Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1978-18
Intern Med 58: 1173-1177, 2019
http://internmed.jp

【 CASE REPORT 】

Giant Cell Arteritis with Generalized Granuloma Annulare

Yuichi Torisu[1], Yoshiro Horai[2,3], Tohru Michitsuji[1,4], Chieko Kawahara[1], Takahiro Mori[1], Nozomi Iwanaga[2], Yasumori Izumi[1] and Atsushi Kawakami[5]

Abstract:
We report the case of an 80-year-old man with generalized granuloma annulare (GGA) who subsequently developed giant cell arteritis (GCA). Steroid treatment was effective for both diseases in this case. Although cases of concomitant GGA and GCA have rarely been reported, previous studies suggest that common histological characteristics underlie the two diseases. It is therefore necessary to recognize that GGA can be complicated by GCA, particularly when typical symptoms, such as headache and visual disturbance, are present.

Key words: giant cell arteritis, generalized granuloma annulare, vasculitis

(Intern Med 58: 1173-1177, 2019)
(DOI: 10.2169/internalmedicine.1978-18)

Introduction

Giant cell arteritis (GCA), also called temporal arteritis, is a granulomatous arteritis that frequently affects the temporal arteries (1). Generalized granuloma annulare (GGA) is one of four subtypes (limited, generalized, perforating, and subcutaneous) of granuloma annulare (GA), and is characterized by inflammatory dermatosis of unknown origin (2). GCA and GGA reportedly share common histological features (3, 4); this suggests that the two diseases might also share some etiologies. However, GCA associated with GGA appears rare, with only four reported cases (5-8). We herein describe the case of an 80-year-old man with GGA and GCA who was successfully treated with oral prednisolone (PSL).

Case Report

An 80-year-old man was admitted to our hospital with a loss of visual acuity. His medical history included iritis and cataract, which were diagnosed four years and two years prior to admission, respectively. Approximately one year prior to admission, he developed generalized erythema and papules on his trunk and extremities; skin biopsy performed in a neighboring dermatology clinic led to a diagnosis of GGA. Treatment for GGA, including topical glucocorticoid and ultraviolet therapy was initiated; however, the effects were not satisfactory. Approximately two weeks before admission, he noticed deterioration in his left visual acuity, followed by pyrexia, headache, jaw claudication, and general malaise. The day after he lost left visual acuity, he lost right visual acuity. GCA was suspected and the patient was admitted to our department for examination and treatment.

When examined upon admission, his vital statistics were as follows: body temperature, 36.6℃, heart rate, 56 bpm; and blood pressure, 139/62 mmHg. The temporal arteries were found to be tender and distended, but no oral ulcers were found. No extra heart sound or murmur was present. Crepitation in the left lung field was audible. No abdominal distension, rigidity or tenderness was noted. Old and new papules were scattered on his trunk and extremities (Fig. 1A). No musculoskeletal abnormalities were identified. The results of laboratory tests on admission were as follows: white blood cell count, 6,400/μL; hemoglobin, 9.2 g/dL; platelet count, 291,000/μL; total protein, 7.7 g/dL; albumin, 2.8 g/dL; total bilirubin, 0.4 mg/dL; aspartate aminotransferase 78 IU/L; alanine aminotransferase, 77 IU/L; lactate dehydrogenase, 177 IU/L; alkaline phosphatase, 913 IU/L; γ-glutamyl transpeptidase, 102 IU/L; creatine kinase, 20 U/

[1]Department of General Internal Medicine, National Hospital Organization Nagasaki Medical Center, Japan, [2]Department of Rheumatology, National Hospital Organization Nagasaki Medical Center, Japan, [3]Clinical Research Center, National Hospital Organization Nagasaki Medical Center, Japan, [4]Department of Rheumatology, Sasebo City General Hospital, Japan and [5]Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Japan
Received: August 15, 2018; Accepted: October 3, 2018; Advance Publication by J-STAGE: December 18, 2018
Correspondence to Dr. Yoshiro Horai, horaiy@nagasaki-mc.com

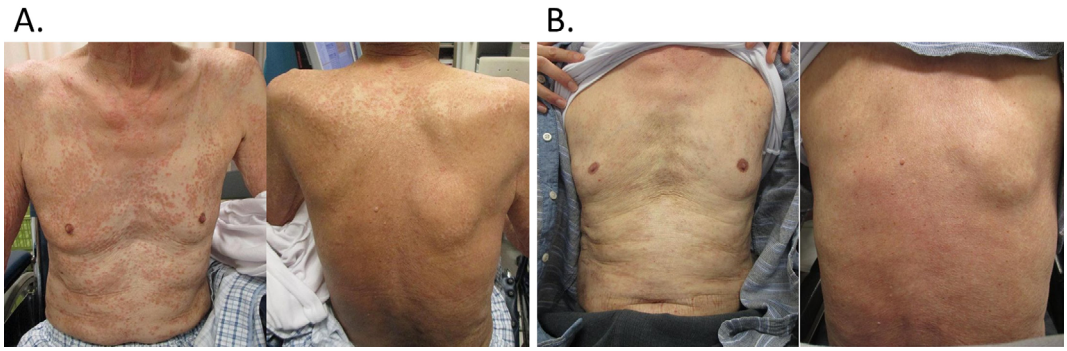

Figure 1. **A: The skin manifestations at admission: old and new papules were scattered on the patient's trunk and extremities. B: The resolution of the skin manifestations at 150 days after the initiation of therapy.**

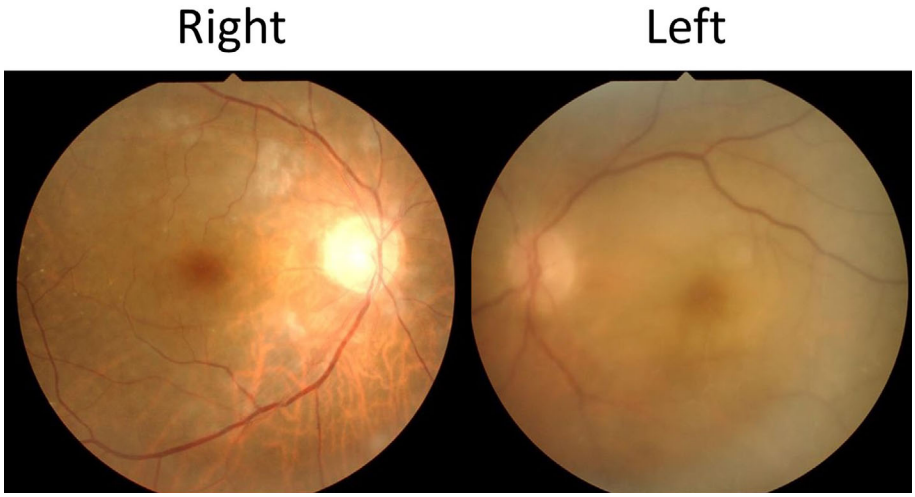

Figure 2. **Ophthalmoscopy: note the vitreous clouding in both eyes, paleness at the left retinal posterior pole and partial opacity at the right retinal posterior pole.**

L; blood urea nitrogen, 22.3 mg/dL; serum creatinine, 1.05 mg/dL; Na, 139 mEq/L; K, 4.1 mEq/L; Cl, 104 mEq/L; total cholesterol, 178 mg/dL; C-reactive protein, 15.97 mg/dL; glucose 87 mg/dL; erythrocyte sedimentation rate, 90 mm/h; immunoglobulin(Ig) G, 1,903 mg/dL; IgA, 413 mg/dL; IgM, 62 mg/dL; IgE, 384 IU/mL; IgD, 1.6 mg/dL; IgG4, 278 mg/dL; hemoglobin A1c, 5.8%; C3, 163 mg/dl; C4, 22 mg/dl; prothrombin time, 83.9%; international normalized ratio, 1.13; activated partial thromboplastin time, 26.3 seconds; fibrinogen, 506.2 mg/dL; fibrinogen degradation product, 7.7 μg/mL; D-dimer, 1.4 μg/mL; soluble interleukin-2 receptor, 1,850 U/mL; and angiotensin converting enzyme, 13.7 U/L. The patient was negative for hepatitis B virus antigen, anti-hepatitis C virus antibody, and syphilis (rapid plasma regain and *Treponema pallidum* hemagglutination). The results of tests to detect autoantibodies were as follows: rheumatoid factor, positive (79 IU/mL); antinuclear antibody, positive (× 40, speckled pattern); anti-cardiolipin antibody IgG, negative (25 U/mL); lupus anticoagulant (dilute Russell's viper venom time), negative (1.0); myeloperoxidase anti-neutrophil cytoplasmic antibodies (ANCA), negative (<1.0 U/mL); proteinase 3-ANCA, negative (<1.0 U/mL); anti-SS-A-antibody, negative (<1.0 U/mL); anti-SS-B-antibody, negative (<1.0 U/mL); and anti-mitochondrial M2 antibody, negative. A liver biopsy specimen showed centrilobular liver damage suggesting acute-phase autoimmune hepatitis, without granuloma or vasculitis. A human leukocyte antigen typing analysis was positive for the A26, A33, B61 and B58 haplotypes. The patient's urine was negative for protein, sugar, and occult blood. Ophthalmoscopy revealed vitreous clouding in both eyes, paleness at the left retinal posterior pole and partial opacity at the right retinal posterior pole (Fig. 2). Contrast-enhanced CT indicated irregularities in the wall thickness and lumen of the superficial temporal arteries, whereas the bilateral ophthalmic arteries appeared normal (Fig. 3A and B). Ultrasonography of the temporal arteries revealed concentric wall thickening, hypoechoic halo, and the lumen was compressed bilaterally. However, ultrasound analyses of the shoulder joints were negative for active synovitis, the presence of which is indicative of polymyalgia rheumatica.

Given the above clinical findings and the criteria proposed by the American College of Rheumatology, the patient was diagnosed with GCA (9), bilateral central retinal artery oc-

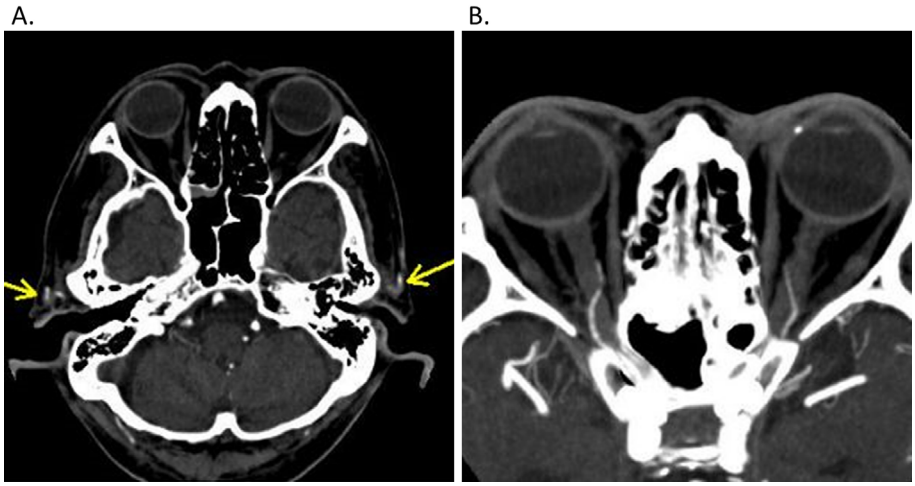

Figure 3. **A: Contrast-enhanced computed tomography: wall thickening and lumen irregularities of the patient's superficial temporal arteries (arrows) were identified, which were compatible with giant cell arteritis. B: In contrast, bilateral ophthalmic arteries were depicted.**

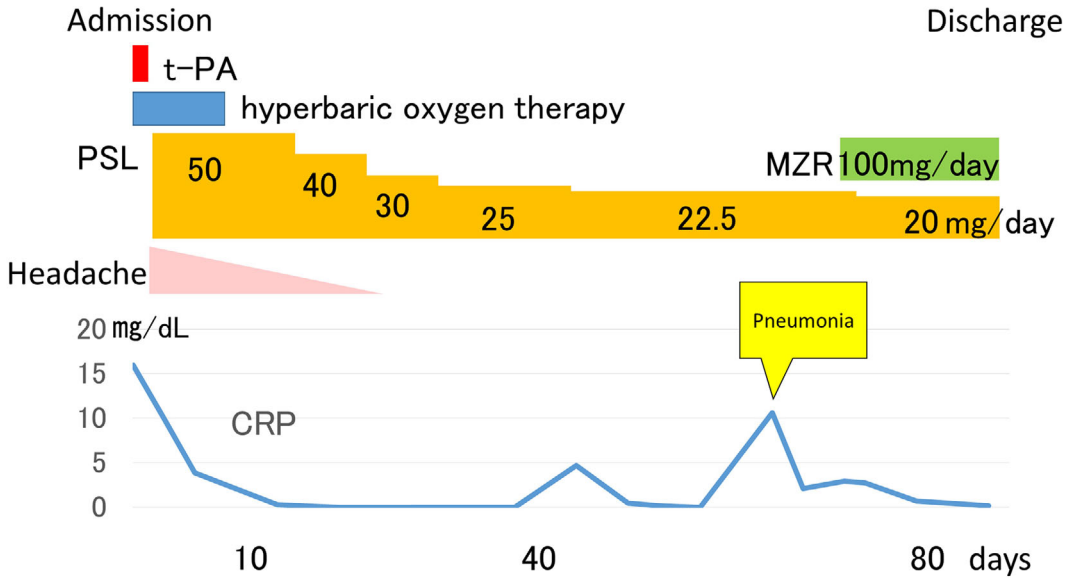

Figure 4. **The clinical course. CRP: C-reactive protein, MZR: mizoribine, t-PA: tissue-plasminogen activator**

clusion (CRAO) and GGA. The administration of tissue plasminogen activator and hyperbaric oxygen therapy were initiated just after admission to treat the CRAO; however, his visual acuity was unresponsive to the treatments. We considered temporal artery biopsy to obtain histological evidence of GCA, however, we prioritized the early introduction of corticosteroids since visual disturbance had already occurred. We then started oral PSL (50 mg/day), which improved not only the GCA-related headache and elevated CRP levels, but also the skin symptoms of GGA (Fig. 1B). We ultimately avoided temporal artery biopsy to prevent biopsy-related problems, such as infection. During the clinical course, the patient's CRP levels were also elevated due to pneumonia, but these were normalized by the administration of antibiotics. After the introduction of immunosuppressive therapy, the liver dysfunction found at admission improved. No relapse occurred even after tapering off the PSL dose and adding mizoribine (MZR) as a steroid-sparing agent (Fig. 4).

Discussion

Although cases in which GCA is associated with GGA have rarely been reported, there are indications that GCA and GGA share common immunohistochemical, therapeutic and genetic features. Although we could not show the histological findings of GCA and GGA in the presented case, previous studies reported that histopathologic evidence of vasculitis in temporal artery biopsy specimens is a typical and important diagnostic manifestation of GCA (10). Liang et al. noted that IgG, IgM and C3 were deposited on GCA-damaged arteries, while Dahl et al. found the deposition of

Table. **Cases of Giant Cell Arteritis (GCA) Complicated with Generalized Granuloma Annulare (GGA).**

Reference	Age	Sex	Preceding symptoms	Complications	Therapy	Outcome
(5)	79	M	GGA 7 months before the onset of GCA	None	PSL (60 mg/day)	Recovered
(6)	69	F	GCA 3 years before the onset of GGA	None	PSL (30 mg/day)	Recovered
(7)	71	M	GGA 5 months before the onset of GCA	Episcleritis	PSL (50 mg/day)	Recovered
(8)	78	M	GGA 1 year before the onset of GCA	Uveitis	PSL (0.7 mg/kg/day)	Recovered
Presented case	80	M	GGA 1 year before the onset of GCA	Uveitis	PSL (50 mg/day)	Recovered

F: female, GCA: giant cell arteritis, GGA: generalized granuloma annulare, M: male, PSL: prednisolone

IgM and C3 on GGA-damaged biopsy specimens (3, 4). Furthermore, the latter specimens demonstrated wall necrosis, fibrinoid changes and thickening or occlusion of blood vessels; taken together, these findings show that immunoglobulin-mediated vasculitis plays an important role in both GGA and GCA (3, 4). Corticosteroids, currently the first-line treatment for GCA (11), have been successfully used in the treatment of a patient with GGA complicated by GCA (5). Corticosteroid-sparing agents are considered for preventing the adverse effects arising from long-term exposure to glucocorticoid: for example, methotrexate is frequently used in combination with corticosteroids (11). However, methotrexate might not have been suitable in the present case because the patient had liver dysfunction. In this case, we chose MZR, a purine anti-metabolic immunosuppressant. MZR is reported to show good corticosteroid-sparing effects and safety in the treatment of lupus nephritis (12). MZR, a drug that has a similar mechanism to mycophenolate mofetil with less hepatotoxity, was also reported to be effective for Takayasu arteritis, another form of large-vessel vasculitis (13). MZR should be considered as a corticosteroid-sparing agent for large-vessel vasculitis with risk factors for drug-related problems.

Gonzalez-Gay et al. reported that human leukocyte antigen-B15, which is reportedly increased in GGA patients (14), was also frequently identified in patients with GCA (15); however, it was not identified in the present case. Thus, GCA and GGA might have common genetic factors. Taken together, these findings support the hypothesis that GCA and GGA share common etiologies. To date, there have only been four case reports of concomitant GCA and GGA (5-8) (Table). Shoimer et al. diagnosed their case as annular elastolytic giant cell granuloma (AEGCG), which they considered to be different from GA (7). However, the differential diagnosis of the two conditions is difficult, and other literature describes AEGCG as a variant of GA (16). Notably, in the case reported by Yáñez et al. (6), GCA was diagnosed three years prior to GGA. However, GGA was followed by GCA in three of the four previously reported cases, as well as ours (5, 7, 8). Since GCA frequently affects the branches of the carotid arteries, 10-20% of patients with GCA develop vision loss due to ischemic optic neuritis (1). Physicians should be aware of the potential for developing GCA during the clinical course of GGA. Further studies are necessary to clarify the pathophysiology underlying the coexistence of GCA and GGA.

In this paper, we reported a case of GCA that emerged one year after the diagnosis of GGA, both of which were effectively treated with oral corticosteroids. Clinicians should be alert for the development of GCA in patients with GGA who develop GCA-diagnostic symptoms such as headache and visual disturbances.

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

References

1. Jodo S, Hisada R. Giant cell arteritis. Nihon Rinsho Meneki Gakkai Kaishi (Jpn J Clin Immunol) **36**: 459-466, 2013 (in Japanese, Abstract in English).
2. Errichetti E, Lallas A, Apalla Z, Di Stefani A, Stinco G. Dermoscopy of granuloma annulare: a clinical and histological correlation study. Dermatology **233**: 74-79, 2017.
3. Liang GC, Simkin PA, Mannik M. Immunoglobulins in temporal arteries. An immunofluorescent study. Ann Intern Med **81**: 19-24, 1974.
4. Dahl MV, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. Arch Dermatol **113**: 463-467, 1977.
5. Fukai K, Ishii M, Kobayashi H, Someda Y, Hamada T, Tsujino S. Generalized granuloma annulare in a patient with temporal arteritis--are these conditions associated? Clin Exp Dermatol **15**: 70-72, 1990.
6. Yáñez S, Val-Bernal JF, Peña-Sagredo JL, Jiménez-Gómez I, Vazquez-Rodriguez TR, Gonzalez-Gay MA. Generalized granuloma annulare and giant cell arteritis. Clin Exp Rheumatol **26**: S108-S110, 2008.
7. Shoimer I, Wismer J. Annular elastolytic giant cell granuloma associated with temporal arteritis leading to blindness. J Cutan Med Surg **15**: 293-297, 2011.
8. Kluger N, Riviere S, Mura F, Guillot B, Girard C. Simultaneous occurrence of generalized granuloma annulare, anterior uveitis and giant cell arteritis: coincidental or not? Presse Med **41**: 548-549, 2012.
9. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum **33**: 1122-1128, 1990.
10. Jakobsson K, Jacobsson L, Mohammad AJ, et al. The effect of clinical features and glucocorticoids on biopsy findings in giant cell arteritis. BMC Musculoskelet Disord **17**: 363, 2016.
11. Watelet B, Samson M, de Boysson H, Bienvenu B. Treatment of giant-cell arteritis, a literature review. Mod Rheumatol **27**: 747-754, 2017.
12. Yumura W, Suganuma S, Uchida K, et al. Effects of long-term treatment with mizoribine in patients with proliferative lupus nephritis. Clin Nephrol **64**: 28-34, 2005.

13. Shimizu M, Ueno K, Ishikawa S, Tokuhisa Y, Inoue N, Yachie A. Successful multitarget therapy using mizoribine and tacrolimus for refractory Takayasu arteritis. Rheumatology (Oxford) **53**: 1530-1532, 2014.

14. Middleton D, Allen GE. HLA antigen frequency in granuloma annulare. Br J Dermatol **110**: 57-59, 1984.

15. Gonzalez-Gay MA, Rueda B, Vilchez JR, et al. Contribution of MHC class I region to genetic susceptibility for giant cell arteritis. Rheumatology (Oxford) **46**: 431-434, 2007.

16. Pham AK, Dinulos JG, Quinn TR. Annular elastolytic giant cell granuloma after a cardiac pacemaker implantation. JAAD Case Rep **2**: 357-359, 2016.