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【 CASE REPORT 】

Nocardiosis in a Patient with Nephrotic Syndrome Treated with Glucocorticoids and Tacrolimus

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Abstract:

Nephrotic syndrome (NS) predisposes patients to immunocompromised hosts owing to the loss of immunoglobulins, immunosuppressant use, and edema complications. In addition, aging impairs the immune system; thus, elderly individuals with NS are vulnerable to infection. Nocardiosis is not a common disease; however, once infected, it can disseminate hematogenously, causing serious health problems. An 88-year-old woman with amyloid light chain amyloidosis-induced NS was treated with prednisolone and tacrolimus and developed nocardiosis and invasive aspergillosis. Protecting the skin and wounds from direct exposure to nocardia is important. Physicians should consider the safe dose and treatment period of immunosuppressants in elderly patients with NS.

Key words: nocardiosis, nephrotic syndrome, amyloidosis, tacrolimus, glucocorticoids

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Introduction

Nephrotic syndrome (NS) is characterized by massive proteinuria responsible for hypoalbuminemia, resulting in hyperlipidemia and edema. Amyloidosis, minor change disease (MCD), and membranous nephropathy (MN) are major causes of NS in the elderly population (1). In addition to excessive loss of immunoglobulins and compliments, the use of immunosuppressants, edema complications, and defects in cellular immunity are associated with an increased risk of various infections, resulting in a negative impact on morbidity and mortality in elderly patients with NS.

Nocardia, a Gram-positive bacillus with a branching filamentous form, can cause critical health issues in immunocompromised patients. *Nocardia* are found in soil, decomposing vegetation, and other organic matter, as well as in water. The primary route of infection is through inhalation of bacteria via environmental sources and the inoculation of traumatic skin lesions or as hospital-acquired infections. Pulmonary nocardiosis is the most common clinical presentation of infection (62-86%), followed by skin abscess of nocardiosis (8-31%) and central nervous system (CNS) nocardiosis (2-26%) (2-4). Once *Nocardia* infection occurs, it can spread hematogenously throughout the body from the local infection site. One-year mortality after nocardiosis has been reported to be around 25% (5), with a particularly high mortality rate in immunocompromised patients (6).

We herein report the clinical course of an elderly patient undergoing treatment with glucocorticoids and calcineurin inhibitors for NS who developed nocardiosis. Hypoimmunoglobulinemia due to NS, in addition to advanced age and glucocorticoid therapy, may have contributed to the susceptibility of this patient to infection. Notably, trimethoprim-sulfamethoxazole (TMP-SMX), an antibiotic used to prevent nocardial infection, was prescribed in this case. Since soil minerals may promote infection by suppressing local host defense (7), it is important to cover skin, wounds, or cuts in extremities when immunocompromised hosts are frequently exposed to soil. Although nocardiosis is not a common disease (5), it should be recognized as a pathogenic bacterium that causes serious conditions in immunocompromised hosts, such as patients with NS taking immunosuppressants.

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Case Report

An 88-year-old woman with longitudinal rheumatoid arthritis treated with tacrolimus (1.5 mg) and IgA-λ type smoldering multiple myeloma (SMM) diagnosed in 2021 developed severe leg edema with a decrease in serum albumin to 2.0-3.0 g/dL from January 2020. Since massive proteinuria was detected and the patient developed NS in January 2021, she was referred to our division for a further examination (Fig. 1A, admission 1).

The clinical characteristics of the present case at admission are shown in Table 1. A renal biopsy could not be performed due to kyphosis; however, the lack of evidence of amyloidosis assessed by a duodenal biopsy with upper endoscopy, no signs of cardiac amyloidosis on echocardiogram, a low selectivity index value of 0.08, and no detection of serum M-type phospholipase A2 receptor antibody led us to suspect the possibility of MCD and initiate diagnostic treatment with prednisolone (PSL) at 40 mg/day (0.8 mg/kg).

Due to the elevation of serum aspartate aminotransferase and alanine aminotransferase levels, tacrolimus was tapered to 1.0 mg per day. As no improvement in proteinuria was acquired by 2-week-treatment, PSL was quickly tapered by 5 mg weekly due to concerns about the adverse effects of PSL.

However, 6 months later, leg ulcers, malaise, and anorexia appeared with high levels of serum C-reactive protein (CRP) while taking methylprednisolone 8 mg per day (Fig. 1A, admission 2). Anorexia caused a weight loss of 3 kg and subsequent prerenal kidney dysfunction, so that the fraction excretion of Na was 0.2% at admission 2. The kidney function improved quickly with intravenous fluid therapy after admission. Chest radiography showing nodular lesions in both lungs and bacterial culture of the wound and sputum revealing *Nocardia* spp. led to a diagnosis of nocardiosis. Although a genetic analysis failed to identify the species, treatment with meropenem (MEPM) and levofloxacin (LVFX) was initiated for pulmonary nocardiosis according to antibiotic susceptibility test results (Table 2). Subsequently, oral administration of amoxicillin/clavulanic acid and TMP-SMX was initiated as a maintenance regimen for immunocompromised patients.

However, abscesses in the right lower limb newly appeared with anorexia and a persistent fever approximately two months later (Fig. 1B). After hospitalization (admission 3 in Fig. 1A-C), wound and sputum culture revealed *Nocardia* spp., and disseminated brain abscess was detected by magnetic resonance imaging (Fig. 1D and Table 2). The patient had no diabetes or chronic obstructive pulmonary disease. Although there was no evidence of human immunodeficiency virus infection, a positive result for human T-lymphotropic virus antibody and low levels of serum IgG and C3 were observed at admission 3. For primary therapy for CNS nocardiosis, administration of MEPM (4 g/day) and linezolid (LZD) 1.2 g per day was immediately initiated according to the results of the antibiotic susceptibility tests. The combination of MEPM and LVFX reduced the mass of the brain abscess, along with a decrease in serum CRP levels (Fig. 1A, E). However, because of thrombocytopenia (60,000/mL), LZD was switched to tedizolid (TZD); however, thrombocytopenia progressed to 26,000/mL. Because of the improvement of the brain abscess due to primary care, we switched to the maintenance regimen with TMP-SMX. However, on day 46 of admission 3, septic shock occurred that resulted in multiple organ failure despite continuous treatment with MEPM and LVFX, and the patient died.

Autopsy revealed a brain abscess in the right frontal lobe that was confirmed macroscopically, and inflammatory cells, mainly histiocytes, accumulated in the right frontal lobe, temporal lobe, and hippocampus, suggesting the post-treatment status of the brain abscess (Fig. 2A). *Nocardia* spp. was confirmed only in the superficial layer of the midbrain, with thickening of the dorsal dura mater and inflammatory cell infiltration, mainly neutrophils (Fig. 2B). While the bacterial body of *Nocardia spp.* could not be found in the lungs, we identified granulomas with Langhans giant cells, which can be considered a manifestation of the chronic phase of nocardiosis (Fig. 2C). In addition, the fungal body of *Aspergillus* was found in the left lung, which can explain the increase in serum β-D-glucan levels in the present case (Fig. 2D). Diffuse deposition of eosinophilic, periodic acid-Schiff stain-positive materials in the mesangium and blood vessels was suggestive of renal amyloidosis (Fig. 2E). The absence of Congo-red$^+$ materials after treatment with permanganic acid and the positivity of λ chain by immunohistochemical staining indicated Amyloid light chain (AL) amyloidosis (Fig. 2F-H). Although spicule, a specific histological feature of amyloidosis, was not observed in the silver stain, Congo-red$^+$ lesions along the glomerular capillary walls were detected, suggesting that AL amyloidosis might predominantly cause NS in the present case. Cast formation was not observed in the lumina, and no abnormalities were detected in glomerular capillaries and podocytes. Left ventricular hypertrophy was observed macroscopically, and Congo-red$^+$ amyloid deposition was found in the vessels of the heart with an increase in cardiac fibrosis assessed by Masson's trichrome staining (Fig. 2I). Solid carcinoma was not detected; however, neutrophils were observed ubiquitously in vessels throughout the body, which is a sign of sepsis that can be thought of as a cause of death.

Discussion

Nocardiosis is most commonly observed in immunocompromised patients, such as those with solid organ transplantation (8), hematopoietic stem cell transplantation (9), cancer (10), and autoimmune diseases with immunosuppressants (11). Furthermore, even if low-dose immunosuppressants are administered, patients with NS are at high risk for infections, including *Nocardia* spp., because of hypogammaglobulinemia and low levels of serum complements,

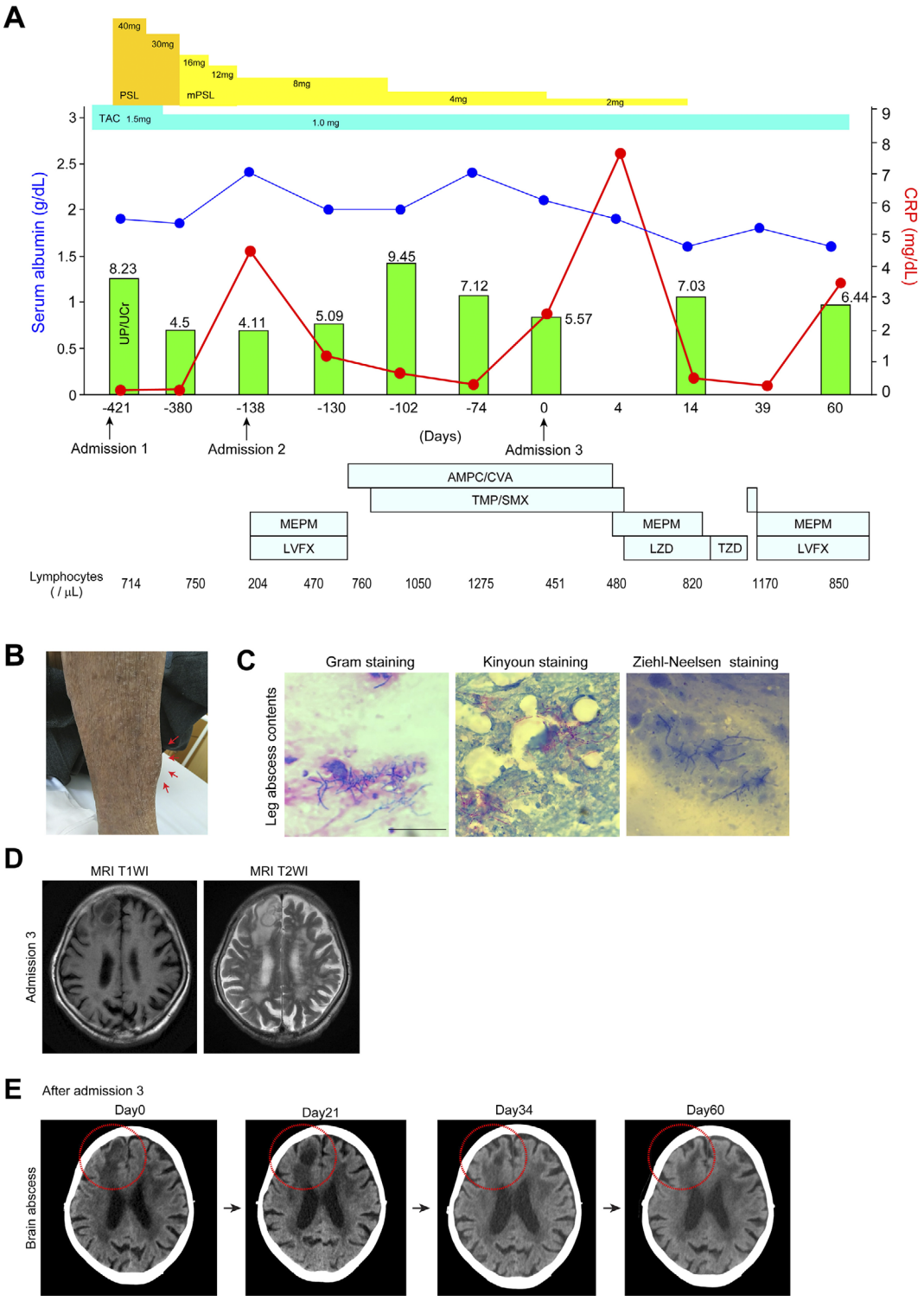

Figure 1. **(A) Clinical course of the present case after initiation of PSL treatment for nephrotic syndrome. The red line indicates the CRP level (mg/dL), and the blue line indicates the serum albumin level (g/dL). Green boxes indicate UP/UCr (g/gCr). The peripheral lymphocyte count (/mL) during the treatment period is shown. (B) The macroscopic appearance of skin abscess in right lower limb is indicated by red arrows. (C) Representative images of *Nocardia* spp. in the skin abscess contents of right lower limb on Gram, Kinyoun, and Ziehl-Neelsen staining. Scale bar: 10 μm. (D) Representative images of T1- or T2-weighted MRI for brain abscess in this patient. (E) Representative images of brain CT over time during treatment with antibiotics. PSL: prednisolone, mPSL: methylprednisolone, TAC: tacrolimus, CRP: C-reactive protein, TMP-SMX: trimethoprim-sulfamethoxazole, MEPM: meropenem, LVFX: levofloxacin, LZD: linezolid, TZD: tedizolid, AMPC/CVA: amoxicillin/clavulanic acid, MRI: magnetic resonance imaging, CT: computed tomography, UP/UCr: urinary protein per urinary creatinine ratio**

Table 1. Clinical Characteristics of the Present Case at Each Admission.

	Admission 1 (Day -402)	Admission 2 (Day -139)	Admission 3 (Day 0)
Hb (g/dL)	9.2	11.3	11.1
WBC (mL)	4,200	13,600	12,200
Neutrophile (%)	68.5	96.0	90.3
TP (g/dL)	5.7	5.0	4.6
Albumin (g/dL)	1.9	2.4	2.2
AST (U/L)	32	43	27
ALT (U/L)	13	39	13
LD (U/L)	324	421	340
ALP (U/L)	76	144	93
γ-GTP (U/L)	44	95	53
BUN (mg/dL)	23	131	52
Cr (mg/dL)	0.84	3.29	1.04
eGFR (mL/min/1.73m^2)	48.2	10.8	38.0
UA (mg/dL)	6.8	7.5	5.9
Na (mmol/L)	141	129	137
K (mmol/L)	4.1	5.3	3.8
Cl (mmol/L)	103	89	103
cCa (mg/dL)	10.0	9.3	9.9
P (mg/dL)	3.8	7.6	4.1
LDL-C (mg/dL)	145	102	83
TC (mg/dL)	161	303	159
CRP (mg/dL)	0.32	1.89	0.83
pH	7.369	7.324	7.353
HCO_3^- (mmol/L)	29.9	26.1	25.7
cAG	11.4	17.8	12.8
UP/UCr (g/gCr)	8.23	6.46	5.57
U-hematuria	(2+)	(+/-)	(-)
ESR 1 h/2 h (mm)	108/113		42/68
GA (%)	10.2	15.4	18.4
IgG (mg/dL)	791	541	700
IgA (mg/dL)	1,482	173	238
IgM (mg/dL)	90	48	66
C3 (mg/dL)	97	87	71
C4 (mg/dL)	13	18	12
β-D-glucan (pg/mL)		155.8	35.6
PCT (ng/mL)		0.58	0.08

Hb: hemoglobin, WBC: white blood cells, TP: total protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, ALP: alkaline phosphatase, g-GTP: gamma-glutamyl transpeptidase, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, Na: sodium, K: potassium, Cl: chlorine, cCa: corrected calcium, P: phosphate, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, HCO_3^-: bicarbonate, cAG: corrected anion gap, ESR: erythrocyte sedimentation rate, GA: glycoalbumin, U: urinary, UP: urinary protein, UCr: urinary creatinine ratio, PCT: procalcitonin

The eGFR was calculated using the following formula: 0.741×175× serum Cr-1.154× age-0.203 (×0.742 if a woman.

edema-induced disruption of cutaneous host defense, and defects in cellular immunity. The serum M protein level was 0.34 g/dL, percentage of clonal bone marrow plasma cells was 12.5%, and serum free light chain ratio was 0.39 in the present case, all of which were within the normal range. Serum b2 microglobulin levels were slightly elevated at 3.4 mg/L. The activity of SMM was relatively low, but the presence of SMM might have caused further susceptibility to infections in the present case (12). Considering *Nocardia* spp. are generally found in soil, preventing direct exposure to pathogens in several ways, such as wearing a face mask, globes, clothes, and socks covering skin, wounds, and cuts in extremities, is very important when patients work in soil.

Initial treatment with two or more antibiotics is recommended for patients with disseminated or severe nocardiosis. TMP-SMX with or without fluoroquinolone is a first-line

Table 2. Antibiotics Susceptibility Tests during the Treatment Period.

Admission 2 (Day -139)	Admission 3 (Day 0)	Admission 3 (Day 0)
Sputum	Sputum	Skin abscess
Nocardia spp.	*Nocardia* spp.	*Nocardia* spp.
Aspergillus fumigatus		
Candida albicans		
Candida glabrata		
Staphylococcus spp. Coagulase (-)		
Antibiotics, MIC (mg/mL)		
PCG, >2	ABPC, >8	A*BPC*, 8
ABPC, >2	PGC, >4	PGC, >4
C/A, 8, S	CTM, >4	CTM, >4
CTRX, >32	CTRX, >4	CTRX, >4
CTX, >32	CTX, 4	CTX, >4
S/A, 8	CFPM, >2	CFPM, >4
P/T, >64	CZOP, >4	CZOP, >4
MNZ, >16	CDTR, >1	CDTR, >1
MINO, >4	MEPM, 2	MEPM, 2
CLDM, >4	C/A, 4	C/A, >4
VCM, >4	EM, >2	EM, >2
LVFX, >4	AZM, >4	AZM, >4
MFLX, 2	CLDM, >1	CLDM, >1
LZD, <2	MINO, >4	MINO, >4
CMZ, >32	LVFX, 2	LVFX, 2
AMK, 8	VCM, >1	VCM, >1
AZM, >8	ST, 4	ST, 4
IPM, 16	RFP, >4	RFP, >4
TOB, 4	CP, >16	CP, >16
CAM, >8		
MEPM, 4		
ST, >2		

MIC: minimum inhibitory concentration, PCG: penicillin G, ABPC: ampicillin, C/A: clavulanic acid/amoxicillin, CTRX: ceftriaxone, CTX: cefotaxime, S/A: sulbactam/ampicillin, P/T: piperacillin/tazobactam, MNZ: metronidazole, MINO: minocycline hydrochloride, CFPM: cefepime, CZOP: cefozopran , CDTR: cefditoren, EM: erythromycin, CLDM: clindamycin, VCM: vancomycin: LVFX: levofloxacin, MFLX: moxifloxacin, LZD: linezolid, AMK: amikacin, AZM: azithromycin, IPM: imipenem, TOB: tobramycin, CAM: clarithromycin, MEPM: meropenem, ST: sulfamethoxazole-trimethoprim, RFP: rifampicin, CP: chloramphenicol

therapy for primary cutaneous nocardiosis (13), and TMP-SMX with ceftriaxone, moxifloxacin, or a combination of imipenem and amikacin has been suggested for pulmonary nocardiosis (14). The combination of imipenem and amikacin with or without TMP-SMX is the first-line regimen (15), and treatment with LZD and MEPM is an alternative for CNS nocardiosis (16). Oral antibiotics, such as TMP-SMX and β-lactams, are preferred for maintenance therapy in immunocompromised patients. However, SMX resistance has recently been reported (17); thus, antibacterial susceptibility testing should continue to be monitored, and careful observation is still required even when patients with NS receive treatment with TMP-SMX.

Although several studies have shown that thrombocytopenia with TZD is less severe than that with LZD (18), we identified thrombocytopenia due to both LZD and TZD. Thrombocytopenia (<100,000/mL) was observed in 32% of patients who received LZD (19) and kidney and liver dysfunction was associated with an increased risk for LZD-induced thrombocytopenia (20). Thus, careful monitoring should be performed when treating patients with kidney dysfunction using LZD or TZD. In addition, a previous study demonstrated that a decrease in serum IgG levels was associated with serious infectious diseases, and intravenous immunoglobulin (IVIG) therapy might be a preventative option in adult NS patients with IgG levels <600 mg/dL (21). In the present case, the serum IgG level was 543 mg/dL at one time point during PSL administration; thus, IVIG may have prevented fatal infection.

After the entry of *Nocardia* spp., neutrophils and macrophages are activated, followed by a T lymphocyte-mediated response, a series of which is involved in host defense mechanisms against *Nocardia* spp. (22, 23). Thus, the reduced functionality of T lymphocytes and subsequent im-

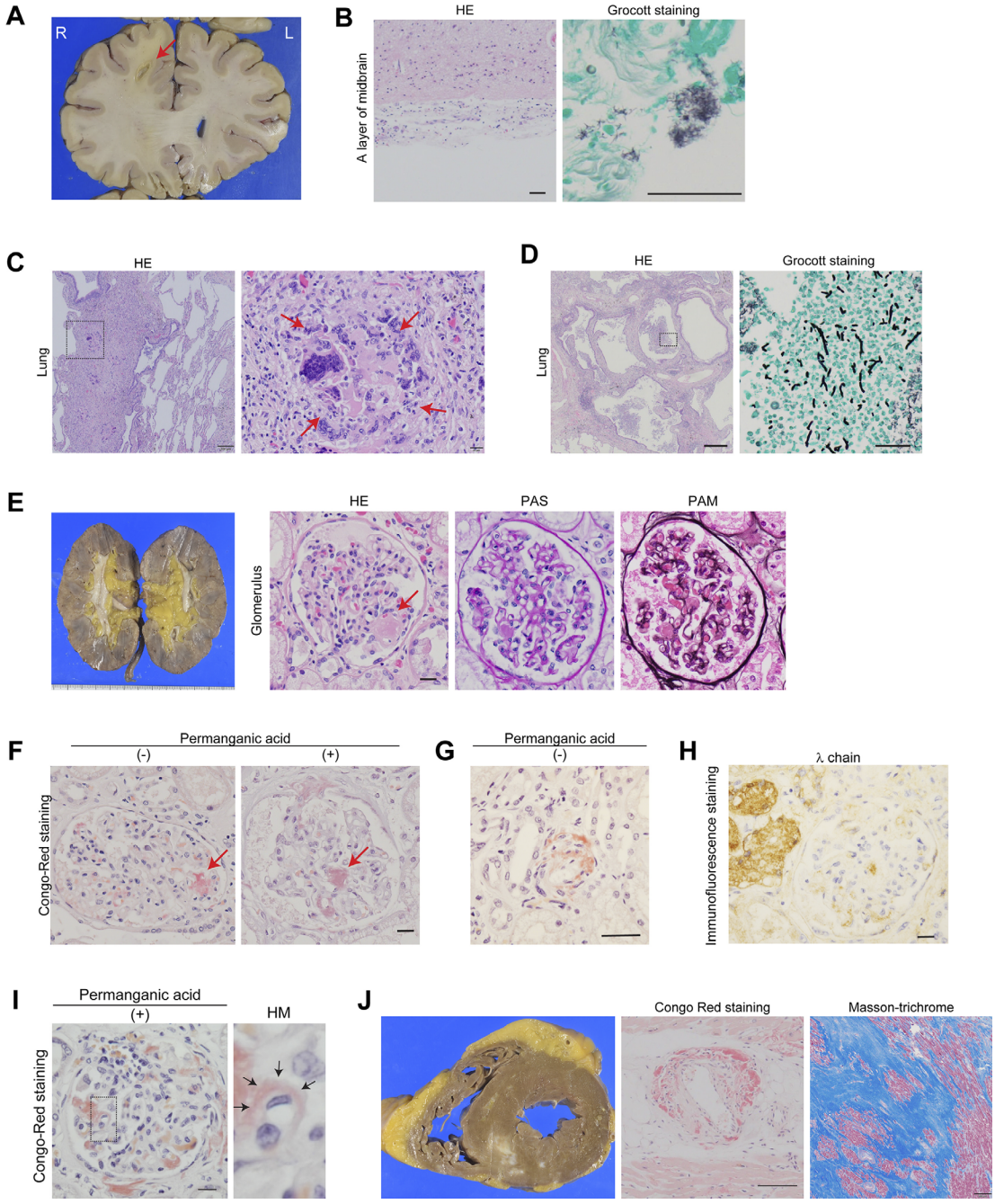

Figure 2. **(A) Macroscopic appearance of sagittal section of the frontal, temporal lobe, and hippocampus. Red arrow indicates brain abscess in the right frontal lobe. (B) Inflammatory cell accumulation in a monolayer of midbrain and the bacterial body of *Nocardia* spp. in Grocott staining. Scale bar; 50 μm. (C) Representative images of inflammatory cells infiltration in the right lung and granuloma with Langhans giant cells in Hematoxylin and Eosin (H&E) staining. Scale bar: 200 μm and 20 μm in the left figure and the right figure, respectively. (D) Representative images of *Aspergillus* spp. in the left lungs on H&E staining and Grocott staining. Scale bar: 500 μm and 20 μm on H&E staining and Grocott staining respectively. (E) Macroscopic appearance of kidneys and representative images of glomerulus on H&E staining, PAS, and PAM staining. Red arrow indicates amyloid deposition in the mesangial area. Scale bar: 50 μm. (F) Representative images of Congo-red staining with or without permanganic acid. Scale bar: 50 μm. (G) Congo-red+amyloid deposition in vessel wall in the kidneys. Scale bar: 50 μm. (H) Representative image of immunofluorescence staining for l chain in the kidneys. Scale bar: 50 μm. (I) Congo-red^{+} amyloid deposition along the glomerular capillary walls. Scale bar: 50 μm. (J) Macroscopic appearance of heart and representative images of Congo-red+amyloid deposition in vessels of the heart and cardiac fibrosis on Masson-trichrome staining. Scale bar: 50 μm and 500 μm on Congo-red and Masson-trichrome staining, respectively. PAS: Periodic Acid-Schiff, PAM: Periodic Acid-Methenamine silver**

pairment of cell-mediated immunity are associated with an increased risk of nocardiosis (15). A previous study showed that mice without γδT lymphocytes exhibited higher mortality against the inoculation of *Nocardia* spp. than control mice (24). In addition, >10 mg/day of glucocorticoids for ≥3 months has been shown to induce CNS nocardiosis (25). Glucocorticoids reportedly modulate the activity of transcription factors, including nuclear factor-κB and nuclear factor of activated T cells (NFAT), and inhibit kinase activity downstream of T cell receptor (TCR), both of which suppresses T cell activation (26). Calcineurin inhibitors also suppress the nuclear translocation of NFAT, leading to the inhibition of T cell activation (27). Therefore, suppression of T cell activation by a combination of glucocorticoids and tacrolimus tends to increase susceptibility to nocardiosis in addition to hypogammaglobulinemia due to NS. We also found *Aspergillus* spp. in the lungs of the patient. T cell immunity, mainly $CD4^+$ T cells, has been shown to be involved in anti-fungal host defense (28), and tacrolimus impaired clearance of *Aspergillus fumigatus* from the airway by inhibiting macrophage and subsequent neutrophil recruitment (29). It should be noted that no consensus has been reached regarding the optimal regimen or the appropriate dosage of corticosteroids in the therapeutic management of elderly patients with NS (30). Therefore, physicians should carefully consider the need for add-on therapy with calcineurin inhibitors and glucocorticoids on a case-by-case basis in patients with NS.

Conclusion

In the present study, we demonstrated that elderly patients with amyloidosis-induced NS taking immunosuppressants developed nocardiosis and systemic dissemination despite receiving preventative antibiotic treatment. A decline in the production of fresh naïve T cells, weak activation of T cells, and greater restriction of the TCR repertoire have a negative impact on both innate and adaptive immunity, leading to increased susceptibility to infections in elderly patients (31). A high rate of infection-related death or hospitalization has been reported in elderly Japanese individuals with MN or MCD who received immunosuppressive therapy (30, 32). Therefore, excessive doses or longitudinal use of immunosuppressants should be avoided in elderly patients with NS, and further investigation is required to determine the optimal doses of immunosuppressants for elderly individuals.

Informed consent for publication was obtained from the patient and patient's family.

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

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