Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6456-20
Intern Med 60: 3137-3142, 2021
http://internmed.jp

【 CASE REPORT 】

Granulomatous-lymphocytic Interstitial Lung Disease Associated with Good's Syndrome That Responded to Immunoglobulin Therapy

Kyoko Gocho[1], Tokuhiro Kimura[2], Shinya Matsushita[1], Saeko Shinozawa[1], Nobuyuki Hamanaka[1], Yoshimasa Inoue[3] and Tamiko Takemura[4]

Abstract:
Good's syndrome is associated with thymoma and acquired immunodeficiency. A 54-year-old man visited our hospital with a complaint of cough. Chest imaging revealed diffuse nodular shadows and anterior mediastinal mass. Hypogammaglobulinemia and a decreased B lymphocyte count were found by a laboratory evaluation. The lung nodules markedly regressed after immunoglobulin therapy. The mediastinal mass and remaining nodule were surgically resected and diagnosed as a type AB thymoma and a necrotizing epithelioid granuloma with T lymphocyte-dominant alveolitis, respectively. The overall appearances of these lesions were mostly in line with the spectrum of granulomatous-lymphocytic interstitial lung disease associated with Good's syndrome.

Key words: Good's syndrome, granulomatous-lymphocytic interstitial lung disease, immunoglobulin therapy, hypogammaglobulinemia

(Intern Med 60: 3137-3142, 2021)
(DOI: 10.2169/internalmedicine.6456-20)

Introduction

Good's syndrome, defined as the presence of a thymoma with immunodeficiency, accounts for as few as 5% of all thymoma cases (1). Lower respiratory tract infections caused by immunodeficiency in Good's syndrome are the most common complications and can affect the patient prognosis (2). In contrast, non-infectious pulmonary involvement is very rare.

Granulomatous-lymphocytic interstitial lung disease (GLILD) is a pulmonary manifestation of common variable immunodeficiency (CVID) characterized by a variable combination of granulomas, follicular bronchiolitis (FB), lymphoid hyperplasia, and lymphocytic interstitial pneumonia (LIP). GLILD is a lymphoproliferative disease associated with primary immune disorders, and an aberrant immune response has been suggested to potentially be involved in its pathogenesis (3).

We herein report a case of GLILD associated with Good's syndrome that followed a very interesting course.

Case Report

A 54-year-old Japanese man was admitted to our hospital with the complaint of a 1-month history of mild cough. He was a former smoker with no history of respiratory disease and no family history of genetic disease.

At his initial visit, his temperature was 36.1℃, pulse rate was 74 beats per minute, blood pressure was 126/80 mmHg, and oxygen saturation was 97% in room air. Chest auscultation did not reveal crackles in the lung fields or a heart murmur. Palpable lymph nodes and splenohepatomegalia were not found. Fatigability and weakness affecting the ocular and limb skeletal muscles were not evident. A laboratory evaluation revealed marked hypogammaglobulinemia (IgG

[1]Department of Respiratory Medicine, Saiseikai Yokohamashi Tobu Hospital, Japan, [2]Department of Diagnostic Pathology, Saiseikai Yokohamashi Tobu Hospital, Japan, [3]Division of Respiratory Surgery, Saiseikai Yokohamashi Tobu Hospital, Japan and [4]Department of Pathology, Kanagawa Cardiovascular and Respiratory Center, Japan
Received: October 9, 2020; Accepted: January 31, 2021; Advance Publication by J-STAGE: March 15, 2021
Correspondence to Dr. Kyoko Gocho, kyokogocho@yahoo.co.jp

Table. **Laboratory Findings on Admission.**

Hematology		**Serology**		**Infection**	
WBC	7,990 /μL	CRP	0.16 mg/dL	Procarcitonin	<0.02 ng/mL
neut	63.0 %	IgG	490 mg/dL	B-D glucan	26.6 pg/mL
eosino	0.1 %	IgA	31 mg/dL	Aspergillus-antigen	(-)
lymph	27.7 %	IgM	23 mg/dL	Cryptococus-antigen	(-)
mono	7.3 %	CD3	77.0 %	Cytomegalovirus antigenemia	(-)
baso	1.9 %	CD4	30.6 %	HIV-antibody	(-)
RBC	481×10^4 /μL	CD8	48.4 %	T-SPOT®	(-)
Hb	14.8 g/dL	CD19	0.0 %	Anti-glycopeptidolipid core IgA antibody	(-)
PLT	36.9×10^4 /μL	CD20	0.2 %		
Biochemistry		CD23	0.0 %		
TP	8.7 g/dL	CD4/8	0.57		
Alb	4.4 g/dL	RF	<5 IU/mL		
AST	21 IU/L	ANA	(-)		
ALT	24 IU/L	Ach-R-Ab	17.3 nmol/L		
LDH	257 IU/L	s-IL2R	819 U/mL		
ALP	227 IU/L	CEA	2.4 ng/mL		
BUN	13.4 mg/dL	ACE	19.5 U/L		
Cr	0.82 mg/dL				

490 mg/dL, IgA 31 mg/dL, and IgM 23 mg/dL) and B-lymphocytopenia (CD19 0.0%, CD20 0.2%, and CD23 0.0%), but the number of T lymphocytes and the ratio of CD4 and CD8 were within normal limits. In addition, the C-reactive protein value and white blood cell count were not elevated. The level of anti-acetylcholine receptor (Ach-R) antibody was elevated (17.3 nmol/L), but the levels of other autoimmune markers were not elevated. The interferon-gamma release assay (T-SPOT. TB; Oxford Immunotec, Abingdon, UK) and anti-glycopeptidolipid-core IgA antibody were both negative (Table).

Chest computed tomography (CT) revealed mildly thickened bronchial walls and diffuse peribronchial nodules. The nodules ranged from very fine to 1-2 cm in diameter on an air bronchogram, and some of the fine nodules had aggregated to irregular patchy shadows (Fig. 1A, B). They were distributed in the central to middle lung region of the upper and middle lobes. Bronchiectasis, pulmonary fibrosis, and lymphadenopathy were not observed. A well-circumscribed mass 5 cm in diameter in the anterior mediastinum was revealed in the mediastinal window (Fig. 1B). Positron emission tomography showed the accumulation of fluorodeoxyglucose in the mediastinal mass as well as in the pulmonary nodules (Fig. 1C).

No pathogen was isolated from the sputum or bronchiolar lavage fluid. The mediastinal mass was diagnosed as a thymoma by a CT-guided needle biopsy. We also diagnosed this patient with Good's syndrome based on the presence of the thymoma and immunodeficiency without active infection. Although the lesion was positive for Ach-R antibody, myasthenia gravis (MG) was not diagnosed in this patient because no abnormality of the muscles or nerves was seen. He was administered immunoglobulin therapy twice at two-week intervals to prevent infection, after which the pulmonary nodules regressed and disappeared by one month after the initial visit (Fig. 2). The thymoma and residual pulmonary nodules of the right middle lobe required resection for a definitive pathological diagnosis, so we performed video-assisted thoracoscopic surgery (VATS) three months after his initial visit. To prevent perioperative infectious complications, immunoglobulin therapy was performed once more on the day before the surgery.

The specimen resected by VATS thymectomy was a lobulated tumor that measured 6.0×5.0×3.5 cm. Histologically, the tumor contained two components: lymphocyte-poor and lymphocyte-rich areas (Fig. 3). The lymphocyte-poor area contained proliferating bland spindle-shaped epithelial cells, whereas the lymphocyte-rich area contained spindle-shaped epithelial cells and numerous small lymphocytes. Immunohistochemically, the spindle-shaped epithelial cells in both areas were positive for cytokeratin AE1/AE3 and were focally positive for CD20. The lymphocytes were positive for CD3 and CD1a, which suggests that they were immature T lymphocytes. Focal microscopic transcapsular invasion was also found. Therefore, the mass was diagnosed as a type AB thymoma, Masaoka stage II, UICC stage pT1a. The surgical margin was negative.

The specimen obtained by the VATS lung biopsy revealed granuloma accompanied by lymphocytic interstitial inflammation in the alveolar walls adjacent to the granuloma (Fig. 4A, F). The granuloma was composed of epithelioid cells and a small number of multinucleated giant cells. Coagulation necrosis was observed at the center of the granuloma. An immunohistochemical analysis revealed that the lymphocytes infiltrating the granuloma (Fig. 4B-E) and the alveolar walls (Fig. 4G-J) contained CD3-positive T cells, whereas CD20-positive B cells were not observed. Among the infiltrating T lymphocytes, CD8-positive cells outnumbered CD4-positive cells. No pathogens were detected by Ziehl-Neelsen and Grocott stains or by tissue culture.

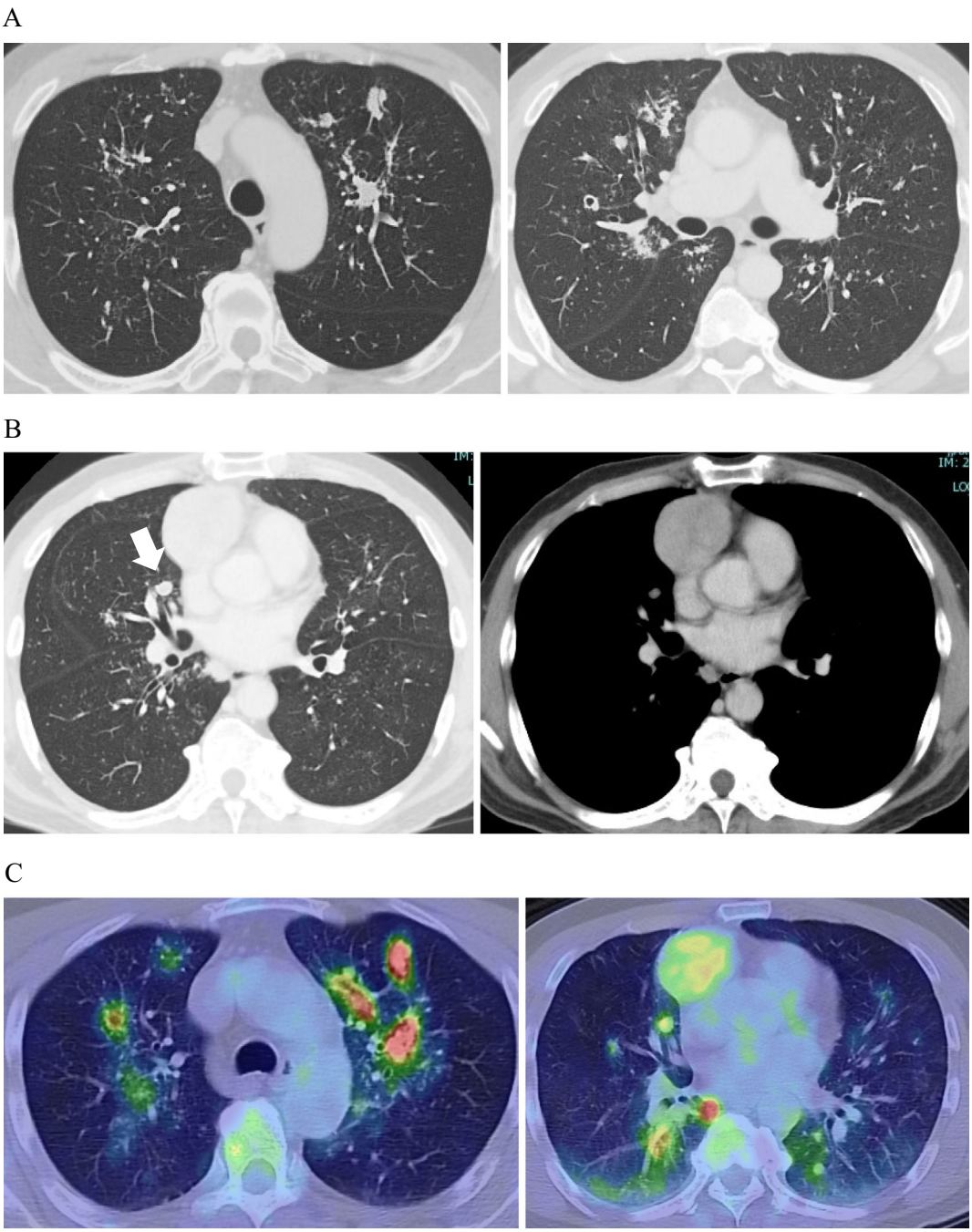

Figure 1. **(A, B) Chest CT revealed mildly thickened bronchial walls and diffuse peribronchial nodules. The nodules were distributed in the central to middle lung regions of the upper and middle lobes. (B) In the mediastinal window, a well-circumscribed mass was revealed in the anterior mediastinum. The white arrow indicates a nodule removed by a surgical lung biopsy. (C) Positron emission tomography (PET) showed the accumulation of fluorodeoxyglucose in both the mediastinal mass and pulmonary nodules.**

The patient had anemia one month before VATS, and pure red cell aplasia was diagnosed by a bone marrow biopsy. The multiple pulmonary nodules had almost disappeared one month after VATS. Finally, he was transferred to a university hospital so that he could receive treatment for pure red cell aplasia.

Discussion

The pathogenesis of Good's syndrome has been unclear since Good first reported this disease in 1954 (1). Although Good's syndrome is a rare complication of thymoma, it is an important complication because of its impact on the patient prognosis (2). In other words, immunodeficiency characterized by hypogammaglobulinemia that results in suscep-

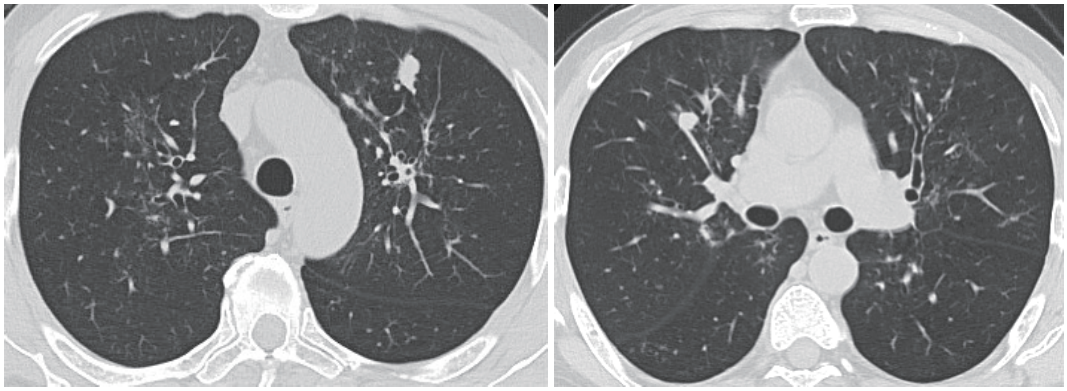

Figure 2. **Chest CT performed one month after the initial visit but after admission showed that most of the nodule shadows had either diminished or completely disappeared, but the relatively large nodules remained.**

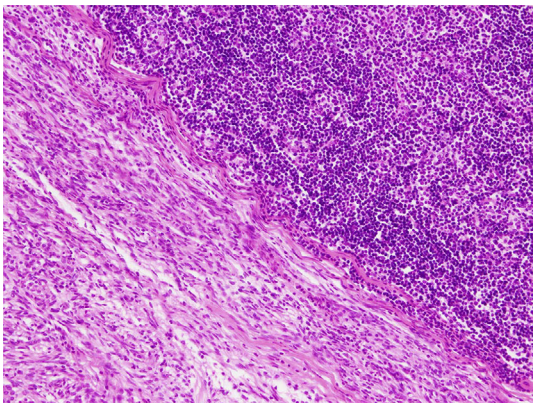

Figure 3. **Histological findings of the resected thymic tumor. The tumor was composed of lymphocyte-poor (lower left) and lymphocyte-rich (upper right) areas and was diagnosed as a type AB thymoma (Hematoxylin and Eosin staining, original magnification ×200).**

tibility to various infections can be a fatal complication compared with the effects of the thymoma itself (4, 5). Our case was already experiencing hypogammaglobulinemia and exhibited a marked decrease in B lymphocytes at his initial visit, but no abnormalities in T cell lymphocyte number or in the CD4/8 ratio were observed. However, in Good's syndrome, the problem is not the total number of T lymphocytes; rather, the T lymphocytes themselves have been suggested to be dysfunctional, and this could not be ruled out in our case (6).

Many studies have been published on infectious diseases and pathogens recovered from patients with Good's syndrome. The most common reports were infections of the upper and lower respiratory tract, and the most common pathogens were typified by encapsulated bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae* (7-9). In our case, a mycobacterial infection was initially suspected because a necrotizing granuloma was revealed in the lung specimen, but no pathogens were detected. Interestingly, unlike human immunodeficiency virus-infected patients, opportunistic infections with mycobacteria have been described as uncommon in patients with Good's syndrome (4, 7, 10). In addition to our inability to detect mycobacterial pathogens, improvement in disease without antibiotic treatment in just a few months eliminated the possibility of mycobacterial infection.

From an immunological point of view, almost half of Good's syndrome patients have some autoimmune manifestations. Similar to our case, pure red cell aplasia is one of the most common manifestations and associated with 20-30% of Good's syndrome cases, and Jansen et al. reported that 17% of Good's syndrome patients had ≥2 autoimmune manifestations (4, 11). MG is a typical autoimmune manifestation of thymoma and Good's syndrome. Marcuse et al. defined thymoma patients with anti-AchR-antibodies in the serum without neurological symptoms as subclinical MG. The prevalence of subclinical MG in thymomas was found to be 10.8%, and 91% of these patients developed clinical MG within 6 years after thymectomy (12). Our case did not develop MG during the course of his hospitalization, but his condition was consistent with subclinical MG, so careful follow-up is required.

Good's syndrome is often compared with CVID. CVID is a heterogeneous syndrome that is characterized by B-cell differentiation failure and defective immunoglobulin production and is immunologically similar to Good's syndrome. Furthermore, 8% to 22% of CVID cases develop an interstitial lung disease termed GLILD, which presents histopathological findings of non-necrotizing granulomatous inflammation and lymphoproliferative changes, including histologic patterns of LIP, FB, and diffuse reactive lymphoid hyperplasia (3, 13). Rao et al. reported that lymphoid infiltration exhibited a predominance of T lymphocytes over B lymphocytes (14). GLILD is intractable and causes pulmonary dysfunction, which affects the patient prognosis. Chest images of GLILD vary among cases because GLILD consists of various histopathological patterns. On CT, as in our case, perilymphatic and randomly distributed small nodules are frequently observed (15). From a clinical, radiological, and histopathological viewpoint, sarcoidosis is one of the most important differential diagnoses of GLILD. Bouvry et

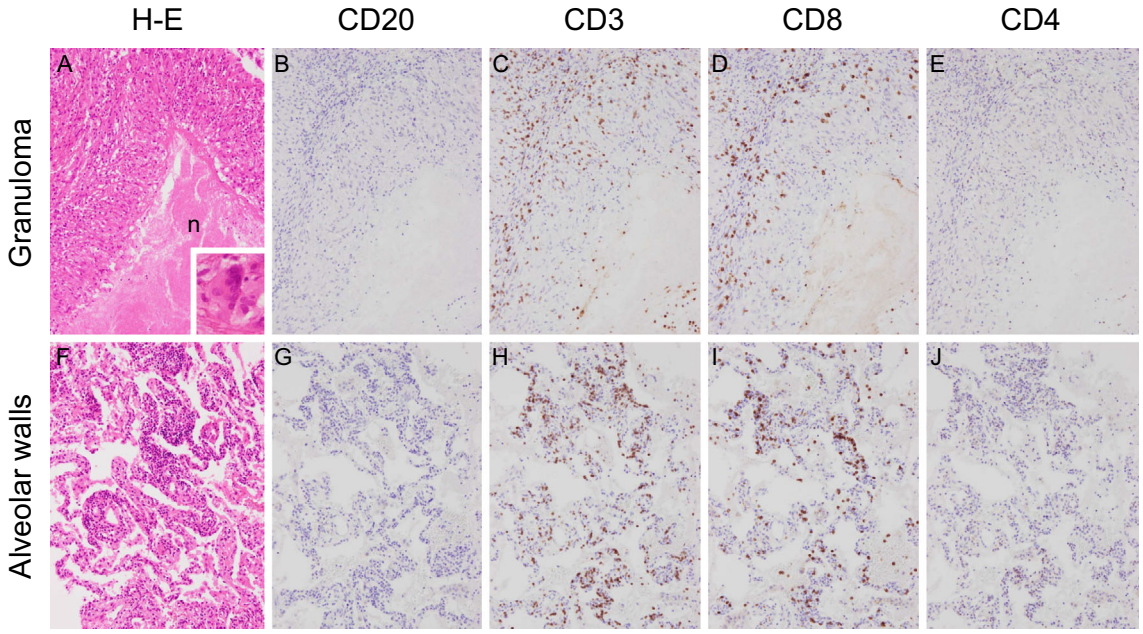

Figure 4. **Histological and immunohistochemical findings of the pulmonary nodule, in which a granuloma (A-E) and interstitial inflammation (F-J) were found. (A) The granuloma was composed of epithelioid cells and a small number of multinucleated giant cells (inset). Necrosis was seen at the center of the granuloma. (B-E) An immunohistochemical analysis of serial sections of a granuloma revealed that the infiltrating lymphocytes were CD3-positive T cells and that CD8-positive cells outnumbered CD4-positive cells. (F) Lymphocytic interstitial inflammation was found in the alveolar walls adjacent to the granuloma. (G-J) An immunohistochemical analysis of serial sections of the alveolar walls showed that the infiltrating lymphocytes were CD3-positive T cells and that CD8-positive cells outnumbered CD4-positive cells. (A and F, Hematoxylin and Eosin staining; B and G, CD20 immunostain; C and H, CD3 immunostain; D and I, CD8 immunostain; E and J, CD4 immunostain; original magnification ×200).**

al. reported that pulmonary nodules are present in both GLILD and sarcoidosis and that nodules of GLILD are larger in size, more randomly distributed, and more frequently accompanied by a halo sign than those of sarcoidosis (16). Histologically, although granuloma is a common finding in both GLILD and sarcoidosis, LIP and FB patterns are characteristic of GLILD but are rarely seen in sarcoidosis (17). GLILD thus has more diverse histopathological features than sarcoidosis, and the chest images reflect this finding. In our case, the primary pattern seen on CT was peribronchial nodules of various sizes, and histopathologically, the nodules were granulomas, and resembled a T-lymphocyte-rich LIP-like lesion devoid of B cells. These findings were consistent with those of GLILD, and most importantly, the presence of hypogammaglobulinemia pathogenically supports the possibility of GLILD. In our case, the granuloma was necrotic, which to our knowledge has not been previously reported. In addition, the predominance of CD8-positive T cells over CD4-positive T cells in the lesion was also peculiar to our case because CD4-positive T cells usually outnumber CD8-positive T cells in GLILD lesions in CVID (14). We speculated that the necrotic granuloma and relative decrease in CD4-positive T cells might be related to the shrinkage and healing process of GLILD lesions because the VATS lung biopsy in our case was performed after regression of the pulmonary nodules due to immunoglobulin therapy.

To our knowledge, only one case of GLILD with Good's syndrome has been reported (18). Interstitial shadows, nodules, and immunodeficiency after thymectomy were observed in that case, and GLILD was diagnosed histopathologically by a lung biopsy. Immunoglobulin and steroid therapy led to complete regression of the lung lesion after two months of treatment. Similarly, in our case, it is speculated that three rounds of immunoglobulin therapy had been effective for GILID, and as a result, the nodular shadow mostly disappeared. The effect of immunoglobulin therapy continued even after the thymectomy. Immunoglobulin therapy is often given as a first-line treatment to patients with GLILD, but in many cases, the effect is insufficient, and consequently, steroids and various immunosuppressants are required for further treatment. Hasegawa et al. reported a case of GLILD for which immunoglobulin therapy was immediately effective for a lung lesion, and the authors suggested that the response to treatment might differ according to the histopathologic pattern and granuloma size (19). In our case, architectural distortions, such as pulmonary fibrosis and bronchiectasis, were not present, but the granuloma and LIP in the lesion suggested reversibility. Therefore, the treatment response was good.

Because of the limited amount of previous data, whether or not GLILD in Good's syndrome is similar to CVID remains unclear. However, because the correct and early recognition can be essential for the patient survival, further discussions are warranted.

Written informed consent for the publication of the clinical details and images was provided by the patient.

The authors state that they have no Conflict of Interest (COI).

References

1. Jeunet FS, Good RA. Thymoma, immunologic deficiencies and hematological abnormalities. Birth Defects **4**: 192-203, 1968.
2. Arend SM, Dik H, van Dissel JT, et al. Good's syndrome: the association of thymoma and hypogammaglobulinemia. Clin Infect Dis **32**: 323-325, 2001.
3. Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). Clin Immunol **134**: 97-103, 2010.
4. Kelesidis T, Yang O. Good's syndrome remains a mystery after 55 years: a systematic review of the scientific evidence. Clin Immunol **135**: 347-363, 2010.
5. Gray GF, Gutowski W III. Thymoma. A clinicopathologic study of 54 cases. Am J Surg Pathol **3**: 235-249, 1979.
6. Kelleher P, Misbah SA. What is Good's syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol **56**: 12-16, 2003.
7. Dong JP, Gao W, Teng GG, Tian Y, Wang HH. Characteristics of Good's syndrome in China: a systematic review. Chin Med J **130**: 1604-1609, 2017.
8. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) **80**: 123-133, 2001.
9. Zaman M, Huissoon A, Buckland M, Patel S, Alachkar H. Clinical and laboratory features of seventy-eight UK patients with Good's syndrome (thymoma and hypogammaglobulinaemia). Clin Exp Immunol **2019**: 132-138, 2019.
10. Chaudhuri AD, Tapadar SR, Dhua A, et al. A case of Good's syndrome presenting with pulmonary tuberculosis. Indian J Chest Dis Allied Sci **57**: 247-250, 2015.
11. Jansen A, Deuren M, Miller J, et al. Prognosis of Good syndrome: mortality and morbidity of thymoma associated immunodeficiency in perspective. Clin Immunol **171**: 12-16, 2016.
12. Marcuse F, Hochstenbag M, Hoeijmakers JGJ, et al. Subclinical myasthenia gravis in thymomas. Lung Cancer **152**: 143-148, 2021.
13. Bates CA, Ellison MC, Lynch DA, et al. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol **114**: 415-421, 2004.
14. Rao N, Mackinnon AC, Routes JM. Granulomatous and lymphocytic interstitial lung disease: a spectrum of pulmonary histopathologic lesions in common variable immunodeficiency--histologic and immunohistochemical analyses of 16 cases. Hum Pathol **46**: 1306-1314, 2015.
15. Tanaka N, Kim JS, Bates CA, et al. Lung diseases in patients with common variable immunodeficiency: chest radiographic, and computed tomographic findings. J Comput Assist Tomogr **30**: 828-838, 2006.
16. Bouvry et al, Mouthon L, Brillet PY, et al. Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. Eur Respir J **41**: 115-122, 2013.
17. Sood AK, Funkhouser W, Handly B, Weston B, Wu EY. Granulomatous-lymphocytic interstitial lung disease in 22q11.2 deletion syndrome: a case report and literature review. Curr Allergy Asthma Rep **18**: 14, 2018.
18. Jensen ML, Bendstrup E, Hilberg O. Granulomatous-lymphocytic interstitial lung disease and recurrent sinopulmonary infections in a patient with Good's Syndrome. BMJ Case Rep **30**: bcr 2014205635, 2015.
19. Hasegawa M, Sakai F, Okabayashi A, et al. Intravenous immunoglobulin monotherapy for granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency. Intern Med **56**: 2899-2902, 2017.