Case report

BAFF-associated granulomatous lung disease in a patient with GATA2 deficiency

Motoko Yasutomi-Sakai, MD, PhD,[a] Taihei Hayashi, MD, PhD,[a] Koji Suzuki, MD, PhD,[a] Hayaki Akeda, MD,[a] Yumekichi Maeda, MD, PhD,[a] Akitoshi Okada, MD,[b] Toshihiro Takeda, MD,[c] Yasuhiro Watanabe, MD,[d] Yoshiaki Imamura, MD, PhD,[e] and Yusei Ohshima, MD, PhD[a] *Fukui, Japan*

A patient with GATA2 deficiency developed corticosteroid-responsive sterile granulomatous lung disease despite monocytopenia. The presence of B-lymphopenia, autoimmunity, an elevated level of serum B-cell–activating factor, and pulmonary plasma cell infiltration, which together suggested an underlying mechanism similar to that of combined variable immunodeficiency lung disease. (J Allergy Clin Immunol Global 2024;3:100336.)

Key words: *B-cell–activating factor, common variable immunodeficiency, GATA 2, granuloma, lung disease*

Abbreviations used
ac: Absolute count
BAFF: B-cell–activating factor
CVID: Common variable immune deficiency
GLILD: Granulomatous lymphocytic interstitial lung disease
MDS: Myelodysplastic syndrome

Heterozygous germline *GATA2* mutations cause a wide spectrum of phenotypes, including immunodeficiency, lymphoedema, and predisposition to myelodysplastic syndrome (MDS),[1,2] in which the numbers of dendritic cells, monocytes, and B or natural killer cells are diminished. Patients with GATA2 deficiency are susceptible to developing nontuberculous mycobacterial infections. Herein we present a case of sterile granulomatous lung disease resembling granulomatous-lymphocytic interstitial lung disease (GLILD), which occurs in patients with common variable immunodeficiency (CVID), as the first manifestation of GATA2 deficiency.

A 12-year-old boy had 3 episodes of fever, cough, and dyspnea over 6 months. He had no history of opportunistic or recurrent infections. Physical examination revealed fine crackles in the right peripheral lung field. Chest radiography showed bilateral ground-glass opacities. Antibiotics (sulbactam/ampicillin and clarithromycin) did not result in improvement, but prednisolone (1 mg/kg per day) significantly ameliorated the symptoms and pulmonary infiltrates, which recurred with tapering doses. Chest computed tomography revealed multiple bilateral lung nodules at the time of the third relapse (Fig 1).

The patient's blood test results before steroid administration were as follows: white blood cell count, 11.0 × 10^9/L (high neutrophil count, 9.57 × 10^9/L; low lymphocyte count, 1.19 × 10^9/L); low monocyte count, 0.055 × 10^9/L (normal range 0.2-0.8, × 10^9/L); C-reactive protein level, 7.83 mg/dL; LDH level, 202 IU/L; IgG level, 642 mg/dL; IgA level, 25 mg/dL; IgM level, 239 mg/dL; KL-6 level, 1508 U/mL; surfactant protein-A level, 73.2 ng/mL (normal range <110 ng/mL); and surfactant protein-D level, 75 ng/mL (normal range <43.8 ng/mL). The results of tests for precipitating antibodies to *Trichosporon asahii* and autoantibodies (antinuclear, anti–MDA-5, anti-ARS, anti-CCP, and rheumatoid factor) were negative.

The cellular composition of the patient's bronchoalveolar lavage fluid consisted of lymphocytes ($CD4^+$, 64.5%; $CD8^+$, 33.7%; and $CD20^+$, 0.2%), macrophages, and neutrophils, with no evidence of malignant cells or alveolar proteinosis. A lung biopsy of the right upper lobe showed accumulation of Langerhans giant cells and granuloma formation (Fig 2, *A*). Despite monocytopenia, the granulomas were composed of $CD68^+$ or $CD163^+$ macrophage, surrounded by $CD4^+$ T cells. $CD8^+$ T cells and $CD20^+$ B cells were scattered within the granulomas. There was a diffuse infiltration of plasma cells. Igκ- and Igλ-producing cells were detected, suggesting a nonmalignant reactive increase in plasma cells (Fig 2, *B-I*). Bacteria, mycobacteria, and fungi were not detected in any of the samples examined (see Table E1 in the Online Repository at www.jaci-global.org). Whole-body positron emission tomography did not show hilar lymphadenopathy or other organ involvement, as occurs in sarcoidosis.

Persistent monocytopenia prompted an investigation into underlying primary immunodeficiency. Genetic analysis (*GATA2, CSF2RA, CSF2RB, IRF7*, and *IRF8*) for defects in monocyte/macrophage numbers or functions revealed a known *GATA2* heteromissense variant (p.R361C). Flow cytometric analysis of the patient's lymphocytes revealed B-lymphopenia, which together

From [a]the Department of Pediatrics and [c]the Third Department of Internal Medicine, Faculty of Medical Sciences, and [b]the Division of Thoracic Surgery, Second Department of Surgery, University of Fukui; [d]the Department of Pediatrics, Fukui Red Cross Hospital; and [e]the Division of Diagnostic Pathology/Surgical Pathology, University of Fukui Hospital.

Informed consent: Informed consent was obtained from the patient's parents.
Received for publication April 16, 2024; revised July 7, 2024; accepted for publication July 9, 2024.
Available online August 28, 2024.

Corresponding author: Motoko Yasutomi-Sakai, MD, PhD, Department of Pediatrics, Faculty of Medical Sciences, University of Fukui, 23-3 Shimoaizuki, Matsuoka Eiheiji-cho Yoshida-gun, Fukui 9101193, Japan. E-mail: yasutomi@u-fukui.ac.jp.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

2772-8293

https://doi.org/10.1016/j.jacig.2024.100336

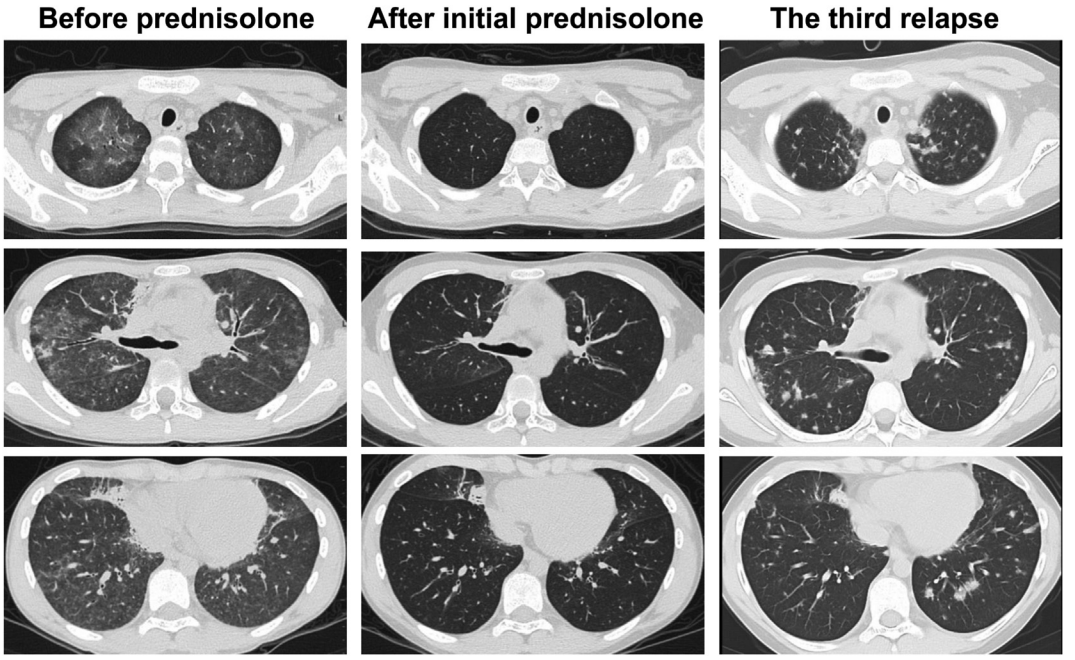

FIG 1. Computed tomography (CT) of the lungs. Lung CT showed ground-glass opacities that resolved after prednisolone therapy. Multiple bilateral lung nodules were present after the third relapse of pneumonia.

with monocytopenia, is a hematologic feature of GATA2 deficiency.[1,2] The analysis results were as follows: T cells, 95% (normal range 66%-89%; absolute count [ac] 2.141 × 10^6/L); B cells, 1% (normal range 4%-13%; ac 22 × 10^6/L); and $CD56^+$ natural killer cells, 7% (normal range 4%-35%; ac, 146 × 10^6/L). Bone marrow aspiration for searching MDS revealed no malignancy. The diagnosis was GATA2 deficiency with sterile granulomatous lung disease.

The patient was treated with oral prednisolone (10 mg per day), itraconazole, clarithromycin, rifampicin, and ethambutol to prevent mycobacterial and fungal infections associated with long-term steroid treatment until he underwent bone marrow transplantation from a matched sibling without a *GATA2* mutation. He transiently lost consciousness during transplant preconditioning but recovered fully. Brain T2-weighted magnetic resonance imaging revealed a high signal around the bilateral caudate nuclei, and anti–N-methyl-D-aspartate receptor autoantibodies were detected in the spinal fluid, leading to a diagnosis of autoimmune encephalitis. The lung involvement remitted after the transplantation.

Patients with a *GATA2* mutation often develop granulomas caused by mycobacterial infection.[2] Noninfectious granulomas in the skin, lung, or muscle that improved with corticosteroids have been reported.[3] Some patients have developed sterile lung granulomas after recurrent lung infections.[3] Previous reports have shown that dermal macrophages are relatively preserved in patients with GATA2 deficiency, whereas dermal monocytes are nearly diminished.[4] In mice, embryonic/fetal progenitor-derived macrophages are distributed to the lungs independently of bone marrow hematopoiesis, in which GATA2 has a critical role.[5] In humans, alveolar macrophages also appear to be maintained independently of circulating monocytes.[4] Consistent with this finding, our patient had an abundance of $CD68^+$ or $CD163^+$ macrophages in the lung tissue (Fig 2, *E* and *F*). Therefore, the absence of circulating monocytes may not protect against granuloma formation in lung tissue.

GLILD occurs in approximately one-third of patients with CVID and is responsible for an increased mortality rate.[6] GLILD is characterized histologically by a combination of noncaseating granulomas and variable lymphoproliferative patterns.[7] Proliferation of tissue B or plasma cells has been reported in some patients.[6] In fact, GLILD improves with rituximab treatment, but one-third of patients relapse.[6] Relapse after rituximab treatment is associated with elevated serum or lung tissue levels of B-cell–activating factor (BAFF), which is produced by activated monocytes in the lung.[8] There have been reports of rituximab-resistant mechanisms in patients with autoimmune cytopenia, in whom B-cell depletion by rituximab paradoxically enhanced BAFF production, and increased long-lived plasma cells accompanied by autoantibody production.[9] The following features in our case were compatible with those of patients with CVID and GLILD: (1) B-lymphopenia at onset of the lung disease; (2) elevated serum BAFF levels (3130 pg/mL at the third lung disease relapse), which decreased to 886 pg/mL after transplantation, suggesting an association with the lung lesions; (3) pulmonary plasma cell infiltration; and (4) comorbid autoimmune encephalitis. Although it is possible that some unknown organism is behind the granuloma formation, we speculate that B-lymphopenia led to incomplete control of infection in the lung, induced activation of alveolar macrophages, and contributed to granuloma formation in this patient.

In conclusion, despite monocytopenia, which is a hallmark of GATA2 deficiency, infectious and noninfectious granulomas can develop in patients with GATA2 deficiency. First-line corticosteroids alone or in combination with immunosuppressive treatment are required until hematopoietic stem cell transplantation together with infection prophylaxis.

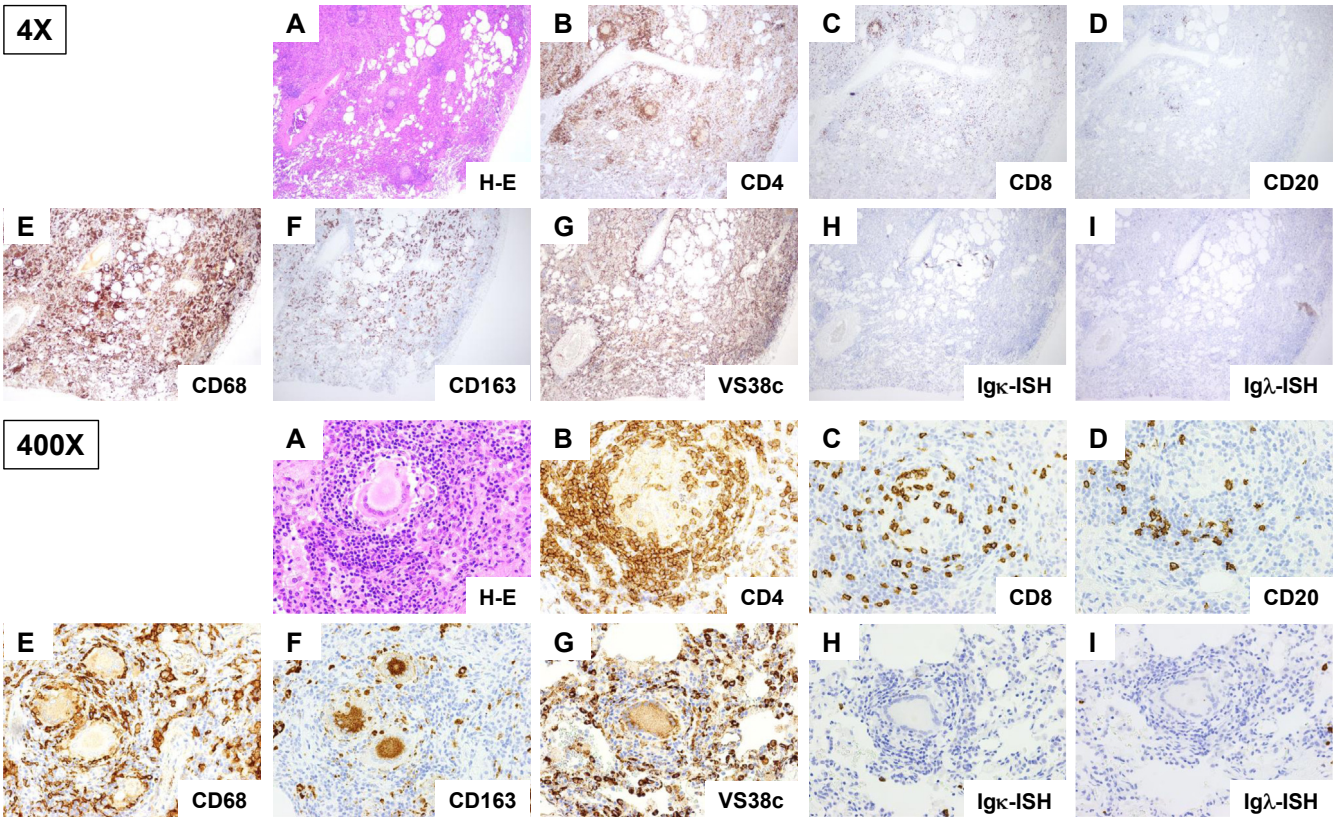

FIG 2. Lung histology showed granulomas. **A,** Hematoxylin and eosin staining. **B-G,** Immunohistochemistry. **H** and **I,** Igκ or Igλ *in situ* hybridization. **G,** VS38c antibody (Agilent, Santa Clara, Calif) was used to detect human plasma cells.

Serum BAFF levels were determined by using the Human BAFF Quantikine ELISA kit (R&D Systems, Minneapolis, Minn).

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Hsu AP, McReynolds LJ, Holland SM. GATA2 deficiency. Curr Opin Allergy Clin Immunol 2015;15:104-9.
2. Donadieu J, Lamant M, Fieschi C, de Fontbrune FS, Caye A, Ouachee M, et al. Natural history of GATA2 deficiency in a survey of 79 French and Belgian patients. Haematologica 2018;103:1278-87.
3. Damian L, Sauvêtre G, Marguet F, Verdalle-Cazes M, Battistella M, Boutboul D. Pseudo-sarcoidosis revealing monoMAC syndrome. J Clin Immunol 2018;38:739-41.
4. Bigley V, Haniffa M, Doulatov S, Wang XN, Dickinson R, McGovern N, et al. The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. J Exp Med 2011;208:227-34.
5. Evren E, Ringqvist E, Willinger T. Origin and ontogeny of lung macrophages: from mice to humans. Immunology 2020;160:126-38.
6. Matson EM, Abyazi ML, Bell KA, Hayes KM, Maglione PJ. B Cell dysregulation in common variable immunodeficiency interstitial lung disease. Front Immunol 2020;11:622114.
7. Gupta S, Pattanaik D, Krishnaswamy G. Common variable immune deficiency and associated complications. Chest 2019;156:579-93.
8. Maglione PJ, Gyimesi G, Cols M, Radigan L, Ko HM, Weinberger T, et al. BAFF-driven B cell hyperplasia underlies lung disease in common variable immunodeficiency. JCI Insight 2019;4:e122728.
9. Mahévas M, Patin P, Huetz F, Descatoire M, Cagnard N, Bole-Feysot C, et al. B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells. J Clin Invest 2013;123:432-42.