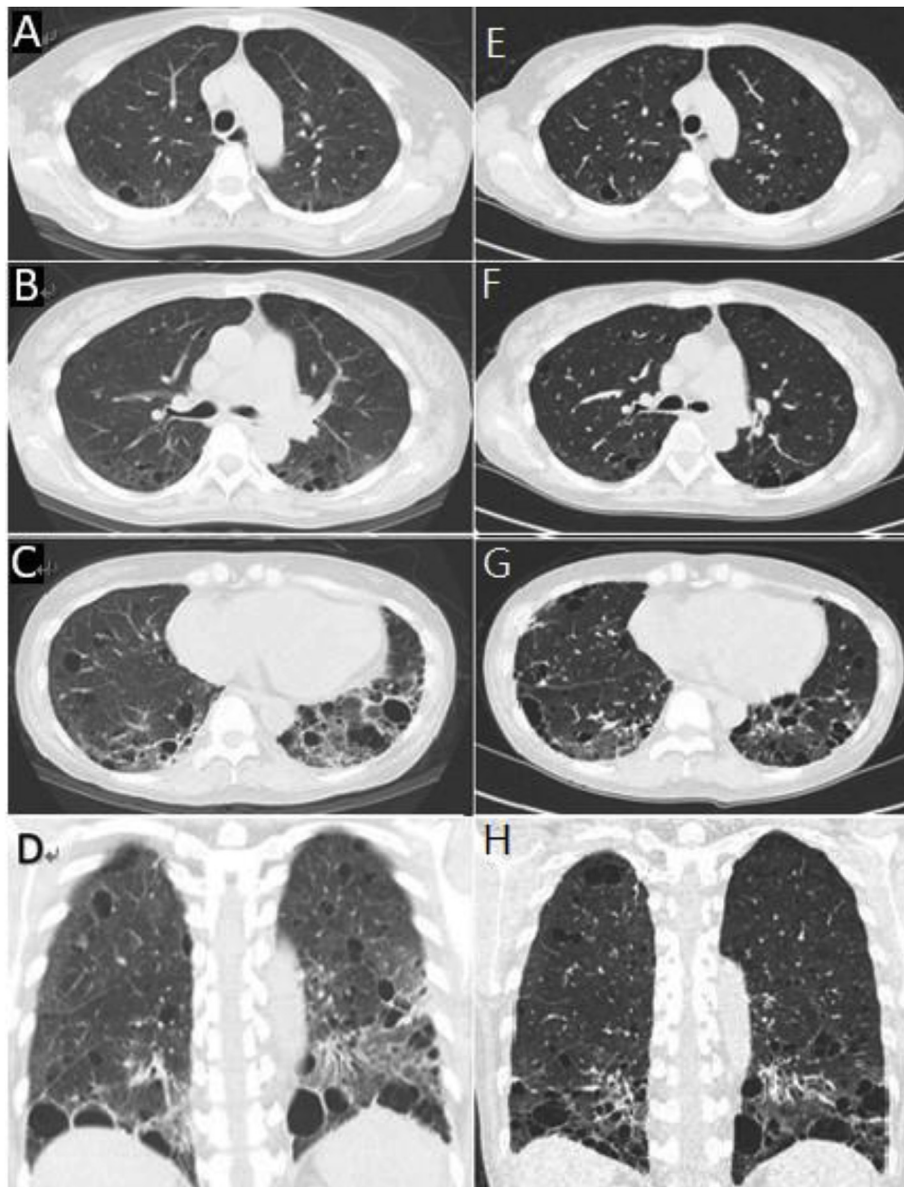


Fig. 2. Comparative images of the computed tomography of chest of the patient in 12–2015 and 07–2016. The left column displays images of transverse sections at the levels of the aortic arch (A), the carina (B), and the lower lungs (C), and coronal reconstruction (D), which show multiple centrilobular nodules, discrete thin-walled cysts, and extensive reticular infiltrates and interlobular septal thickening in bilateral lungs that are particularly prominent in the lower lung fields. The right column displays images of the same levels (E, F, G, H) that were taken approximately seven months later.

Table 2
Raw measurements of the serial pulmonary function tests of the patient.

Date of tests	Dec. 30, 2015	Jan. 26, 2017	Jul. 4, 2017
FVC, L (%pred)	1.69 (61)	2.42 (88)	2.46 (90)
FEV ₁ , L (%pred)	1.09 (43)	1.53 (61)	1.41 (57)
FEV ₁ /FVC, %	64	63	57
TLC, L (%pred)	3.39 (82)	3.94 (94)	3.68 (88)
DLco, %pred	26	49	39

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLco, diffusion capacity for carbon monoxide; %pred, percentage of the predicted value

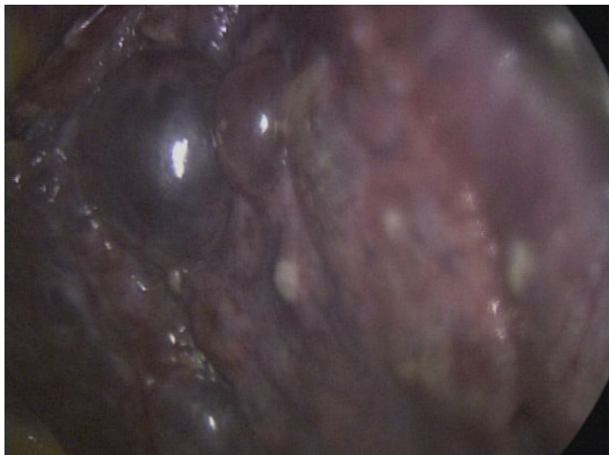


Fig. 3. Gross appearance of the patient's lung under thoracoscopy. Multiple nodular and cystic lesions over the right lung surface of the patient were observed under video-assisted thoracoscopy.

histologic features of this patient were compatible with those described for LIP. Polyclonality of the infiltrating lymphoid cells was confirmed by a multiplex PCR with heteroduplex analysis [7,8]. Fibrinoid vasculitis was also observed in a small and localized focus, which was not a dominant histologic pattern and was likely associated with the presence of her high-titer anti-SS-A (anti-Ro) autoantibody [9]. The fibrinoid material stained negative by Congo red.

The association between LIP and various autoimmune diseases such as Sjögren's syndrome [10], systemic lupus erythematosus [11], rheumatoid arthritis, Hashimoto's disease, primary biliary cirrhosis [12], pernicious anemia [13], and chronic active hepatitis [14] has been repeatedly reported. Apart from this patient's MCTD, we did not identify other autoimmune diseases possibly associated with LIP.

Nevertheless, we did not check the serology for human immunodeficiency virus and Epstein Barr virus due to the absence of compatible clinical features and a negative history for high-risk behavior.

MCTD is a systemic autoimmune disease [15,16] with a plethora of clinical presentations including Raynaud's phenomenon, polyarthritis, sclerodactyly, esophageal dysmotility, renal disease, and inflammatory myositis. Anti-U1 RNP antibodies are highly correlated with MCTD [17,18]. The clinical features of our patient met Alarcón-Segovia's and Kahn's criteria [19], and her diagnosis of MCTD was therefore solid.

Common CT findings of pulmonary involvement by MCTD include ground glass attenuation, subpleural micronodules, interlobular septal thickening, and fibrosis [20]. Most commonly, the radiographic and histopathological findings of MCTD-associated interstitial lung disease are those of nonspecific interstitial pneumonia (NSIP) [21,22]. Shahoub et al. reported a patient with MCTD who had interstitial lung disease that manifested radiographically as lower-lobe predominant ground-glass opacities and pathologically as a mixed pattern of NSIP and LIP [23]. In contrast, the radiographic features of our patient (particularly the presence of centrilobular nodules and discrete cysts) were compatible with those of LIP rather than NSIP, which was supported by the histologic findings from a sufficiently large piece of biopsied lung parenchyma in which no concurrent features of NSIP was observed.

One unusual presentation in our patient was the obstructive ventilatory defect that was repeatedly revealed by serial pulmonary function tests (Table 2) and that differed from the typical restrictive defect as reported previously [2,24]. The patient had no clinical, radiographic, or histological evidence of asthma or other obstructive lung diseases such as emphysema, chronic bronchitis or bronchiolitis, bronchiectasis, bronchiolitis obliterans, cystic fibrosis, or respiratory bronchiolitis-interstitial lung disease. A possible explanation for this feature is the increase in the airway resistance that was caused by the lymphoid follicles formed by the densely infiltrating lymphocytes.

3. Conclusion

In this report, we present a case of MCTD-associated LIP. Future work is needed to investigate the actual prevalence, to elucidate the pathogenesis, and to determine the optimal treatment strategy, for this rare pulmonary presentation of MCTD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to disclose.

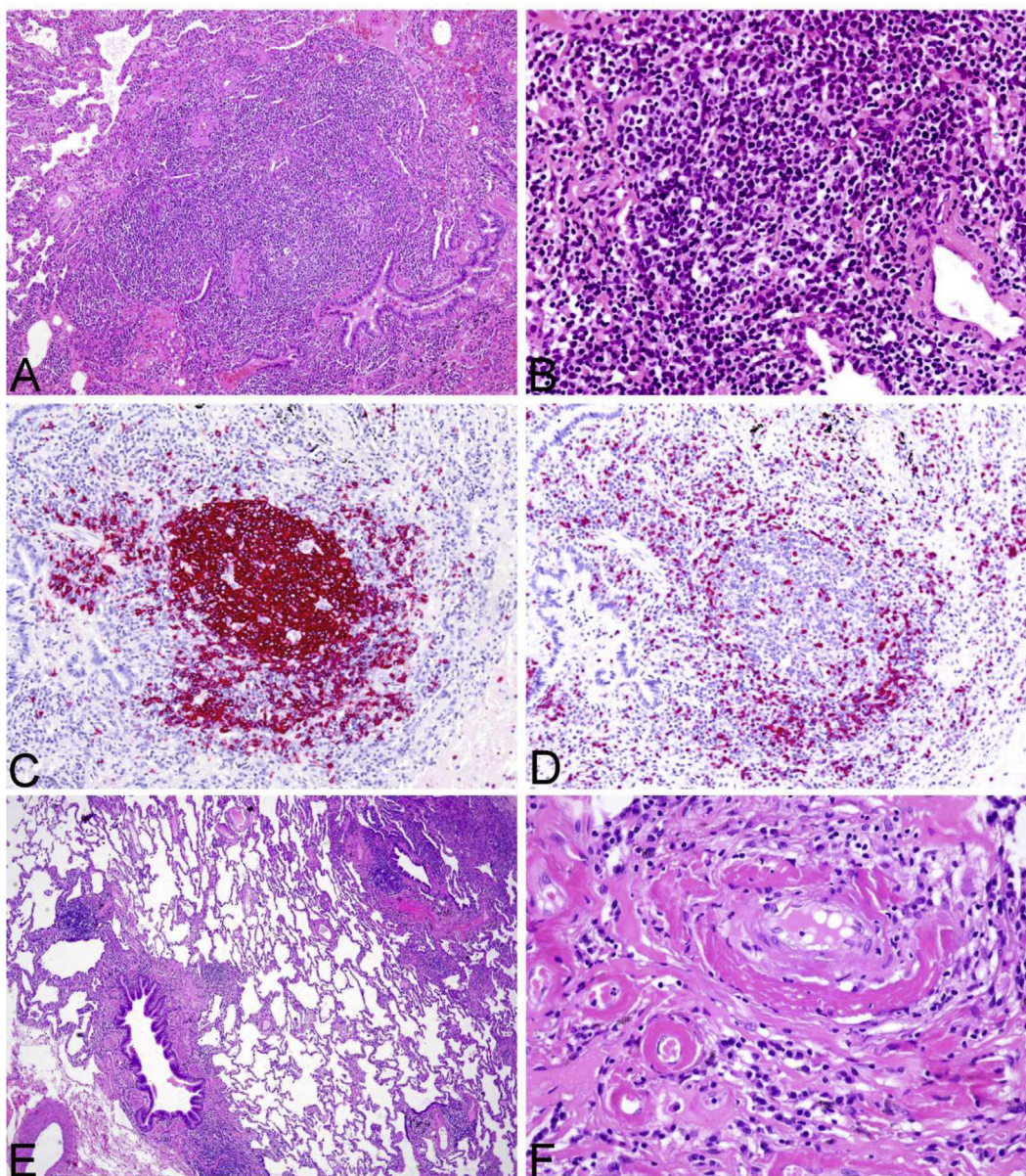


Fig. 4. Pathologic features of the biopsied lung parenchyma of the patient. Under lower power (100x), the hematoxylin and eosin (H&E) stained section shows dense infiltration of small mononuclear cells forming follicles adjacent to the respiratory bronchioles (A). Under higher power (400x), the infiltrating cells are small to medium-sized lymphoid cells with scanty cytoplasm, angulated nuclei, and indistinct nucleoli and clumping chromatin. They are mixed with some plasma cells and histiocytes (B). Immunohistochemically, these lymphoid follicles are composed of CD20-positive B cells at the germinal centers (C) and CD3-positive T cells at the periphery (D). No features of non-specific interstitial pneumonia (NSIP) was identified (E), and a small localized focus of fibrinoid vasculitis (which stained negative by Congo red) was observed (F).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmcr.2018.06.003>.

References

- [1] M.N. Koss, L. Hochholzer, J.M. Langloss, W.D. Wehunt, A.A. Lazarus, Lymphoid interstitial pneumonia: clinicopathological and immunopathologic findings in 18 cases, *Pathology* 19 (1987) 178–185.
- [2] S.I. Cha, M.B. Fessler, C.D. Cool, M.I. Schwarz, K.K. Brown, Lymphoid interstitial pneumonia: clinical features, associations and prognosis, *Eur. Respir. J.* 28 (2) (2006) 364 Epub 2006 Mar 29.
- [3] S.S. Hare, C.A. Souza, G. Bain, J.M. Seely, Frcpc, M.M. Gomes, M. Quigley, The radiological spectrum of pulmonary lymphoproliferative disease, *Br. J. Radiol.* 85 (1015) (2012) 848.
- [4] N. Gupta, R. Vassallo, K.A. Wikenheiser-Brokamp, F.X. McCormack, Diffuse cystic lung disease Part II, *Am. J. Respir. Crit. Care Med.* 192 (1) (2015) 17–29.
- [5] Y. Ichikawa, M. Kinoshita, T. Koga, K. Oizumi, K. Fujimoto, N. Hayabuchi, Lung cyst formation in lymphocytic interstitial pneumonia: CT features, *J. Comput. Assist. Tomogr.* 18 (1994) 745–748.
- [6] A. Liebow, C.B. Carrington, The interstitial pneumonias, in: M. Simon, E.J. Potchen, M. LeMay (Eds.), *Frontiers of Pulmonary Radiology*, first ed., Grune & Stratton, New York, 1969, pp. 102–141.
- [7] R. Ponti, P. Quaglino, M. Novelli, M.T. Fierro, A. Comessatti, A. Peroni, L. Bonello, M.G. Bernengo, T-cell receptor gamma gene rearrangement by multiplex polymerase chain reaction/heteroduplex analysis in patients with cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome) and benign inflammatory disease: correlation with clinical, histological and immunophenotypic findings, *Br. J. Dermatol.* 153 (3) (2005 Sep) 565–573.
- [8] D.J. Park, H.C. Cho, J.H. Kwon, J.Y. Park, Utility of an immunoglobulin gene rearrangement assay based on multiplex PCR in detecting bone marrow involvement in B-cell non-Hodgkin lymphoma, *Blood Res* 52 (2) (2017 Jun) 141–143.
- [9] E.L. Alexander, F.C. Arnett, T.T. Provost, M.B. Stevens, Sjogren's syndrome: association of anti-Ro(SS-A) antibodies with vasculitis, hematologic abnormalities, and serologic hyperreactivity, *Ann. Intern. Med.* 98 (1983) 155–159.

- [10] J.Y. Kim, S.H. Park, S.K. Kim, D.S. Hyun, Y.S. Kum, K.J. Jung, J.Y. Choe, Lymphocytic interstitial pneumonia in primary Sjögren's syndrome: a case report, *Korean J Intern Med* 26 (2011) 108–111.
- [11] Daniel Garcia, Lary Young, Lymphocytic interstitial pneumonia as a manifestation of SLE and secondary Sjogren's syndrome, *BMJ Case Rep.* (2013), <http://dx.doi.org/10.1136/bcr-2013-009598>.
- [12] H. Miyamoto, A. Azuma, Y. Taniguchi, T. Takahashi, A. Yoshimura, S. Hemmi, Y. Fukuda, S. Kudoh, Interstitial pneumonia complicated by Sjögren's syndrome, Hashimoto's disease, rheumatoid arthritis and primary biliary cirrhosis, *Intern. Med.* 39 (2000) 970–975.
- [13] K. Tamaki, D. Nabeya, T. Tsuji, M. Aoyama, Y. Kubo, A case of interstitial pneumonia with autoimmune hemolytic anemia, *Nihon Kokyuki Gakkai Zasshi* 48 (2010) 426–431.
- [14] H. Hasegawa, Y. Nakamura, Y. Kaida, N. Enomoto, D. Hashimoto, N. Inui, T. Suda, K. Chida, A case of desquamative interstitial pneumonia associated with hepatitis C virus infection, *Nihon Kokyuki Gakkai Zasshi* 47 (2009) 698–703.
- [15] G.C. Sharp, W.S. Irvin, E.M. Tan, R.G. Gould, H.R. Holman, Mixed connective tissue disease – an apparently distinct rheumatic disease, *Am. J. Med.* 52 (2) (1972 Feb) 148–159.
- [16] R. Kasukawa, T. Tojo, S. Miyawaki, Preliminary diagnostic criteria for classification of mixed connective tissue disease, in: R. Kasukawa, G.C. Sharp (Eds.), *Mixed Connective Tissue Diseases and Antinuclear Antibodies*, Elsevier, Amsterdam, 1987, pp. 41–47.
- [17] Rajendram CP, Nedumaram, R. Porkodi, R. Parthiban, Mixed connective tissue disease – clinical and immunological profile, *J. Assoc. Phys. India* 49 (2001) 412–414.
- [18] I. Garcia-de la Torre, M. Salazar-P'aramo, G. Salm'on-de la Torre, Mixed connective tissue disease. A clinico-serological study of 17 cases, *Mol. Biol. Rep.* 23 (1996) 153–157.
- [19] D. Alarcón-Segovia, M.H. Cardiel, Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients, *J. Rheumatol.* 16 (3) (1989) 328.
- [20] E. Bodolay, Z. Szekanecz, K. Dévényi, L. Galuska, I. Csípo, J. Vègh, I. Garai, G. Szegedi, Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD), *Rheumatology* 44 (2005) 656–661.
- [21] D.J. Hurst, W.M. Baker, G. Gilbert, Lung collagen synthesis and type analysis in patients with mixed connective tissue disease (MCTD), *Arthritis Rheum.* 19 (1980) 801–804.
- [22] T. Hosoda, Review of pathology of mixed connective tissue disease, in: R. Kasukawa, G.C. Sharp (Eds.), *Mixed Connective Tissue Disease and Anti-nuclear Antibodies*, Elsevier Science, Amsterdam, 1987, pp. 281–290.
- [23] I. Shahoub, F. Zeid, P. Ottaviano, Patient with mixed connective tissue disease (MCTD) and interstitial lung disease (ILD) with features of both non specific/lymphocytic interstitial pneumonia NSIP/LIP, *Am. J. Respir. Crit. Care Med.* 191 (2015) A1179.
- [24] C.V. Strimlan, E.C. Rosenow 3rd, L.H. Weiland, L.R. Brown, Lymphocytic interstitial pneumonitis: review of 13 cases, *Ann. Intern. Med.* 88 (1978) 616–621.