CASE REPORT

Granulomatous-lymphocytic Interstitial Lung Disease Associated with Good’s Syndrome that Responded to Immunoglobulin Therapy

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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 Advance Publication)
(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°C, 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 splenohepatomegaly were not found. Fatigability and weakness affecting the ocular and limb skeletal muscles were not evident. A laboratory evaluation revealed marked hypogammaglobulinemia (IgG

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Received: October 9, 2020; Accepted: January 31, 2021; Advance Publication by J-STAGE: March 15, 2021
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lavage fluid. The mediastinal mass was diagnosed as a thy-
mass 5 cm in diameter in the anterior mediastinum was re-

Table. Laboratory Findings on Admission.

| Hematology          | Serology   | Infection                      |
|---------------------|------------|-------------------------------|
| WBC 7,990 /μL       | CRP 0.16 mg/dL | Procarcinatin <0.02 ng/mL |
| neut 63.0 %         | IgG 490 mg/dL | B-D glucan 26.6 pg/mL       |
| eosin 0.1 %         | IgA 31 mg/dL  | Aspergillus-antigen (-)     |
| lymph 27.7 %        | IgM 23 mg/dL  | Cryptococcus-antigen (-)    |
| mono 7.3 %          | CD3 77.0 %   | Cytomegalovirus antigenemia (-) |
| baso 1.9 %          | CD4 30.6 %   | HIV-Antibody (-)            |
| RBC 481x10^6 /μL    | CD8 48.4 %   | T-SPOT® (-)                  |
| Hb 14.8 g/dL        | CD19 0.0 %   | Anti-glycopeptidolipid-core IgA antibody (-) |
| PLT 36.9x10^9 /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 anti-
body were both negative (Table).

Chest computed tomography (CT) revealed mildly thick-
ened 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 aggre-
gated 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 re-
vealed in the mediastinal window (Fig. 1B). Positron emis-
sion tomography showed the accumulation of fluorodeoxy-
glucose 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 thym-
aoma 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 infec-
tion. 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 pulmo-
nary nodules regressed and disappeared by one month after
the initial visit (Fig. 2). The thymoma and residual pulmo-
nary 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 complica-
tions, immunoglobulin therapy was performed once more on
the day before the surgery.

The specimen resected by VATS thymectomy was a lobu-
lated tumor that measured 6.0x5.0x3.5 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. Immuno-
histochemically, the spindle-shaped epithelial cells in both
areas were positive for cytokertatin AE1/AE3 and were fo-
cally 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 inflam-
mation 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. Co-
agulation necrosis was observed at the center of the granu-
łoma. 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 outnum-
bered CD4-positive cells. No pathogens were detected by
Ziehl-Neelsen and Grocott stains or by tissue culture.
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-
gens 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 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).
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 (11). 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 GLILD, 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 (18). 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.

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).
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.

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

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

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