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【 CASE REPORT 】

Atypical Cogan's Syndrome Mimicking Giant Cell Arteritis Successfully Treated with Early Administration of Tocilizumab

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Abstract:
A 49-year-old Japanese man with a 2-month history of a fever, headache, and bilateral conjunctival hyperemia was admitted. His condition fulfilled the giant cell arteritis classification criteria (new headache, temporal artery tenderness, elevated ESR) and atypical Cogan's syndrome (CS) with scleritis and sensorineural hearing loss (SNHL). The interleukin (IL)-6 serum level was extremely high. Two weeks after his insufficient response of SNHL and scleritis to oral prednisolone, we administered tocilizumab (TCZ); rapid improvements in scleritis and SNHL occurred. Early IL-6 target therapy can help prevent irreversible CS-induced sensory organ damage.

Key words: Cogan's syndrome, giant cell arteritis, interleukin-6, tocilizumab

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Introduction

Cogan's syndrome (CS) is a rare autoimmune disease characterized by ocular inflammation and vestibuloauditory dysfunction, often with symptoms of systemic vasculitis (1, 2). Typical CS is defined with non-syphilitic interstitial keratitis and audiovestibular symptoms, occurring in a period of less than two years (1). After its establishment, a group later suggested that other types of ocular involvements (such as episcleritis, scleritis, retinitis, retinal artery occlusion, choroiditis, papilledema, exophthalmos, or tendonitis) with audiovestibular symptoms should be considered atypical CS (2). Many patients with CS become deaf and blind and suffer from a relapse of the disease despite treatments (3, 4). The mechanisms underlying the sensory organ damage caused by CS are not yet known, and the optimal therapeutic strategy has not been established.

Giant cell arteritis (GCA) and Takayasu arteritis (TA) are forms of systemic vasculitis that mainly affect large vessels (5). Several reports have shown that CS can overlap with large vessel vasculitis (LVV) (6-9). Evidence concerning the efficacy of the anti-interleukin-6 (IL-6) receptor antibody tocilizumab (TCZ) for treating patients with LVV including GCA has been accumulating (10-14).

We herein report a patient who met both the CS criteria and GCA classification criteria in whom the early administration of TCZ was effective for the patient's ocular inflammation and sensorineural hearing loss (SNHL).

Case Report

A 49-year-old Japanese man developed conjunctival congestion with pain in both eyes, a fever, headache, tinnitus, and ear fullness in both ears. Two months later, he was admitted to our hospital due to the elevated C-related protein

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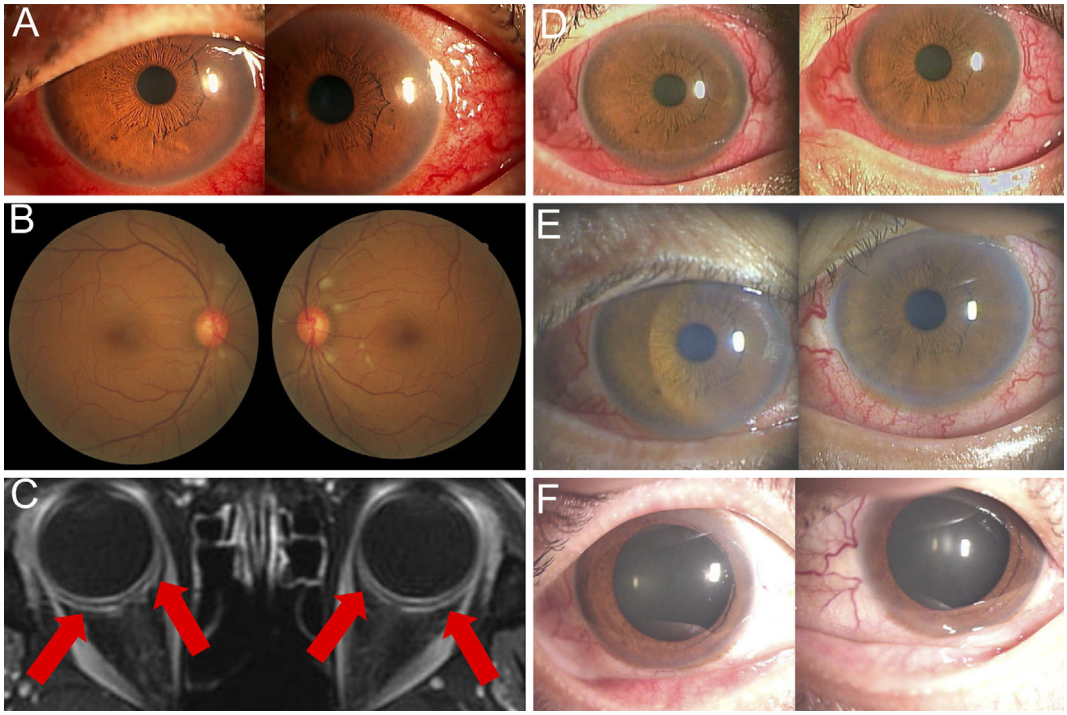

Figure 1. **Ophthalmological findings. A: Severe ocular conjunctiva scleritis was observed in both eyes. B: Cotton wool spots around the optic nerves were observed on ophthalmofundoscopy images. C: Cerebral contrast-enhanced T1-weighted MRI revealed enhancement of the bilateral sclera (arrows). D: At 13 days after the administration of prednisolone (PSL), scleritis persisted in both eyes. E: The day after the administration of tocilizumab (TCZ), which was 18 days after the administration of PSL, the scleritis showed rapid improvement. F: Five weeks after the administration of TCZ, further improvement of scleritis was observed.**

(CRP), bilateral scleritis, and soft vitiligo around the optic disc. He had no significant past medical or surgical history, and he was not taking any medications. There was no family history of vascular disease or collagen disease. He smoked two packs of cigarettes per day and denied the use of alcohol and recreational drugs.

On admission, his body temperature, blood pressure, pulse rate, and respiratory rate were normal. No marked difference was observed in his blood pressure between arms. A physical examination revealed tenderness at the temporal arteries. Severe hyperemia was observed in bilateral bulbar conjunctiva (Fig. 1A). Vascular bruit in the chest was not observed. The results of the rest of the patient's neurological, systemic, and general physical examinations were unremarkable. An examination by an ophthalmologist revealed cotton wool spots around the optic nerves and scleritis in both eyes, but interstitial keratitis was not observed (Fig. 1A, B).

Laboratory test results showed the following: white blood cells 16,600/μL (neutrophils 68%, lymphocytes 15%, monocytes 15%), and the erythrocyte sedimentation rate (ESR) of 58 mm/h. Coagulation was significant only for elevated fibrinogen at 816 mg/dL. The results of a basic metabolic panel, lipid panel, and urinary tests were unremarkable. The hepatic function panel showed that alkaline phosphatase (ALP) and gamma-glutamyl transferase were both elevated at 695 and 475 U/L respectively. The inflammatory biomarkers were highly elevated, with CRP at 8.96 mg/dL and ferritin at 658 mg/mL. Immunological studies, including results for antinuclear antibodies (ANA), myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), proteinase 3-ANCA, rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-ds DNA antibody, were all negative. The treponema pallidum antibodies were negative.

A cytokine multiplex array using the serum at the time of the patient's admission to our hospital revealed a remarkedly elevated titer of IL-6: 47.92 ng/mL (Table). His electrocardiogram, transthoracic echocardiogram, and chest X-ray findings were all normal. Thoracic and abdominal contrast-enhanced computed tomography (CT) showed wall thickening and enhancement of the aorta arch, brachiocephalic trunk, left common carotid artery, and left subclavian artery (Fig. 2A). Cerebral contrast-enhanced MRI showed enhancement of the bilateral sclera (Fig. 1C), wall thickening of bilateral superficial temporal arteries (Fig. 2C), and vessel wall enhancement in the internal carotid arteries (Fig. 2E). MR angiography (MRA) also showed narrowing of the bilateral superficial temporal arteries (Fig. 2D). However, the results of the biopsy from the lateral superficial temporal artery were unremarkable. An audiogram showed a pattern of steep high-frequency SNHL with a moderate level in both ears (Fig. 3A).

Table. The Results of the Cytokine Multiplex Array: Our Patient's Data at Admission and Those of 57 Healthy Individuals.

	Present case	Healthy individuals (95% CI)
IFN-γ	33.64	14.7-32.9
IL-1β	1.62	1.48-4.07
IL-6	47.92	1.22-6.24
IL-12 p40	Undetectable	14.39-40.54
IL-12 p70	0.32	6.29-36.0
TNFα	19.2	8.78-11.8
IL-17	33.72	4.96-42.78

The 95% CI of the serum cytokine level from healthy individuals (n=57) is indicated as a control. Units: pg/mL. CI: confidence interval

The patient's symptoms met the criteria for the classification of GCA (new onset of localized headache, temporal artery tenderness, elevated ESR ≥50 mm/h) proposed by the American College of Rheumatology (ACR) in 1990 (15). The case also met the criteria for atypical CS (scleritis as inflammatory ocular manifestations and audiovestibular symptoms) proposed by Haynes et al. in 1980 (2).

Based on these findings, we administered oral prednisolone (PSL) (60 mg/day, 1 mg/kg/day) (Fig. 4). Even though the titer of CRP decreased two weeks after this administration of PSL, the scleritis and moderate level of SNHL persisted, and the patient's tinnitus and hearing difficulty in his daily life worsened (Figs. 1D, 3B, 4). We therefore decided to initiate TCZ (162 mg/week subcutaneous injection) on the 16th day after the administration of PSL. After the induction of TCZ, the scleritis showed a rapid improvement (Fig. 1E, F), and the patient's hearing loss recovered to a

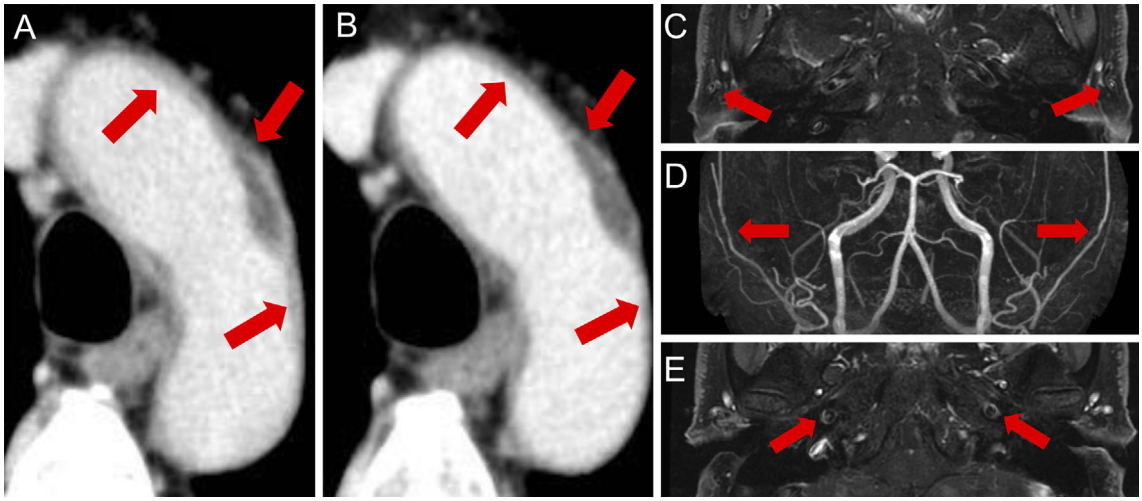

Figure 2. The vascular findings by imaging modalities. A: Thoracic and abdominal contrast-enhanced CT showed wall thickening and enhancement of the aorta arch (arrows). B: At 10 weeks after the induction of treatment, the aortic wall thickening and enhancement showed improvement. C: Cerebral contrast-enhanced T1-weighted MRI showed enhancement of wall thickening in the bilateral superficial temporal arteries (arrows). D: MR angiography (MRA) showed narrowing of the bilateral superficial temporal arteries (arrows). E: Cerebral contrast-enhanced T1-weighted MRI showed vessel wall enhancement in the bilateral internal carotid arteries (arrows).

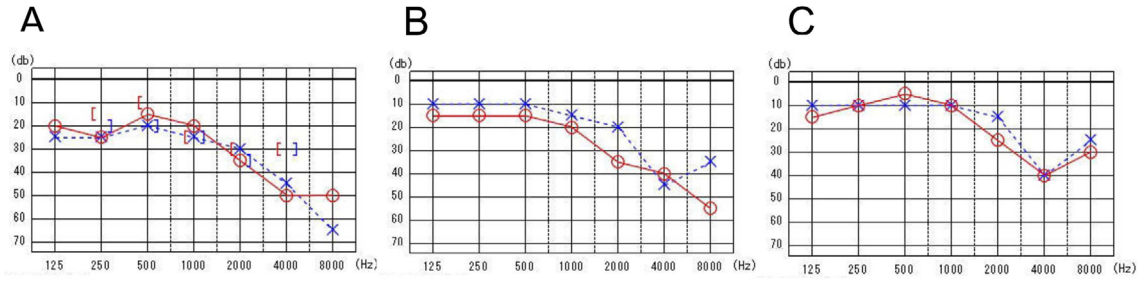

Figure 3. The time course of audiogram tests. A: A moderate level of steep high-frequency sensorineural hearing loss (SNHL) was shown by the audiogram in both ears. B: At 16 days after the administration of PSL, a moderate level of high-frequency SNHL was still observed. C: At 5 weeks after the induction of TCZ, the SNHL had recovered to the level of mild hearing loss.

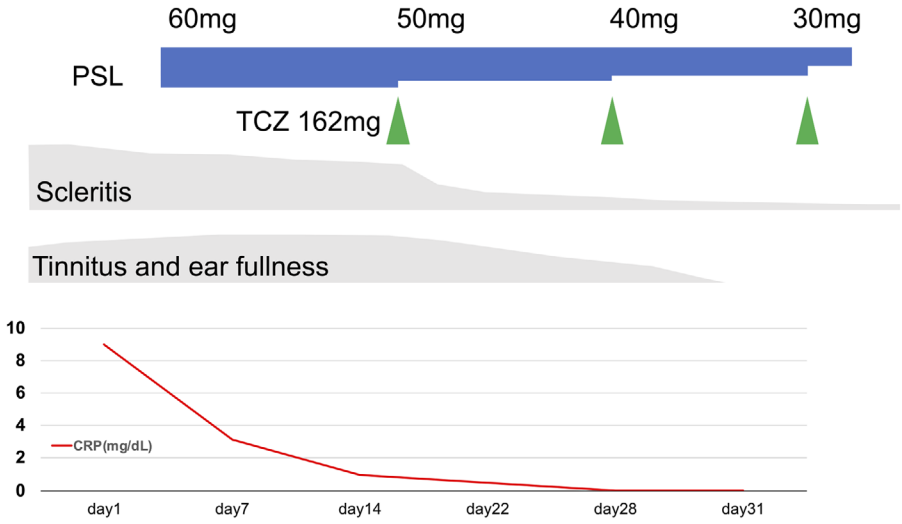

Figure 4. **The patient's clinical course.**

level at which he reported not having any hearing difficulty in his daily life (Fig. 3C). The wall thickening and enhancement of the aorta on enhanced CT were also improved (Fig. 3B). His headache and temporal artery tenderness were also improved. No side effects of TCZ were observed. Tapering of the dosage of prednisolone has been successful, and flares of disease have been inhibited under our follow-up.

Discussion

In the present case, the early administration of TCZ had a positive effect on both SNHL and scleritis. It has been reported that 75% of patients with CS experience disease relapse (3). The prognosis of sensory organ damage in patients with CS has been reported to be poor. In the context of audiovestibular manifestations, hearing loss develops in a sudden, bilateral, fluctuating, and progressive manner (3). Of note, complete hearing loss was reported in 45-52% of patients with CS (2-4), and 5% of the cases were reported to result in blindness (3).

Although the outcome of sensory organ damage in CS is poor, there is no established treatment for patients with CS. Corticosteroid therapy and several immunosuppressive therapies have been used as treatment options for CS, including methotrexate (MTX), mycophenolate mofetil, azathioprine, cyclosporine, and cyclophosphamide (16-20). However, none of these treatments have been investigated in randomized trials.

Several reports have shown the effectiveness of biological agents for patients with CS. Infliximab was administered to two patients with CS whose disease had relapsed, and the infliximab inhibited the disease relapse (hearing loss and scleritis, respectively) (21). An open-label pilot study of etanercept for patients with immune-mediated cochleovestibular disorders, including CS, did not report any substantial efficacy of this approach for improving hearing loss, but a positive effect for improving word recognition was noted (22). A case report indicated that rituximab was effective for a patient with CS whose hearing loss had progressed under a combined immunosuppressive treatment (23). There is also a report of TCZ being effective for treating a patient with relapse of CS who did not show a response to various immunosuppressive agents, including MTX, cyclosporine, azathioprine, and adalimumab (7). In that report, TCZ (which was administered 10 years after the diagnosis of CS) improved the patient's aortitis, elevated CRP levels, and quality of life but did not improve the audiometry or visual acuity, presumably due to the history of inflammation (7).

Early intervention by treatment is important for the prevention of irreversible sensory organ damage caused by CS. It was reported that the hearing acuity improved in 10 of 18 (55%) patients with CS treated by a corticosteroid within the first 2 weeks after the onset of hearing loss, whereas such an improvement was achieved in only 1 of 12 (8%) CS patients treated beyond 2 weeks after the onset (2). With the early induction of TCZ, our present patient achieved a good therapeutic outcome, i.e. no visual disturbance and no hearing difficulty in daily life.

In the context of rheumatoid arthritis (RA), the treat-to-target treatment strategy in the early stage of RA yields good outcomes, such as the achievement of remission and prevention of joint destruction (24). Furthermore, a treat-to-target strategy using TCZ for early RA was reported to result in better disease activity values and a better remission rate than MTX and PSL treatment (25). Given the therapeutic outcome of our present patient, the early administration TCZ may be a good treatment strategy for preventing sensory organ damage due to inflammation induced by CS.

To our knowledge, the present report is the first of a case that met both the GCA classification criteria and the CS criteria. Earlier studies indicated that 16.7% of patients with CS develop systemic vasculitis (4), and approximately 10% of CS patients develop vasculitis in large vessels, including

the aorta (26). Three cases of CS that fulfilled the classification criteria for Takayasu arteritis have been reported (6, 8, 9), while the present case didn't meet this criteria. Regarding GCA, acute sensorineural hearing loss rarely occurs in patients with GCA (27). Common ocular involvements in GCA are amaurosis and diplopia (28), and there have been few reports of patients with GCA who developed scleritis (29-31). Since CS is defined as variable vessel vasculitis (VVV) by the 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides (32), we considered the present case to be one of CS mimicking GCA.

IL-6 coordinates the disease development of LVV including GCA and TA. IL-6 was reported to be elevated in serum and at focal inflammation sites in both GCA and TA (33-35). TCZ as an IL-6 blockade therapy has already been clinically applied for LVV (10-14).

The inflammatory cytokine profile in CS is poorly understood. A previous case report describing the efficacy of TCZ for CS mentioned an elevated IL-6 concentration in both the serum and cerebrospinal fluid (7). Our patient showed an extremely high serum IL-6 concentration, whereas his Th1- and Th17-related cytokine levels were not clearly elevated. Given the cytokine profile and the efficacy of IL-6 blockade therapy, it seems that IL-6 had a central role in the disease development in the present case.

CS and LVV share similar clinical presentations and treatment response to IL-6 blockade therapy. A further accumulation of cases is required to confirm the efficacy of TCZ as an early treatment for CS to prevent irreversible sensory organ damage, and additional research is needed to elucidate the precise biomolecular mechanisms underlying the pathogenesis of CS that underlie the increased production of IL-6.

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

References

1. Cogan D. Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. Arch Ophthalmol **33**: 144-149, 1945.
2. Haynes BF, Kaiser-Kupfer MI, Mason P, Fauci AS. Cogan syndrome: studies in thirteen patients, long-term follow-up, and a review of the literature. Medicine **59**: 426-441, 1980.
3. Gluth MB, Baratz KH, Matteson EL, Driscoll CL. Cogan syndrome: a retrospective review of 60 patients throughout a half century. Mayo Clin Proc **81**: 483-488, 2006.
4. Grasland A, Pouchot J, Hachulla E, et al. Typical and atypical Cogan's syndrome: 32 cases and review of the literature. Rheumatology (Oxford, England) **43**: 1007-1015, 2004.
5. Kermani TA. Takayasu arteritis and giant cell arteritis: are they a spectrum of the same disease? Int J Rheum Dis **22**: 41-48, 2019.
6. Raza K, Karokis D, Kitas GD. Cogan's syndrome with Takayasu's arteritis. Br J Rheumatol **37**: 369-372, 1998.
7. Shibuya M, Fujio K, Morita K, Harada H, Kanda H, Yamamoto K. Successful treatment with tocilizumab in a case of Cogan's syndrome complicated with aortitis. Mod Rheumatol **23**: 577-581, 2013.
8. Kawasaki Y, Uehara T, Kawana S. Cutaneous vasculitis in Cogan's syndrome: a report of two cases associated with chlamydia infection. J Nippon Med Sch **85**: 172-177, 2018.
9. Morinaka S, Takano Y, Tsuboi H, Goto D, Sumida T. Familial HLA-B*52 vasculitis: maternal, atypical Cogan's syndrome with Takayasu arteritis-mimicking aortitis and filial takayasu arteritis. Intern Med **59**: 1899-1904, 2020.
10. Mekinian A, Resche-Rigon M, Comarmond C, et al. Efficacy of tocilizumab in Takayasu arteritis: multicenter retrospective study of 46 patients. J Autoimmun **91**: 55-60, 2018.
11. Nakaoka Y, Isobe M, Tanaka Y, et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology (Oxford, England) **59**: 2427-2434, 2020.
12. Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis **77**: 348-354, 2018.
13. Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet **387**: 1921-1927, 2016.
14. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med **377**: 317-328, 2017.
15. 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.
16. Riente L, Taglione E, Berrettini S. Efficacy of methotrexate in Cogan's syndrome. J Rheumatol **23**: 1830-1831, 1996.
17. Hautefort C, Loundon N, Montchilova M, Marlin S, Garabedian EN, Ulinski T. Mycophenolate mofetil as a treatment of steroid dependent Cogan's syndrome in childhood. Int J Pediatr Otorhinolaryngol **73**: 1477-1479, 2009.
18. Shahid FL, Mukherjee R, Knapp C. Cogan's syndrome associated with orbital inflammation. Orbit **32**: 206-207, 2013.
19. Allen NB, Cox CC, Cobo M, et al. Use of immunosuppressive agents in the treatment of severe ocular and vascular manifestations of Cogan's syndrome. Am J Med **88**: 296-301, 1990.
20. Watanabe K, Nishimaki T, Yoshida M, et al. Atypical Cogan's syndrome successfully treated with corticosteroids and pulse cyclophosphamide therapy. Fukushima J Med Sci **46**: 49-54, 2000.
21. Fricker M, Baumann A, Wermelinger F, Villiger PM, Helbling A. A novel therapeutic option in Cogan diseases? TNF-alpha blockers. Rheumatol Int **27**: 493-495, 2007.
22. Matteson EL, Choi HK, Poe DS, et al. Etanercept therapy for immune-mediated cochleovestibular disorders: a multi-center, open-label, pilot study. Arthritis Rheum **53**: 337-342, 2005.
23. Orsoni JG, Lagana B, Rubino P, Zavota L, Bacciu S, Mora P. Rituximab ameliorated severe hearing loss in Cogan's syndrome: a case report. Orphanet J Rare Dis **5**: 18, 2010.
24. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis **79**: 685-699, 2020.
25. Verhoeven MM, de Hair MJ, Tekstra J, et al. Initiating tocilizumab, with or without methotrexate, compared with starting methotrexate with prednisone within step-up treatment strategies in early rheumatoid arthritis: an indirect comparison of effectiveness and safety of the U-Act-Early and CAMERA-II treat-to-target trials. Ann Rheum Dis **78**: 1333-1338, 2019.
26. Singer O. Cogan and Bechet syndromes. Rheum Dis Clin North Am **41**: 75-91, viii, 2015.
27. Le N, Vickers A, Prospero Ponce C, Chevez-Barrios P, Lee AG. Vestibulocochlear symptoms as the initial presentation of giant cell arteritis. Can J Ophthalmol **54**: e1-e3, 2019.
28. Vodopivec I, Rizzo JF 3rd. Ophthalmic manifestations of giant cell arteritis. Rheumatology (Oxford, England) **57**: ii63-ii72, 2018.
29. Awh C, Reichstein DA, Thomas AS. A case of giant cell arteritis

presenting with nodular posterior scleritis mimicking a choroidal mass. Am J Ophthalmol Case Rep **17**: 100583, 2020.

30. Erdogan M, Sayin N, Yildiz Ekinci D, Bayramoglu S. Bilateral posterior scleritis associated with giant cell arteritis: a case report. Ocul Immunol Inflamm **26**: 1244-1247, 2018.

31. Cavallini GM, Volante V, Bigliardi MC, Mascia MT, Forlini M. Bilateral posterior scleritis as a presenting manifestation of giant cell arteritis: a case report. Can J Ophthalmol **49**: e141-e143, 2014.

32. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol **17**: 603-606, 2013.

33. Emilie D, Liozon E, Crevon MC, et al. Production of interleukin 6 by granulomas of giant cell arteritis. Hum Immunol **39**: 17-24, 1994.

34. Park MC, Lee SW, Park YB, Lee SK. Serum cytokine profiles and their correlations with disease activity in Takayasu's arteritis. Rheumatology (Oxford, England) **45**: 545-548, 2006.

35. Kong X, Sun Y, Ma L, et al. The critical role of IL-6 in the pathogenesis of Takayasu arteritis. Clin Exp Rheumatol **34**: S21-S27, 2016.