AARD
Allergy Asthma Respir Dis 12(3):155-159, July 2024 https://doi.org/10.4168/aard.2024.12.3.155
pISSN: 2288-0402
eISSN: 2288-0410
CASE REPORT

Cerebral toxoplasmosis in a patient with Good's syndrome: A case report and literature review

Seoyoung Choi,[1] Mi Jung Kwon,[2] Eun Soo Kim,[3] Heui Seung Lee,[4] Younghee Jung,[5] Joo-Hee Kim,[1] Seung Hun Jang[1]

[1]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; [2]Department of Pathology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; [3]Department of Radiology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; [4]Department of Neurosurgery, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; [5]Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea

Good's syndrome is a rare cause of combined B- and T-cell immunodeficiency in adults with a history of thymectomy. The patients with Good's syndrome are susceptible to encapsulated bacterial infections and opportunistic viral/fungal infections. We report a 63-year-old female patient who was diagnosed with cerebral toxoplasmosis in the middle of monthly immunoglobulin treatment for Good's syndrome. She was referred owing to progressive dizziness for one week without any neurologic deficits. Although routine laboratory tests and toxoplasma serology exams were within the normal range, brain image studies suggested cerebral toxoplasmosis, which was confirmed by pathology of brain lesions. She was treated with pyrimethamine and sulfadiazine as well as with systemic corticosteroids, and improved without sequelae. Later, her medication was switched to trimethoprim/sulfamethoxazole as a second-line treatment due to sulfadiazine-related neuropathy. (*Allergy Asthma Respir Dis 2024;12:155-159*)

Keywords: Cerebral toxoplasmosis, Primary immunodeficiency disease, Thymoma, Cell-mediated immunity, Hypogammaglobulinemia

INTRODUCTION

Good's syndrome is an immune-deficient status with low or absent B cells, pan hypogammaglobulinemia and a decrease in T-cell immunity. It is associated with thymoma, and the onset of immunodeficiency may occur either before or after the diagnosis of thymoma.[1] One prominent clinical manifestation is increased susceptibility to bacterial sinopulmonary infections, though patients with Good's syndrome also present defects in the T-cell response and opportunistic viral and fungal infections.[2] Toxoplasmosis is an intracellular parasitic infection that often affects immunocompromised patients.[3] Approximately 30 cases of *Toxoplasma gondii* infection have been reported in Korea, but no case has been reported in patients with Good's syndrome. We describe the first domestic cerebral toxoplasmosis in a patient with Good's syndrome that was being treated with monthly immunoglobulin treatment.

CASE REPORT

A 63-year-old female visited our Emergency Department (ED) with progressive dizziness and headache over a week. She had received thymectomy in 2008 and was later diagnosed with Good's syndrome due to recurrent sinopulmonary infection, including cytomegalovirus pneumonia and panhypoglobulinemia. Since then, she has received monthly immunoglobulin replacement. A neurologic exam at the time of her ED visit showed no focal neurologic deficit. Routine laboratory tests, including for infection markers, were within the normal range, except for mild leukopenia and lymphopenia (Table 1, CD4+ T cells 167 cell/μL). However, in her brain imaging work-up, computed tomography showed multiple hypodense lesions, and magnetic resonance imaging (MRI) showed multiple nodular and peripheral rim enhanced masses with surrounding edema in the entire brain (Fig. 1A–C). As she was an immunocompromised host with a history of dog

Correspondence to: Joo-Hee Kim https://orcid.org/0000-0002-1572-5149
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea
Tel: +82-31-380-3715, Fax: +82-31-380-6028, Email: luxjhee@gmail.com

• This work was supported by a research grant (NRF-2021-R1I1A3050318) from the National Research Foundation (NRF) of Korea.

Received: October 16, 2023 **Revised:** December 26, 2023 **Accepted:** January 4, 2024

Table 1. Laboratory test results of the patient at the first manifestation

Analyte	Value	Reference range
White blood cell (×10³/μL)	3.9	4–10
Hemoglobin (g/dL)	10.8	14–17
Platelets (×10³/μL)	265	130–450
Neutrophil (%)	77.3	40–74
Lymphocyte (%)	10.2	19–48
Monocyte (%)	12.2	0–9
Eosinophil (%)	0	0–7
Basophil (%)	0.3	0–1.5
IgG (mg/dL)	457.7	700–1,600
IgA (mg/dL)	<50.00	70–400
IgM (mg/dL)	<25.00	40–230
T cell (CD3)	2,832 (72.9)*	53.8%–81.8%
Th cell (CD4)	1,638 (42.0)*	28.4%–56.4%
Ts cell (CD8)	1,189 (30.5)*	20.9%–46.9%
Th/Ts ratio	1.4	≥1.0
B cell (CD19)	0 (0.0)	6.2%–22.7%
NK cell (CD16+/CD56)	1,041 (26.7)*	7.2%–34.5%
CRP (mm/hr)	5	0–26
ESR (mg/L)	5.4	0–5

NK, natural killer; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
*Number (%).

ownership, we conducted several serologic tests, including toxocara IgG, cysticercosis (IgG), antitoxoplasmosis IgG and IgM. However, no detectable antibodies were found. To further diagnose the condition, a brain open biopsy was performed, revealing necrosis with vasculitis and bradyzoite-like cysts. These pathological findings were consistent with cerebral toxoplasmosis (Fig. 2). The initial treatment was a combination of pyrimethamine 50 mg daily, followed by a 200 mg loading dose, and sulfadiazine 1,000 mg 4 times daily with systemic corticosteroids. The immunoglobulin replacement treatment was continued. Her symptoms had mostly recovered after 6 weeks of treatment, and the follow-up MRI showed more improved toxoplasmosis. At the time of diagnosis, multiple nodular contrast-enhancing masses were present, measuring from 11 to 15 mm, with surrounding edema in the entire brain, including the cerebral hemispheres, cerebellum, and brain stem. After 6 weeks of treatment, the enhancing nodules had decreased in number and size, with lessening of the surrounding edema, on follow-up MRI (Fig. 1D–F). During the treatment, she developed sulfadiazine-related neuropathy, so her medication was changed to trime-

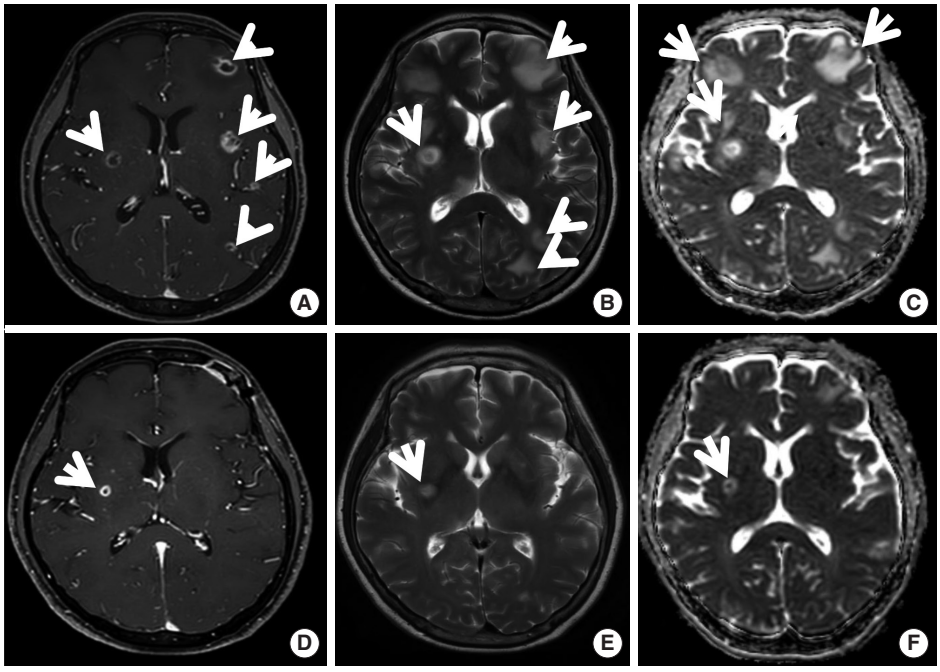

Fig. 1. Brain magnetic resonance image of the patient at the time of diagnosis (A-C) and after 6 weeks of treatment (D-F). At the time of diagnosis, multiple nodular contrast-enhancing masses (white arrow) measuring from 11 to 15 mm with surrounding edema in the entire brain, including cerebral hemispheres, cerebellum, and brain stem on contrast-enhanced T1-weighted image (A). The lesions (white arrow) are hyperintense on T2-weighted image (B) and involve the subcortical regions, white matter, and basal ganglia. Focal areas (white arrow) of restricted diffusion in the central portion or periphery rim of the lesions of both frontal lobes and left insula on apparent diffusion coefficient (ADC) map (C). After six weeks of treatment, multiple enhancing nodules (white arrow) decreased in number and size on the contrast-enhanced T1-weighted image (D), and their surrounding edema (white arrow) decreased on the T2-weighted image (E). In addition, markedly improved toxoplasmosis (white arrow) was also shown on the ADC map (F).

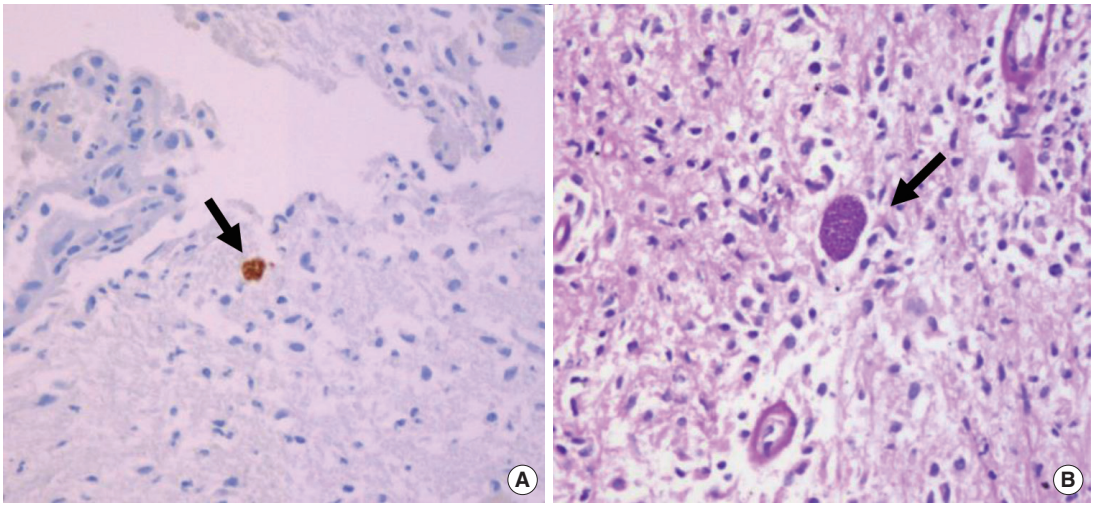

Fig. 2. Immunohistochemistry staining showed a positive result for Toxoplasma antibodies (black arrow) in the brain biopsy (×200, A). A cyst with multiple clusters of bradyzoites (black arrow) was noted in the brain tissue using Periodic Acid Schiff staining (×400, B).

thoprim/sulfamethoxazole at a maintenance dose of 960 mg once daily. She was still receiving monthly immunoglobulin replacement therapy and was closely monitored through an outpatient clinic.

This study was approved by the Ethics Committee of Hallym Sacred Heart University School of Medicine in August 2023 (IRB number: 2023-08-005). We received informed consent from the study patient for publication.

DISCUSSION

Good's syndrome, known as a thymoma with immunodeficiency, was first reported by Dr. Robert Good in 1954 as a case of thymoma and adult-onset hypogammaglobulinemia, but it has been a mysterious disease with obscure pathology for decades.[4,5] Good's syndrome is difficult to diagnose due to the absence of obvious symptom onset and its wide range of clinical manifestations.[1,4] The immunologic abnormalities of Good's syndrome include low or absent B cells in the peripheral blood, hypogammaglobulinemia, and defects in cell-mediated immunity with CD4+ T lymphopenia and an inverted CD4+:CD8+T-cell ratio.

Good's syndrome is found worldwide, and approximately half of the cases (46.9%) have been described in Europe, followed by the Americas (29.5%), Asia (22.8%), and Africa and Oceania (0.4% each).[1] Patients with Good's syndrome from Western countries are between the ages of 40 and 70 years, with a similar incidence in males and females.[1,6] The average duration from the onset of initial symptoms to the diagnosis of Good's syndrome is approximately 6 years.[6] According to our literature review on Korean cases (Supplementary Table 1),[7-17] 12 cases have been reported, and the patients' ages ranged from 40 to 60 years, with a female predominance (male:female, 5:8). The average delay before diagnosis was 3 years in Korean patients. Over 60% of them had respiratory infections (8 of 12), followed by brain abscess or meningitis in 3 patients.

It is still controversial whether this clinically rare syndrome is a unique disease or a subset of common variable immune deficiency (CVID). Recently, studies distinguished these 2 syndromes by emphasizing deficits in different B-cell and T-cell lineages and phenotypes of hematologic cytopenia.[5,6] Good's syndrome predominantly affects adults with markedly reduced or absent peripheral B-cell counts. Nearly 100% of Good's syndrome patients exhibit low serum IgG, 86% have low IgA, and 92.6% have low IgM.[1,2,6,18,19] CVID often occurs in childhood, and 90% of the patients have normal to moderate peripheral B-cell levels.[20] Two possible pathogenic mechanisms explaining the correlation between antibody deficiency and thymoma have been proposed for Good's syndrome. The first explanation suggests that autoantibodies and interferon-like cytokines potentially secreted by bone marrow stromal cells can impact the growth and differentiation of both thymic and B-cell precursors.[1,2,5] The second hypothesis is that the thymic tumor microenvironment can cause aberrant maturation of T-cell precursors, alter the T-cell subset composition in the blood, and further inhibit immunoglobulin production by B cells and pre-B-cell

growth.[2,5] *Kelesidis et al*. found that over 60% of Good's syndrome patients can have T-cell defects, as demonstrated by cutaneous anergy to 2 or more test antigens and a weak response to mitogens, indicating delayed hypersensitivity.[1] In 2 tested patients, decreased interleukin 2 production was observed in T cells upon stimulation, which may explain the dysregulated cytokine production by activated memory T cells among Good's syndrome patients. Still, the pathogenesis of Good's syndrome remains elusive, and more investigations are required to fully understand this immunologically tangled syndrome.

Approximately 3%–6% of thymoma patients develop Good's syndrome.[6] In 30%–40% of Good's syndrome patients, thymoma is identified before hypogammaglobulinemia, and individuals may experience associated symptoms such as cough, swallowing difficulty, and hoarseness.[1,6] Invasive bacterial, viral, and fungal infections are frequently reported worldwide, primarily affecting the sinopulmonary system (over 50%) and gastrointestinal tract (20%–50%).[1,2,6,18,19] Commonly isolated pathogens include *Haemophilus influenzae*, *Pseudomonas species* (spp.), *Streptococcus pneumonia*, opportunistic infections such as *Pneumocystis jirovecii* pneumonia and mucocutaneous candidiasis, and cytomegalovirus in patients.[2,6,19] About 50% of Good's syndrome patients also have concurrent autoimmune diseases, including pure red cell aplasia (31.3%), myasthenia gravis (27.7%), lichen planus (22.9%), and other hematologic abnormalities.[2,6,19] A recent systematic review including 162 patients with Good's syndrome showed significantly lower survival rates in the presence of various infectious conditions than in the presence of an active disease status of thymoma.[19] The study employed clustering analyses to identify specific clinical subgroups, revealing 3 clusters. Among these, cluster 1, characterized by infections related to cellular defects, exhibited the poorest prognosis compared to cluster 2, associated with infections related to other defects, or cluster 3, linked to humoral/phagocytic defects.[19] Infection was the primary cause of death, accounting for 92%. Over a 20-year period, a single center observed that only 33% of patients with Good's syndrome survived for 10 years after diagnosis, while 95% of patients with X-linked agammaglobulinemia and CVID did.[6,19] Therefore, early diagnosis of immunodeficiency, treated with Ig replacement and close surveillance of opportunistic infection, are strongly recommended in the patients with thymoma.

Toxplasmosis is an important zoonotic disease caused by protozoan parasite *Toxoplasma gondii*. However, *T. gondii* primary infection is asymptomatic in immunocompetent individuals, and it is a self-limited, nonspecific illness that needs treatment in only 10% of primary infections.[3] By contrast, the disease can be life-threatening in immunocompromised patients. The central nervous system (CNS) is the most affected organ, and the clinical presentation varies from a subacute gradual process evolving over weeks to an acute confessional state, with or without focal neurological deficits. Symptoms include mental status changes, seizures, focal motor deficits, cranial nerve disturbances, sensory abnormalities, cerebellar signs, movement disorders, and neuropsychiatric findings. Meningeal signs are rare. Constitutional symptoms and signs such as fever and malaise can vary. The differential diagnosis includes CNS lymphoma, progressive multifocal leukoencephalopathy, cytomegalovirus ventriculitis and encephalitis, focal lesions caused by other organisms, including *Cryptococcus*, *Aspergillus* spp., *Mycobacterium tuberculosis*, and *Nocardia* spp., and bacterial brain abscess. Toxoplasma infection seems to be more frequent in recipients of bone marrow transplants and in patients with acquired immunodeficiency syndrome. Only one case of *Toxoplasma* infection in a Good's syndrome patient has been reported.[1,4] Therefore, our case report is the first domestic case of cerebral toxoplasmosis, marking it as a significant clinical finding.

The initial therapy of choice for toxoplasma encephalitis consists of the combination of pyrimethamine, sulfadiazine, and leucovorin.[3] Our patient was treated with the recommended regimen, followed by alternative therapy with trimethoprim-sulfamethoxazole due to neuropathy. There are no data on the duration and dose of this regimen that will have long-term suppressive efficacy, especially in patients with Good's syndrome.

To our knowledge, this is the first report of cerebral toxoplasmosis in a patient with Good's syndrome in Korea. This case, along with other diagnostic work, demonstrates the importance of undertaking immunological investigations in patients who have thymoma and infection, even with monthly Ig replacement. For opportunistic infections such as cerebral toxoplasmosis, indirect serological methods to detect the toxoplasmosis are widely used in immunocompetent patients; however, a definitive diagnosis in immunocompromised patients is mostly made by direct detection of the parasite in the target tissue. A high index of suspicion and appropriate confirmative investigations are required for the early diagnosis of Good's syndrome. In addition, appropriate diagnostic work-up and treatment for infectious complications will improve the overall survival of patients with Good's syndrome.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 can be found via http://www.aard.or.kr/src/sm/aard-12-155-s001.pdf.

REFERENCES

1. Kelesidis T, Yang O. Good's syndrome remains a mystery after 55 years: a systematic review of the scientific evidence. Clin Immunol 2010;135:347-63.
2. Kelleher P, Misbah SA. What is Good's syndrome? Immunological abnormalities in patients with thymoma. J Clin Pathol 2003;56:12-6.
3. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1-207; quiz CE1-4.
4. RA G. Agammaglobulinaemia- a provacative experiment of nature. Bull Univ Minn Hosp Med Found 1945;26:1-19.
5. Kabir A, Alizadehfar R, Tsoukas CM. Good's syndrome: time to move on from reviewing the past. Front Immunol 2022;12:815710.
6. Tarr PE, Sneller MC, Mechanic LJ, Economides A, Eger CM, Strober W, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) 2001;80:123-33.
7. Kim GW, Park JH, Nam EJ, Kim SW, Kang YM, Lee JM, et al. A case of Good's syndrome. J Asthma Allergy Clin Immunol 2002;22:142-7.
8. Ryoo JY. Good's syndrome (thymoma with immunodeficiency): a case report. Korean J Thorac Cardiovasc Surg 2006;39:85-8.
9. Kim JY, Chin JY, Lee SS, Jung H, Lee HK, Lee HP, et al. A case of Good syndrome: immunodeficiency syndrome associated with a thymoma. Korean J Med 2008;75:935-41.
10. Song KH, Kim KH, Kim CJ, Park KU, Jheon S, Kim HB, et al. A case of Good's syndrome. Infect Chemother 2007;39:259-62.
11. Lee SH, Lee SM, Yang SC, Yoo CG, Kim YW, Shim YS, et al. A case of granulomatous lung disease in a patient with Good's syndrome. Korean J Intern Med 2008;23:219-22.
12. Kim HI, Chang HH, Park GY, Kwon EG, Kim HH, Kim SW, et al. Two cases of cytomegalovirus retinitis as a manifestation of Good's syndrome. Korean J Med 2011;81:266-72.
13. Chung S, Lee K, Kim MJ, Chang HE, Song SH, Kim HB, et al. A case of Good's syndrome with weak ABO reverse type. Korean J Blood Transfus 2011;22:54-8.
14. Jung H, Sohn KM, Kim YS, Song CH, Sohn EH. A case of thymoma with immunodeficiency (Good's syndrome) with disseminated tuberculosis. Korean J Med 2013;85:329-33.
15. Kim SY, Kim JH, Hwang HW, Kim KY, Park S, Hwang YI, et al. Opportunistic lung infections as a manifestation of Good's syndrome. Allergy Asthma Respir Dis 2015;3:365-9.
16. Kwon N, Kim HS. Tuberculosis Meningoencephalomyelitis in Good's Syndrome: a case report. Brain Neurorehabil 2020;13:e16.
17. Ryu GH, Moon JW, Shin JM, Park IH. Good's syndrome presenting with chronic rhinosinusitis (1 case report). Korean J Otorhinolaryngol-Head Neck Surg 2022;65:169-73.
18. Dong JP, Gao W, Teng GG, Tian Y, Wang HH. Characteristics of Good's syndrome in China: a systematic review. Chin Med J (Engl) 2017;130:1604-9.
19. Shi Y, Wang C. When the Good syndrome goes bad: a systematic literature review. Front Immunol 2021;12:679556.
20. Ahn S, Cunningham-Rundles C. Role of B cells in common variable immune deficiency. Expert Rev Clin Immunol 2009;5:557-64.