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【 CASE REPORT 】

Medium-vessel Vasculitis Presenting with Myalgia Following COVID-19 Moderna Vaccination

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Abstract:
Coronavirus disease 2019 (COVID-19) vaccines have been delivered worldwide to prevent the spread of the disease, and almost all Japanese have received the mRNA vaccines "BNT162b2" (Pfizer-BioNTech) or "mRNA-1273" (Moderna). These vaccines have shown efficacy and safety with only minor adverse drug reactions. However, some patients develop severe adverse drug reactions, including autoimmune reactions. In addition, systemic vasculitis, mainly small-vessel vasculitis, following COVID-19 vaccination, has been reported. However, only a few investigators have reported medium-vessel vasculitis following vaccination. We herein report a case of medium-vessel vasculitis presenting with myalgia as the initial clinical manifestation following COVID-19 Moderna vaccination.

Key words: COVID-19, mRNA vaccine, autoimmune phenomena, medium-vessel vasculitis, myalgia

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Introduction

Coronavirus disease 2019 (COVID-19) has spread worldwide and caused the death of almost six million people globally. COVID-19 vaccines have been rapidly delivered worldwide, and almost all Japanese residents have received the mRNA vaccines "BNT162b2" (Pfizer-BioNTech) or "mRNA-1273" (Moderna), which were approved in 2021. These vaccines have proven excellent in reducing the morbidity and severity of the disease and shown to be safe with only minor adverse drug reactions, such as a fever, fatigue, and swollen arms. However, some patients develop severe adverse drug reactions, anaphylactic shock, and autoimmune phenomena, such as myocarditis, thrombosis with thrombocytopenia, and vasculitis (1-3).

Several investigators have reported small-vessel vasculitis following COVID-19 vaccination, including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (4, 5). However, only a few have reported medium-vessel vasculitis following vaccination (6, 7).

We herein report a case of medium-vessel vasculitis presenting with myalgia as the initial clinical manifestation after COVID-19 mRNA Moderna vaccination.

Case Report

A 41-year-old woman was referred to our hospital with a fever and myalgia. She had no history of chronic disease or allergies, new medications, or infectious symptoms before vaccination. The patient and her family had no documented history of COVID-19 infection. In 2021 September, she received a second dose of the Moderna vaccine. Thirty-five days after vaccination, she developed myalgia that did not resolve. She developed a fever of 38.0°C at 42 days after vaccination. She visited the clinic 57 days after vaccination because of her persistent fever and myalgia.

Blood tests showed a high C-reactive protein (CRP) level. She received loxoprofen and prednisolone (PSL) 15 mg/day in the clinic; however, it failed to alleviate her fever and muscle pain. Therefore, she was referred to our department 71 days after vaccination.

On admission, her body temperature, blood pressure, pulse, and SpO_2 were 36.6°C, 129/93 mmHg, 94 beats/min,

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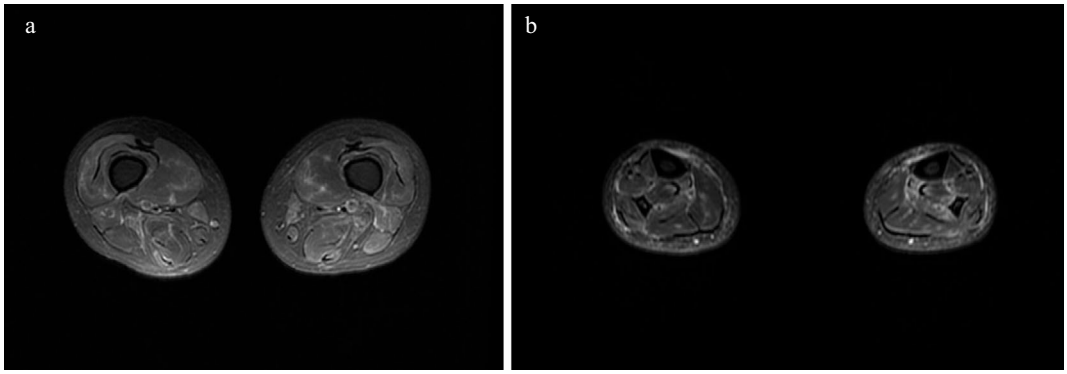

Figure 1. MRI findings. MRI showed a hyperintense signal on the short-tau inversion recovery in her quadriceps (a), and gastrocnemius muscle (b). MRI: magnetic resonance imaging

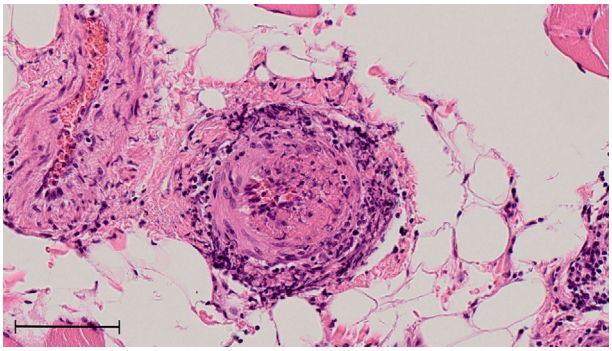

Figure 2. Pathological findings. Pathological findings showed necrotizing vasculitis. Bar size is 100 μm.

and 99% (room air), respectively. She had no weight loss, skin rash, numbness, muscle weakness, or difficulty moving her upper or lower extremities, but she had myalgia in her lower legs. Superficial lymph nodes were not palpable. No swollen or tender joints or skin lesions were observed. Her manual muscle testing (MMT) was complete, but muscle grasping pain was noted in her lower legs. The results of her hematological examination were as follows: white blood cells, 7,130/μL; neutrophil, 5,626/μL; lymphocyte, 827/μL; red blood cells, 392×10^4/μL; hemoglobin, 11.8 g/dL; hematocrit, 37.6%; platelets, 35.6×10^4/μL; prothrombin time, 12.4 s; activated partial thromboplastin time, 37.1 s; fibrinogen, 597 mg/dL; D-dimer, 1.5 μg/mL; erythrocyte sedimentation rate, 35 mm/h; total protein, 5.9 g/dL; albumin, 2.7 g/dL; aspartate transaminase, 28 U/L; alanine transaminase, 34 U/L; lactate dehydrogenase, 208 U/L; creatinine kinase, 15 U/L; creatinine, 0.53 mg/dL; total cholesterol, 208 mg/dL; triglyceride, 75 mg/dL; ferritin, 135.6 ng/mL; blood sugar level, 98 mg/dL; CRP, 9.47 mg/dL; IgG, 1,001 mg/dL; IgA, 150 mg/dL; IgM, 42 mg/dL; matrix metalloproteinase-3, 46.3 ng/mL; angiotensin-converting enzyme, 12.0 U/L; rheumatoid factor, 1.0 IU/mL; and soluble interleukin-2 receptor, 1,080 U/mL. Tests for antinuclear antibodies showed 160 (homogenous and speckled pattern), and anti-CCP, DNA, SS-A, SS-B, and RNP antibodies were negative. Tests for myeloperoxidase-ANCA, proteinase-3-ANCA, perinuclear-ANCA, and cytoplasmic perinuclear ANCA were negative, and a urinalysis showed no blood, 1-4 red blood cells/high-power field, 1-4 white blood cell/high-power field, and no protein. Tests for hepatitis B surface antigen, human parvovirus B-19 IgM, and T-spot.TB for tuberculosis were negative. The sputum COVID-19 polymerase chain reaction test was negative. Blood culture results were negative.

Computed tomography (CT) showed no specific lesions, and CT angiography showed no aneurysms. An echocardiography cardiogram showed normal wall movement with no pericardial effusion. Magnetic resonance imaging (MRI) showed a hyperintense signal on short-tau inversion recovery in the quadriceps and gastrocnemius muscles (Fig. 1). A muscle biopsy of the left gastrocnemius also showed fibrinoid necrosis, which was consistent with necrotizing vasculitis (Fig. 2). She did not meet the 1990 criteria for the classification of polyarteritis nodosa (PN) (8), but she had a persistent fever with myalgia and high CRP levels in her blood test despite low-dose PSL. In addition, pathological findings showed necrotizing vasculitis. Therefore, she was treated with a moderate dose of PSL (30 mg/day) based on PN on day 15 after admission. The clinical course is shown in Fig. 3. After treatment, the patient became afebrile without myalgia. At the last observation, her condition was stable with PSL 10 mg/day.

Discussion

Systemic vasculitis (SV) is an autoimmune disease that affects blood vessels via inflammation. SV includes small-vessel vasculitis, medium-vessel vasculitis, and large-vessel vasculitis. Small-vessel vasculitis includes IgA vasculitis, cryoglobulinemia, and AAV, such as microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangitis (9). Medium-vessel vasculitis includes PN. Small- and medium-vessel vasculitis result in ischemic, hemorrhagic, and inflammatory impairment and infiltration of inflammatory cells.

Musculoskeletal involvement is very common in patients with AAV and PN and has been reported in 50-70% of AAV patients and 30-59% of PN patients (10, 11). In addition, one report indicated that myalgia, especially in the lower

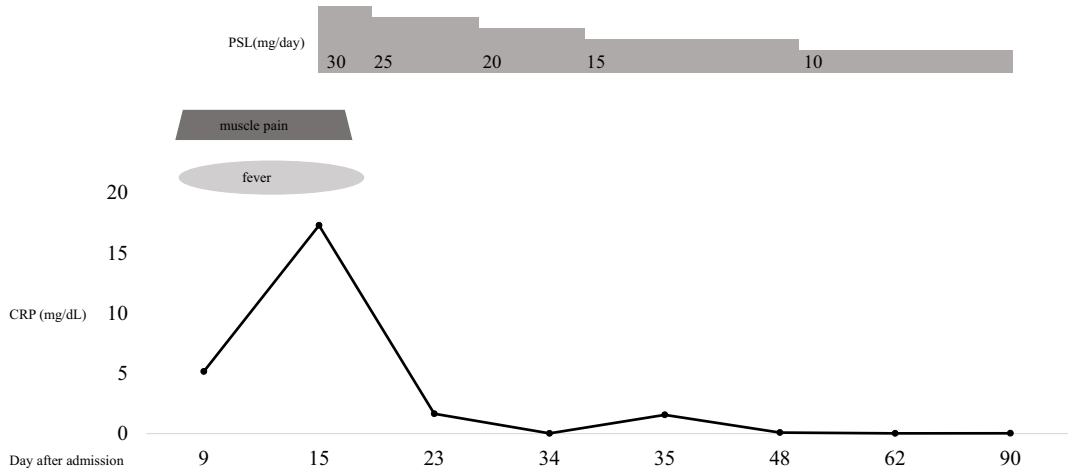

Figure 3. **Clinical course. CRP: C-reactive protein, PSL: prednisolone**

limbs, is the initial manifestation of small- and medium-vessel vasculitis, and patients with AAV and PN with myalgia had more arthritis but no mononeuritis multiplex (12). In our case, the patient had myalgia in the lower limbs as the initial symptom but did not have mononeuritis multiplex, which is consistent with previous reports.

Several investigators have reported SV following influenza vaccines, and an association between SV and vaccines has been reported (13). Vaccines contain adjuvants that can induce autoimmune responses and cause autoimmune syndromes. The influenza antigen and vaccine proteins have structural similarities, and the influenza vaccine may activate the same autoimmune mechanisms as infectious antigens (14). Among previously reported patients with vasculitis after influenza vaccination, 13 had large-vessel vasculitis, 2 had medium-vessel vasculitis, 42 had small-vessel vasculitis, 5 had single-organ vasculitis, and 1 had vasculitis associated with systemic disease. In addition, most cases of vasculitis following COVID-19 vaccination have been small-vessel vasculitis, including AAV (4, 5). One report suggested that vaccine components induced pathogenic ANCA production via molecular similarity of vaccine components to antigens on the surface of neutrophils in individuals with an abnormal regulatory T and B cell function (15).

However, mRNA vaccines may produce autoinflammation due to the stimulation of myeloid and dendritic cells (16). mRNA vaccines induce robust CD8- and CD4-positive T-cell mediated responses and may cause enhanced stimulation of innate and acquired immunity compared to other vaccines (17-20). Eventually, mRNA vaccines also induce the production of neutralizing antibodies and memory T and B cells (20). A previous report indicated that autoinflammation occurs in genetically predisposed individuals (19).

According to the influenza vaccination report of the Ministry of Health, Labour and Welfare from 2019 to 2020 in Japan, 1 patient (0.000002%) developed vasculitis (20). In contrast, according to the COVID-19 mRNA vaccination report of the Ministry of Health, Labour and Welfare from February 2021 to May 2022 in Japan, 64 patients (0.00002%) developed vasculitis, which might be a higher rate than that associated with the influenza vaccine (21).

Regarding the vaccine type in patients with giant cell arteritis (GCA) and polymyalgia rheumatic following COVID-19 vaccination, 61.9% of patients received mRNA vaccines, and 37.4% received viral vectors. In contrast, regarding patients with AAV, 22 of 29 patients received mRNA vaccines, including 4 with ChAdOx1nCoV-19, 2 with BBV152, and 1 with Ad26.COV2.S vaccination. According to the COVID-19 mRNA Pfizer and Moderna vaccination report of the Ministry of Health, Labour and Welfare from February 2021 to May 2022 in Japan, 61 patients (0.00003%) with Pfizer-BioNTech, 3 with Moderna (0.000001%), and no patients with virus vector developed vasculitis (21). Which type of vaccination induces vasculitis most frequently is thus unclear.

In patients with AAV following COVID-19 vaccination, the median time from vaccination to first symptoms was 14 (2-37) days. Furthermore, according to the COVID-19 vaccination report of the Ministry of Health, Labour and Welfare from 2021 to 2022 in Japan, 94.5% of vasculitis developed within 30 days after vaccination. These results showed that vasculitis patients typically developed vasculitis within 30 days of vaccination. However, some patients developed vasculitis more than 30 days after vaccination, including the present case.

In addition, regarding AAV, 14 developed it after the first dose, and 15 developed it after the second dose. In contrast, regarding GCA, 9.1% of patients developed it after the second dose of the vaccine. According to the COVID-19 mRNA Pfizer and Moderna vaccination report of the Ministry of Health, Labour and Welfare from February 2021 to May 2022 in Japan, 59 patients developed vasculitis after the first or second dose of a vaccine, while 5 developed it after the third dose of a vaccine.

The present patient developed PN after the second dose of the Moderna vaccine. Whether or not booster vaccination affects the development of vasculitis is unclear at present. Further prospective studies are thus warranted to investigate the

Table. Characteristics of Patients with Medium Vessel Vasculitis Following COVID-19 Vaccine.

Clinical characteristics	Patient 1	Patient 2	Patient3
Age (years old)	73	46	41
Gender	Male	Male	Female
Comorbidity	Chronic hepatitis B	HT	-
New-onset or relapse	New-onset	New-onset	New-onset
Vaccine type	NA	Pfizer	Moderna
Number of vaccination	First	Second	Second
Time to onset (days)	21	7	35
Symptoms of vasculitis	Fever, arthralgia, purpura, orchitis	Fever, rigor abdominal pain	Fever, myalgia
Cutaneous lesion	+	-	-
Peripheral neuropathy	-	-	-
Visceral involvement	Kidney	Aortitis	Muscle
MPO-ANCA	Negative	Negative	Negative
PR3-ANCA	Negative	Negative	Negative
CRP (mg/dL)	NA	20.3	9.47
Biopsy site for vasculitis	Kidney	None	Muscle
Treatment for vasculitis	Glucocorticoid cyclophosphamide	Glucocorticoid	Glucocorticoid
Outcome	Improve	Improve	Improve
Reference	6)	7)	Our patient

ANCA: anti-neutrophil cytoplasmic antibody, CRP: C-reactive protein, HT: hypertension, NA: not assessed

effect of booster vaccination on the development of vasculitis.

There have been only three cases of medium vessel-vasculitis following COVID-19 vaccination (including our case) reported thus far (Table) (6, 7). The median age was 46 years old, and 2 patients were men. One patient received the Pfizer vaccine, and the other received the Moderna vaccine. All cases were new-onset, and two patients developed vasculitis after the second dose of the vaccine. All patients developed vasculitis within 35 days of vaccination. All cases had a fever, and one had cutaneous lesions; no patients had peripheral neuropathy. Tests for ANCA were negative in all patients, and all patients responded to immunosuppressive treatment and had good outcomes.

However, several investigators have reported large-vessel vasculitis following COVID-19 vaccination (22-27). COVID-19 vaccines were associated with an increasing risk of GCA (reported reaction 2.7, 95% confidence interval: 2.3, 3.2) (27). Among patients with GCA following COVID-19 vaccination, most developed GCA after the first dose of the vaccine, and the median time to reaction was 2.5 days, which differed from the course with medium-vessel vasculitis (6, 7, 27).

One study reported a case of transient large-vessel vasculitis after COVID-19 mRNA vaccination. In that case, the patient's condition improved within two weeks after treatment with naproxen (28). However, our patient did not improve after treatment with low-dose prednisolone or loxoprofen, suggesting that the persistent fever for several weeks despite antipyretic drugs might have been related to the initial vasculitis symptoms after COVID-19 vaccination.

No factors associated with the development of vasculitis following COVID-19 vaccination, including the vasculitis type, vaccine type, or vaccine dose, have yet been identified. A larger prospective study is therefore warranted to investigate the details of vasculitis after COVID-19 vaccination.

In conclusion, COVID-19 vaccines may induce autoimmune diseases, including vasculitis, and clinicians should be alert for the occurrence of these diseases after COVID-19 vaccination.

Written informed consent for this case report was obtained from the patient.

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

References

1. Polack FP, Thomas SJ, Kitchin N, et al.; the C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **383**: 2603-2615, 2020.
2. Baden LR, El Sahly HM, Essink B, et al.; the COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **384**: 403-416, 2021.
3. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol **16**: 413-414, 2020.
4. Prabhahar A, Naidu GSRSNK, Chauhan P, et al. ANCA-associated vasculitis following ChAdOx1 nCoV19 vaccination: case-based review. Rheumatol Int **42**: 749-758, 2022.
5. Abdelmaksoud A, Wollina U, Temiz SA, Hasan A. SARS-CoV-2 vaccination-induced cutaneous vasculitis: report of two new cases and literature review. Dermatol Ther **35**: e15458, 2022.
6. Fillon A, Sautenet B, Barbet C, Moret L, et al. *De novo* and relapsing necrotizing vasculitis after COVID-19 vaccination. Clin Kidney J **15**: 560-563, 2021.
7. Al-Allaf AW, Razok A, Al-Allaf Y, Aker L. Post-COVID-19 vaccine medium-vessel vasculitis and acute anterior uveitis, causation vs temporal relation; case report and literature review. Ann Med Surg (Lond) **75**: 103407, 2022.

8. Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum **33**: 1088-1093, 1990.

9. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum **65**: 1-11, 2013.

10. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med **337**: 1512-1523, 1997.

11. Hernández-Rodríguez J, Alba MA, Prieto-González S, Cid MC. Diagnosis and classification of polyarteritis nodosa. J Autoimmun **48-49**: 84-89, 2014.

12. Ushiyama S, Shimojima Y, Ueno KI, Kishida D, Miyazaki D, Sekijima Y. Clinical characteristics of patients with myalgia as the initial manifestation of small and medium-sized vasculitis: a retrospective study. Rheumatol Int **40**: 1667-1674, 2020.

13. Watanabe T. Vasculitis following influenza vaccination: a review of the literature. Curr Rheumatol Rev **13**: 188-196, 2017.

14. Shoenfeld Y, Agmon-Levin N. 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun **36**: 4-8, 2011.

15. Jeffs LS, Nitschke J, Tervaert JW, Peh CA, Hurtado PR. Viral RNA in the influenza vaccine may have contributed to the development of ANCA-associated vasculitis in a patient following immunisation. Clin Rheumatol **35**: 943-951, 2016.

16. Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". Clin Immunol **224**: 108665, 2021.

17. Wang F, Kream RM, Stefano GB. An evidence based perspective on mRNA-SARScov-2 vaccine development. Med Sci Monit **26**: e924700, 2020.

18. Li NL, Coates PT, Rovin BH. COVID-19 vaccination followed by activation of glomerular diseases: does association equal causation? Kidney Int **100**: 959-965, 2021.

19. Pelka K, Shibata T, Miyake K, Latz E. Nucleic acid-sensing TLRs and autoimmunity: novel insights from structural and cell biology. Immunol Rev **269**: 60-75, 2016.

20. Adverse Reaction Study Subcommittee, Subcommittee on Immunization and Vaccine, 48th Health Sciences Council and FY2020 4th Meeting of the Safety Measures Committee of the Pharmaceutical Affairs Subcommittee of the Pharmaceutical Affairs and Food Sanitation Council Pharmaceutical Affairs and Food Sanitation Council, Japan [Internet]. [cited 2020 Jul 7]. Available from: https://www.mhlw.go.jp/content/10906000/000710864.pdf (in Japanese).

21. Adverse Reaction Study Subcommittee, Subcommittee on Immunization and Vaccine, 80th Health Sciences Council and The fifth meeting in 2022 of the Pharmaceutical Affairs and Food Sanitation Council, Pharmaceutical Affairs Subcommittee, Committee on Safety Measures for Drugs, etc. Pharmaceutical Affairs and Food Sanitation Council, Subcommittee on Pharmaceutical Affairs, Committee on Safety Measures for Drugs and Other Drugs, Investigative Committee on Safety Measures for Drugs and Other Drugs [Internet]. [cited 2022 Jun 10]. Available from: https://www.mhlw.go.jp/content/10601000/000948860.pdf (in Japanese).

22. Gilio M, De Stefano G. Large-vessel vasculitis following the Pfizer-BioNTech COVID-19 vaccine. Intern Emerg Med **17**: 1247, 2022.

23. Wack S, Patton T, Ferris LK. COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: review of available evidence. J Am Acad Dermatol **85**: 1274-1284, 2021.

24. Mejren A, Sørensen CM, Gormsen LC, Tougaard RS, Nielsen BD. Large-vessel giant cell arteritis after COVID-19 vaccine. Scand J Rheumatol **51**: 154-155, 2022.

25. Greb CS, Aouhab Z, Sisbarro D, Panah E. A case of giant cell arteritis presenting after COVID-19 vaccination: is it just a coincidence? Cureus **14**: e21608, 2022.

26. Anzola AM, Trives L, Martínez-Barrio J, Pinilla B, Álvaro-Gracia JM, Molina-Collada J. New-onset giant cell arteritis following COVID-19 mRNA (BioNTech/Pfizer) vaccine: a double-edged sword? Clin Rheumatol 1-3, 2022.

27. Mettler C, Jonville-Bera AP, Grandvuillemin A, Treluyer JM, Terrier B, Chouchana L. Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study. Rheumatology (Oxford) **61**: 865-867, 2022.

28. Aoki K, Yamamoto S, Tochitani K. Transient large-vessel vasculitis after Covid-19 mRNA vaccination. Intern Med **61**: 2083-2084, 2022.