



Clinical characteristics of immunoglobulin G₄-positive interstitial pneumonia

Copyright ©The authors 2021

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 13 Feb 2021
Accepted: 23 June 2021

To the Editor:

Immunoglobulin G₄-related disease is a systemic disease characterised by tumefactive lesions with abundant IgG₄-positive plasma cells and elevated serum IgG₄ concentrations [1–4]. We previously assessed IgG₄-related respiratory disease (IgG₄-RRD) with extrathoracic manifestations [5]. IgG₄-RRD develops through the lymphatic routes in the lungs and responds well to corticosteroid therapy with a benign prognosis [5–7]. However, whether interstitial pneumonia (IP) with IgG₄-positive plasma cell infiltration in the lungs without the extrathoracic lesions of IgG₄-related disease could be considered a type of IgG₄-RRD is controversial.

Here, we aimed to elucidate the clinico–radio–pathological characteristics of IP with abundant IgG₄-positive cells in the lungs and elevated serum IgG₄ levels without extrathoracic lesions. We defined this IP as “IgG₄-positive IP” in this study.

We recruited patients suspected of having IgG₄-positive IP nationwide from March 2019 to May 2019. This study was conducted by the Tokyo Diffuse Lung Disease Study Group. All procedures involving human participants were approved by the Ethics Committee of the Shinshu University School of Medicine (approval number 4465) and the relevant participating institutions. This study was performed in accordance with the Declaration of Helsinki and its subsequent amendments. Additionally, the review board waived the need for patient approval or informed consent because the study involved a retrospective review of patient records.

We reviewed the cases of 28 patients with suspected IgG₄-positive IP from 17 institutions throughout Japan. All participants were diagnosed with IP *via* chest high-resolution computed tomography (HRCT), elevated serum IgG₄ concentrations (≥ 135 mg·dL⁻¹), and infiltrations of abundant IgG₄-positive plasma cells (IgG₄-positive/IgG-positive cell ratio >40% and IgG₄-positive cells >10 per high-power field from the specimens obtained by surgical lung biopsies). HRCT and histopathology patterns of IP were determined according to the 2018 guidelines regarding interstitial pulmonary fibrosis [8] and the 2013 statement regarding idiopathic interstitial pneumonias (IIPs) [9]. Lung specimens were immunostained for IgG and IgG₄ in addition to staining with haematoxylin-eosin and Elastica-Masson or Elastica-van Gieson. Patients’ clinical records and radiological and histopathological data were reviewed, and the final diagnoses were established after multidisciplinary discussion (MDD).

Of the 28 patients, 16 were diagnosed with IgG₄-positive IP by MDD. Extrathoracic lesions suggesting IgG₄-related disease were not present in these 16 patients during the study period. Of the remaining 12 patients, seven patients were diagnosed with IgG₄-RRD with extrathoracic lesions, three were diagnosed with multicentric Castleman disease, one had rheumatoid arthritis, and one had lung cancer.

The median age of the 16 patients with IgG₄-positive IP at the time of diagnosis was 66 years (range: 49–74 years), and 12 were male. 13 of the 16 patients had a history of smoking. In addition, 13 of the 16 patients had respiratory symptoms, such as cough or dyspnoea, at diagnosis.



Shareable abstract (@ERSpublications)

This study suggests that IgG₄⁺ IP with abundant IgG₄⁺ cells and elevated serum IgG₄ levels could be treated differently from IgG₄-related respiratory disease due to potential differences in disease behaviour and response to corticosteroid therapy <https://bit.ly/3dUo2cu>

Cite this article as: Komatsu M, Yamamoto H, Matsui S, *et al.* Clinical characteristics of immunoglobulin G₄-positive interstitial pneumonia. *ERJ Open Res* 2021; 7: 00317-2021 [DOI: 10.1183/23120541.00317-2021].

Almost all 16 patients had abnormally high serum concentrations of Krebs von Lungen-6 and surfactant protein-D. Contrarily, the white blood cell count and C-reactive protein concentrations were nearly normal. Bronchoalveolar lavage was performed in eight patients; there were no specific trends in the cell fractions of bronchoalveolar lavage fluid. In pulmonary function tests, four patients showed restrictive changes (percentage of predicted vital capacity <80%). The median percentage of the predicted diffusing capacity of the lungs for carbon monoxide was 57.9% (range: 29.9–81.4%).

The most common characteristic findings observed on chest HRCT imaging were ground-glass opacities (n=16), reticular opacities (n=11), traction bronchiectasis (n=10), thickening of the interlobular septal wall (n=9), and hilar mediastinal lymphadenopathy (n=6). Ground-glass and reticular opacities were predominant in the lower and peripheral lung zones. Representative HRCT images are shown in figure 1a. The HRCT patterns found in the 16 patients were as follows: indeterminate for usual interstitial pneumonia (UIP) (n=8), desquamative interstitial pneumonia (DIP) (n=3), unclassifiable IIPs (n=3; two patients had nonspecific interstitial pneumonia (NSIP) with organising pneumonia and one patient had pleuroparenchymal fibroelastosis (PPFE) with UIP), and NSIP (n=2).

Marked numbers of lymphoplasmacytic cells in the fibrous parenchyma were observed in the histopathology of 14 patients. However, none of these patients had either obliterative vasculitis or storiform fibrosis, which are characteristic findings of IgG₄-related disease [1–3]. The representative pathological findings are shown in figure 1e–h. IgG₄-positive plasma cells were conspicuously present in the fibrous parenchyma. The histopathology patterns of the 16 patients were as follows: unclassifiable IIPs (n=9; four patients had coexisting UIP and NSIP), NSIP (n=3), UIP (n=1), probable UIP (n=1), DIP (n=1), and PPFE (n=1).

The median follow-up period was 59 months (range: 13–126 months). All but one of the 16 patients were treated with corticosteroid monotherapy as initial therapy. With treatment, ground-glass opacities on HRCT improved in all 15 patients (figure 1b). By contrast, the reticular opacities deteriorated after initiation of treatment in six of the 15 patients. The typical HRCT findings before and after treatment are shown in figure 1c–d. The patients who did not receive corticosteroid treatment had a stable clinical course during the follow-up period.

Immunosuppressant and antifibrotic agents were administered as additional therapies to two patients owing to disease progression. Acute exacerbation occurred in two patients. Three patients died during the follow-up period: two patients due to chronic respiratory failure and one patient due to an acute exacerbation.

In this study, we examined the clinico–radio–pathological characteristics of IgG₄-positive IP in 16 cases. On HRCT, ground-glass opacities were predominant in peripheral and peribronchovascular areas, and traction bronchiectasis and reticular opacities were observed. Lymphoplasmacytic inflammation into peribronchiolar regions and interlobular septa was seen in many patients. In addition, various types of fibrosis, such as UIP, NSIP, and DIP, were present. We found a correlation between the distribution of ground-glass opacities in HRCT and the lymphoplasmacytic inflammation in the lung tissue. Additionally, a correlation existed between the patterns of traction bronchiectasis and the reticular opacities at HRCT and histopathological fibrosis.

15 of the 16 patients received corticosteroid therapy. Although the ground-glass opacities improved on HRCT for all patients after treatment, reticular opacities, which indicate fibrosis, deteriorated in six patients despite treatment. Furthermore, despite treatment, three patients died during the follow-up period due to disease progression.

Notably, the clinical courses in the study participants differed significantly from that of the previously reported conventional IgG₄-RRD [5]. Corticosteroid therapy is fully effective in patients with IgG₄-RRD [5–7]. We speculate that the improvement in ground-glass opacities on HRCT reflected the elimination of IgG₄-positive lymphoplasmacytic cell infiltration from the perilymphatic stromal area in the surgical lung biopsy specimens. Residual fibrosis may have been the essence of IP, leading to progressive fibrosis, even though the ground-glass opacities improved with corticosteroid treatment.

Some limitations of this study were its retrospective nature and the small sample size, although we did recruit patients with IgG₄-positive IP throughout Japan. Further prospective research is necessary to confirm the disease behaviour of IgG₄-positive IP.

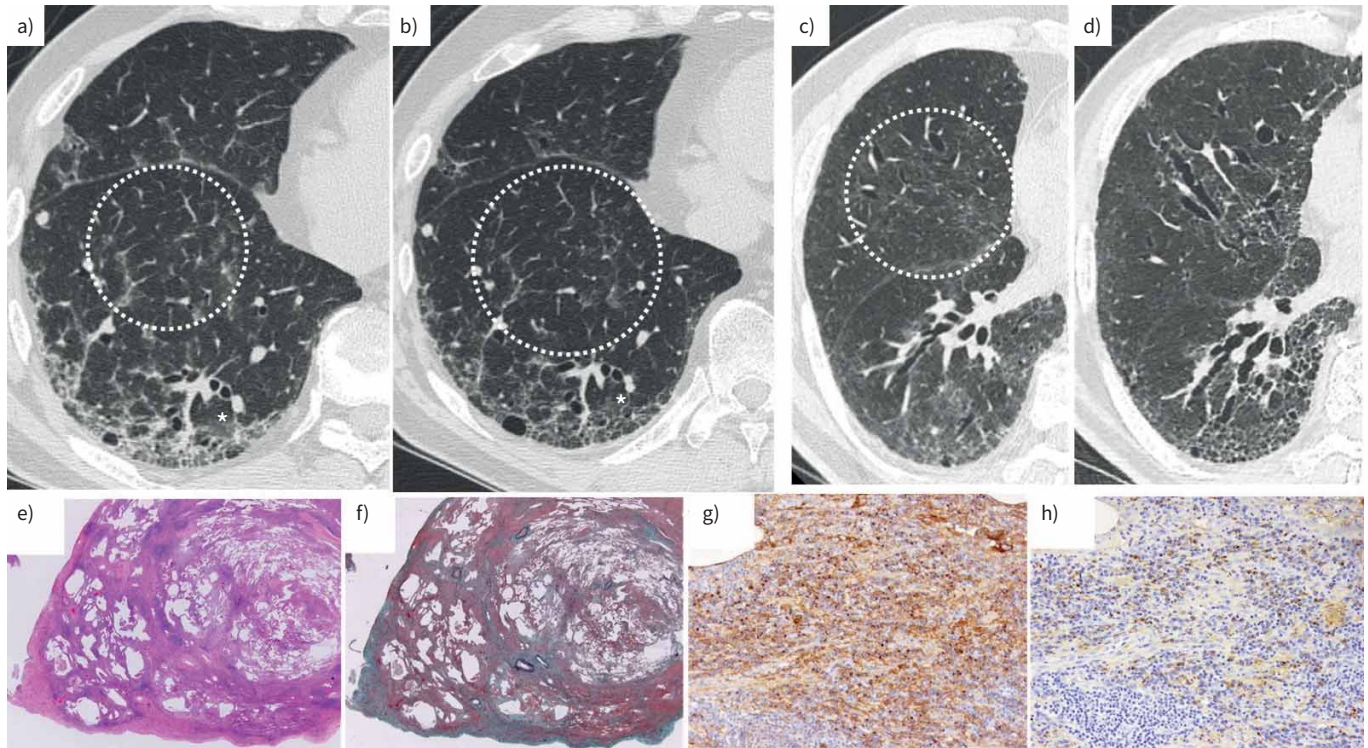


FIGURE 1 Radiographic and pathological findings of IgG₄-positive interstitial pneumonia. **a–d**) Transverse section of high-resolution computed tomography (HRCT) images of two cases of IgG₄-positive interstitial pneumonia. **a**) Before treatment and **b**) 2 years after initiation of corticosteroid treatment. The HRCT pattern was indeterminate for usual interstitial pneumonia (UIP). The peribular ground-glass opacities (circle) improved with corticosteroid treatment; however, reticular opacities remained (asterisk). **c**) Before treatment and **d**) 6 years after initiation of corticosteroid treatment. Ground-glass opacities and thickening of the interlobular septal wall (circle) improved with corticosteroid treatment, but traction bronchiectasis and reticular opacities deteriorated. The patient was also treated with an antifibrotic agent, but he eventually died because of an acute exacerbation. **e–h**) Histopathological features of a representative IgG₄-positive interstitial pneumonia case. **e**, **f**) Architectural distortion with marked lymphoplasmacytic cell infiltration is seen at a low-power magnification (**e**) haematoxylin and eosin staining; **f**) Elastica-Masson staining; magnification 1.25×). The case was of interstitial pneumonia with an unclassifiable pattern because of the combined presentation of usual interstitial pneumonia and nonspecific interstitial pneumonia pattern. **g**, **h**) Images showing an increase in the IgG-positive and IgG₄-positive cells in the fibrous parenchyma (**g**) IgG; **h**) IgG₄ immunohistochemistry, respectively; magnification 20×).

In summary, we revealed the clinical characteristics of IgG₄-positive IP. We believe that IgG₄-positive IP needs to be treated as a separate entity from conventional IgG₄-RRD because of the relative differences in disease behaviour and responses to corticosteroid therapy.

Masamichi Komatsu¹, Hiroshi Yamamoto¹, Shoko Matsui², Yasuhiro Terasaki³, Akira Hebisawa⁴, Tae Iwasawa⁵, Takeshi Johkoh⁶, Tomohisa Baba⁷, Atsushi Miyamoto⁸, Tomohiro Handa⁹, Keisuke Tomii¹⁰, Yuko Waseda¹¹, Masashi Bando¹², Haruyuki Ishii¹³, Yasunari Miyazaki¹⁴, Akihiko Yoshizawa¹⁵, Tamiko Takemura¹⁶, Yoshinori Kawabata¹⁷, Takashi Ogura⁷ and the Tokyo Diffuse Lung Disease Study Group

¹First Dept of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan. ²Health Administration Center, University of Toyama, Toyama, Japan. ³Dept of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan. ⁴Division of Clinical Pathology, Asahi Central Hospital, Asahi, Japan. ⁵Dept of Radiology, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan. ⁶Dept of Radiology, Kansai Rosai Hospital, Amagasaki, Japan. ⁷Division of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan. ⁸Dept of Respiratory Medicine, Respiratory Center, Toranomon Hospital, Tokyo, Japan. ⁹Dept of Advanced Medicine for Respiratory Failure, Graduate School of Medicine, Kyoto University, Kyoto, Japan. ¹⁰Dept of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan. ¹¹Third Dept of Internal Medicine, Faculty of

Medical Sciences, University of Fukui, Fukui, Japan. ¹²Division of Pulmonary Medicine, Dept of Medicine, Jichi Medical University, Tochigi, Japan. ¹³Dept of Respiratory Medicine, Kyorin University School of Medicine, Tokyo, Japan. ¹⁴Dept of Respiratory Medicine, Tokyo Medical and Dental University, Tokyo, Japan. ¹⁵Dept of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan. ¹⁶Dept of Pathology, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan. ¹⁷Division of Diagnostic Pathology, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan.

Corresponding author: Hiroshi Yamamoto (yama5252@shinshu-u.ac.jp)

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors thank Shinichi Sasaki (Juntendo University Urayasu Hospital) and Shinyu Izumi (Central Hospital of the National Center for Global Health and Medicine), who supported the clinical and pathologic review conferences. We also thank Kiminobu Tanizawa (Kyoto University Hospital), Sho Yamada (Kitano Hospital), Machiko Arita, Shinya Yokoe (Kurashiki Central Hospital), Ryosuke Hirabayashi (Kobe City Medical Center General Hospital), Takafumi Yamaya, Masato Asaoka (Kanagawa Cardiovascular and Respiratory Center), Miwa Yamanaka (Shinshu University School of Medicine), Yuhei Ito (Ise Red Cross Hospital), Naoki Hamada (Kyushu University), Toshikazu Takasaki, Hiroyoshi Yamauchi (Jichi Medical University), Nobuhito Arakawa (International University of Health and Welfare Hospital), Hiromi Tomioka (Kobe City Medical Center West Hospital), Kosuke Okuma, Kojiro Honda (Kyorin University School of Medicine), Seiko Takasawa (Tokyo Medical and Dental University), Shun Shinomiya (Saitama Medical University) and Yutaro Nakamura (Hamamatsu University School of Medicine) for case registrations from their respective institutions.

Author contributions: M. Komatsu, H. Yamamoto, S. Matsui, M. Bando, H. Ishii, Y. Miyazaki and T. Ogura conceptualised the study. M. Komatsu, H. Yamamoto, S. Matsui and T. Ogura designed the study. M. Komatsu, H. Yamamoto, S. Matsui, Y. Terasaki, A. Hebisawa, T. Iwasawa, T. Johkoh, T. Baba, A. Miyamoto, T. Handa, K. Tomii, Y. Waseda, M. Bando, H. Ishii, Y. Miyazaki, A. Yoshizawa, T. Takemura and Y. Kawabata acquired and analysed the data. M. Komatsu performed the statistical analysis and interpreted the data. M. Komatsu, H. Yamamoto, S. Matsui and T. Ogura wrote the manuscript. H. Yamamoto, S. Matsui, Y. Terasaki, A. Hebisawa, T. Iwasawa, T. Johkoh, T. Baba, A. Miyamoto, M. Bando, H. Ishii, Y. Miyazaki and T. Ogura provided administrative support.

Conflict of interest: None declared.

Support statement: This study was supported by the Ministry of Health, Labour and Welfare Research Program on Rare and Intractable Diseases (No. JPMH20FC1040), the Japan Society for the Promotion of Science (No. 21K08175), the Tokyo Diffuse Lung Disease Study Group and Shionogi Pharmaceutical, Co., Ltd. Funding information for this article has been deposited with the Crossref Funder Registry.

References

- 1 Umehara H, Okazaki K, Masaki Y, *et al*. Comprehensive diagnostic criteria for IgG₄-related disease (IgG₄-RD), 2011. *Mod Rheumatol* 2012; 22: 21–30.
- 2 Umehara H, Okazaki K, Kawa S, *et al*. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG₄-RD. *Mod Rheumatol* 2021; 31: 529–533.
- 3 Wallace ZS, Naden RP, Chari S, *et al*. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG₄-related disease. *Ann Rheum Dis* 2020; 79: 77–87.
- 4 Stone JH, Zen Y, Deshpande V. IgG₄-related disease. *N Engl J Med* 2012; 366: 539–551.
- 5 Matsui S, Hebisawa A, Sakai F, *et al*. Immunoglobulin G₄-related lung disease: clinicoradiological and pathological features. *Respirology* 2013; 18: 480–487.
- 6 Sun X, Liu H, Feng R, *et al*. Biopsy-proven IgG₄-related lung disease. *BMC Pulm Med* 2016; 16: 20.
- 7 Kang J, Park S, Chae EJ, *et al*. Long-term clinical course and outcomes of immunoglobulin G₄-related lung disease. *Respir Res* 2020; 21: 273.
- 8 Raghu G, Remy-Jardin M, Myers JL, *et al*. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
- 9 Travis WD, Costabel U, Hansell DM, *et al*. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.