American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2024; 25: e945301
DOI: 10.12659/AJCR.945301

Received: 2024.05.27
Accepted: 2024.08.13
Available online: 2024.08.23
Published: 2024.09.30

Otitis Media with ANCA-Associated Vasculitis Following COVID-19 mRNA Vaccination: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Yuta Yoshino
CD 2 Yurika Yamanaka
CD 1 Aya Oda

1 Department of Internal Medicine, Saitama Citizens Medical Center, Saitama, Japan
2 Department of Otorhinolaryngology, Saitama Citizens Medical Center, Saitama, Japan

Corresponding Author: Yuta Yoshino, e-mail: yy_yopi@yahoo.co.jp
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 74-year-old
Final Diagnosis: Otitis media with ANCA-associated vasculitis
Symptoms: Hearing loss
Clinical Procedure: —
Specialty: Immunology • Otolaryngology • Rheumatology

Objective: Unknown etiology

Background: SARS-CoV-2 caused a worldwide pandemic, and mRNA vaccines against the SARS-CoV-2 spike protein were developed to avoid SARS-CoV-2 infection. Short-term adverse events, such as fever, malaise, body aches, and headaches, develop within a few days following COVID-19 vaccination. Those adverse events are common and widely known as transient reactions. Recently, an association with COVID-19 vaccine as an inducer of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been noted. Furthermore, a relationship between COVID-19 vaccination and the development of autoimmune diseases has been reported and termed rheumatoid immune-mediated inflammatory disease. However, the mechanisms of the immune response following COVID-19 vaccination in relation to ANCA-associated vasculitis development remain unclear.

Case Report: We report a case of a female patient who developed otitis media with ANCA-associated vasculitis following the third dose of COVID-19 mRNA vaccination. A 74-year-old woman presented with bilateral hearing loss and malaise for 1 month after COVID-19 vaccination. Serum myeloperoxidase-ANCA levels were confirmed to be elevated, and pure-tone audiometry revealed moderate bilateral mixed hearing loss. Treatment with steroids and rituximab led to recovery of hearing loss and a reduction in myeloperoxidase-ANCA titre.

Conclusions: The pathogenesis of adverse events following COVID-19 vaccination are still unclear. This report has indicated that ANCA-associated vasculitis can be related to COVID-19 mRNA vaccines. As our knowledge of autoimmune disease developing after COVID-19 vaccination is still in the accumulation phase, it is relevant to amass such case reports and use them for assistance in diagnosis in the future.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Otitis Media • COVID-19 Vaccine • SARS-CoV-2

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/945301

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the global COVID-19 pandemic. Consequently, mRNA vaccines that elicit an immune response against the SARS-CoV-2 spike protein have been developed, and data on the prevention of COVID-19 and reduction in the rate of severe illness have been published [1]. Common adverse events reported with COVID-19 mRNA vaccination include fever, fatigue, myalgia, arthralgia, and headache [2,3]. Furthermore, COVID-19 mRNA vaccination can directly induce myositis at the injection site [4]. Post-marketing surveillance has identified adverse events associated with the COVID-19 vaccine, and the accumulation of this data has led to ongoing safety surveillance [5]. Recently, an association with COVID-19 vaccine as an inducer of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been noted [6]. In addition, Nune et al [7] reported that the COVID-19 vaccine could cause rheumatoid immune-mediated inflammatory disease (R-IMID). Although a temporal association between COVID-19 vaccination and the development of ANCA-associated vasculitis (AAV) has been demonstrated [8], the mechanisms of the immune response following COVID-19 vaccination in relation to AAV development remain to be clarified. Symptoms of AAV, such as fever, malaise, anorexia, and weight loss, are nonspecific, and most of these symptoms are mild. The detection of AAV can frequently be delayed because patients do not consider the clinical presentation of vasculitis to be significant [6]. Here, we report a case of bilateral otitis media following COVID-19 vaccination, which was diagnosed and treated as otitis media with AAV (OMAAV). OMAAV is characterized by otitis media unresponsive to conventional therapies, such as those for acute otitis media or otitis media with effusion. According to clinical signs, serum levels of ANCA, and pathological findings, the diagnostic criteria for OMAAV have been proposed by the Japan Otological Society [9].

Case Report

A 74-year-old Japanese woman with no relevant medical history presented to our hospital with bilateral hearing loss and malaise for 1 month. She had never experienced any hearing loss and had no history of chronic inflammatory diseases, such as vasculitis. Furthermore, there were no cases of R-IMID in her family history. The bilateral hearing loss was diagnosed as bilateral otitis externa at a local otolaryngology clinic 2 weeks before the visit. Although the patient was treated for otitis externa with corticosteroid eardrops, her symptoms did not improve. One week before the onset of hearing loss and malaise, the patient received a third dose of COVID-19 mRNA vaccine.

At the first visit, the patient reported concerns of anorexia and weight loss of 3 kg in 1 month; she had no headache, abdominal pain, arthralgia, or skin rash. Laboratory test findings revealed a high inflammatory response, with aspartate aminotransferase of 15 U/L, alanine aminotransferase of 11 U/L, creatinine of 0.65 mg/dL, blood urea nitrogen of 12.7 mg/dL, C-reactive protein of 11.59 mg/dL, and a white blood cell count of 21 300/mm^3. Urine test findings showed urinary protein 2+ (1.03 g/g/Cr) and urinary occult blood 2+ (6 red blood cells/high-power field). The results of antinuclear antibodies, proteinase 3-ANCA, IgG4, syphilis serodiagnosis, and blood cultures were negative. The serum myeloperoxidase-ANCA was 21.7 U/mL (reference range <3.4 U/mL). Whole-body computed tomography (CT), performed as a systemic survey, did not reveal any lesions suggestive of malignancy or infection (**Figure 1A**). Chronic inflammatory changes, mainly reticular and trabecular shadows, were present just below the pleura in both lower lobes of the lungs (**Figure 1B**). Although the lung biopsy indicated organization of the alveolar region and mononuclear cell infiltration of the alveolar wall, there were no obvious findings of vasculitis or hemosiderosis. The bilateral temporal bone CT showed soft tissue density of the tympanic cavity and mastoid cells with no bone destruction (**Figure 1C, 1D**). Otoscopic examination revealed bilateral middle ear effusions and partial thickening of the eardrums (**Figure 2**), although no pyogenic otorrhea or perforation of the eardrums was found. Pure-tone audiometry revealed bilateral moderate mixed hearing loss (**Figure 3A**). The levels of pure-tone average were 53.3 dB (bone conduction, 30.0 dB) on the right and 58.8 dB (bone conduction, 36.7 dB) on the left. Eosinophils in puncture fluid from the middle ear were negative. Furthermore, the interferon-gamma release assay by T-SPOT was also negative. Treatment of localized diseases, such as acute otitis media or otitis media with effusion, was not considered in the present case, because the main physical signs were generalized wasting. Although no prior antimicrobial treatment or placement of tympanic ventilation tubes was performed, this case revealed clinical features that met the diagnostic criteria for OMAAV in the absence of those procedures [9]; thus, we diagnosed OMAAV following COVID-19 mRNA vaccination.

As initial treatment, the patient was administered prednisolone at a dose of 60 mg daily (1 mg/kg/day), followed by 500 mg of rituximab on day 14 of treatment. After the first dose of rituximab, the prednisolone dose was reduced according to the glucocorticoid tapering regimen used in the PEXIVAS trial [10]. Rituximab was administered at a dose of 500 mg weekly for a total of 4 doses. The patient was discharged on 20 mg of prednisolone on day 40 of treatment.

Serum levels of myeloperoxidase-ANCA decreased to 1.9 U/mL after 2 weeks of treatment. Two months after treatment initiation, the mixed hearing loss improved, with a pure-tone average of 26.7 dB (bone conduction, 20.0 dB) on the right and 23.3 dB (bone conduction, 21.7 dB) on the left (**Figure 3B**).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

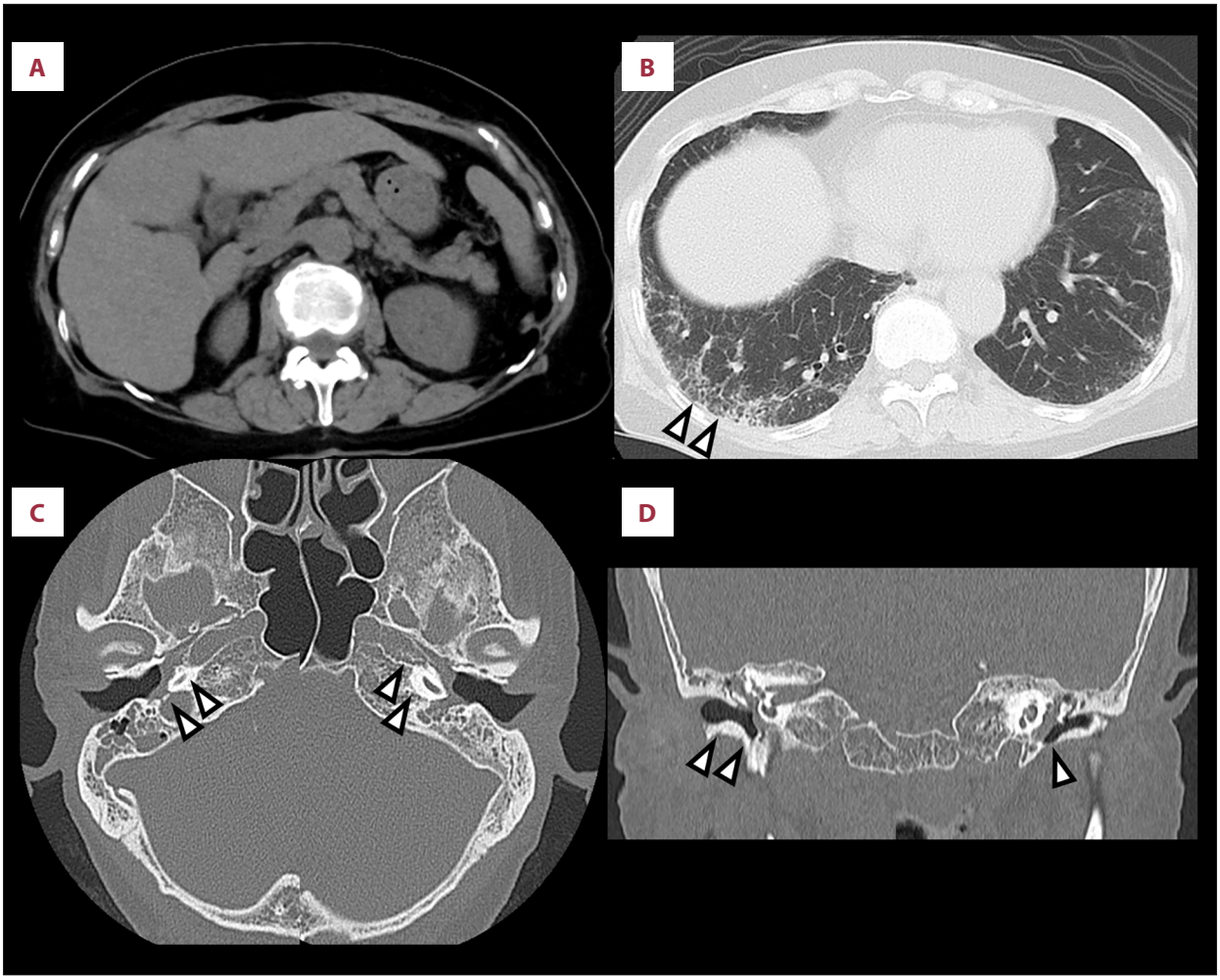

Figure 1. Whole-body computed tomography findings. (**A**) Systematic survey to investigate any malignant or infectious lesions. (**B**) Surveillance for detecting lung lesions associated with vasculitis. The lung biopsies revealed chronic inflammatory changes (arrows). Vasculitis or hemosiderosis were not found. (**C, D**) Screening to detect the bony destruction and abnormalities within the tympanic cavity and mastoid cells. No bone destruction was found (arrows).

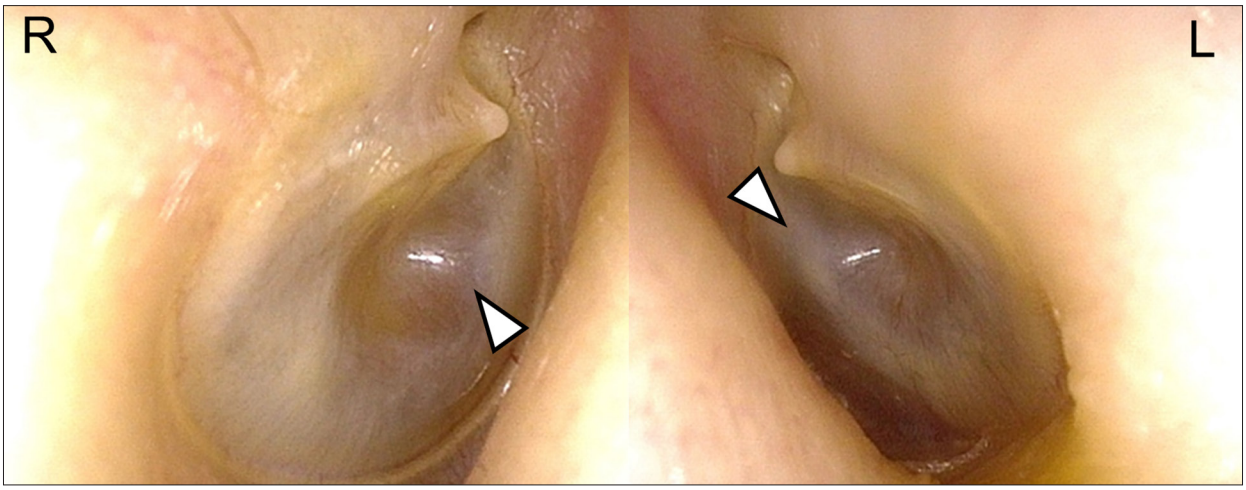

Figure 2. Otoscopic examination revealed bilateral middle ear effusions and partial thickening of the eardrums (arrows).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

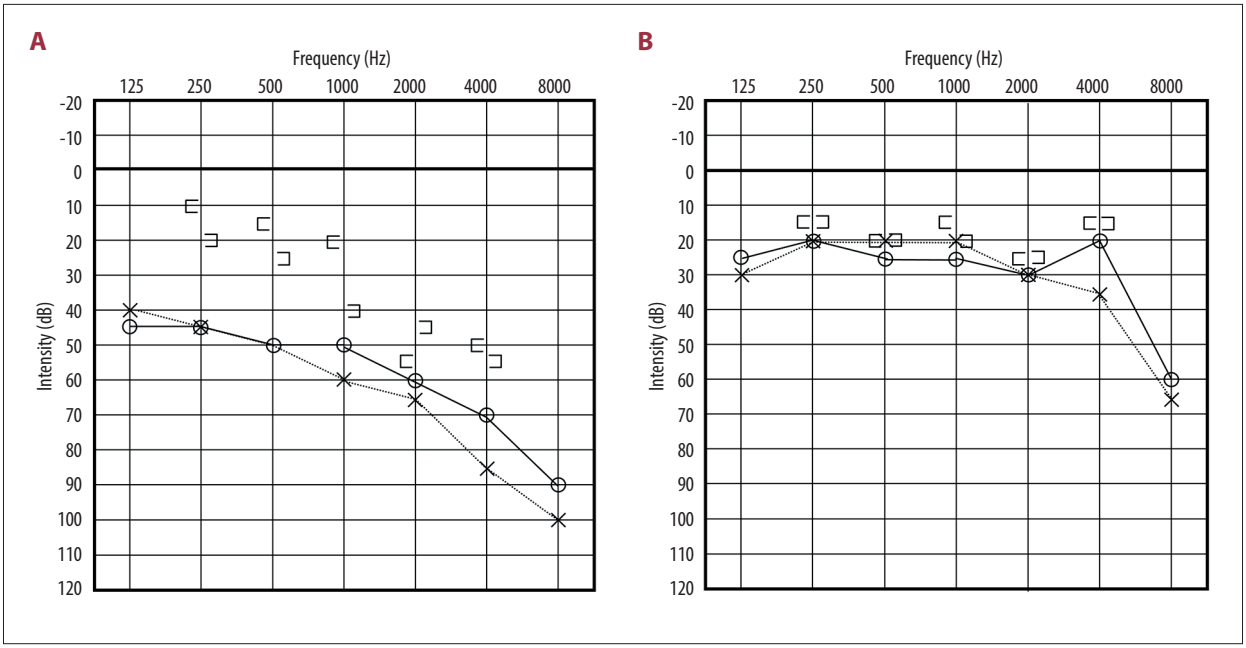

Figure 3. Audiometric levels as indicated by pure-tone audiometry before and after the treatment. (**A**) Pure-tone audiometry before the treatment. (**B**) Pure-tone audiometry 2 months after the treatment initiation.

Subsequently, 6 mg of methotrexate was added weekly, and the dose of prednisolone was reduced to 5 mg. To date, no OMAAV relapse has been observed.

Discussion

This case describes the characteristics of OMAAV that developed following COVID-19 vaccination. Recently, a relation between the development of AAV and COVID-19 vaccination as an inducing factor has been described [6]. The clinical characteristics of AAV following COVID-19 vaccination can present with rapidly progressive glomerulonephritis and pulmonary hemorrhage [8]. Reports of AAV following COVID-19 vaccination included cases of bilateral or unilateral sensorineural hearing loss and tinnitus, which were diagnosed as otitis media [11-13]. Acute hearing loss, particularly bilateral hearing loss with appetite loss or underweight, can be considered a sign of systemic disease, such as OMAAV, rather than of otitis media caused by viral or bacterial infection. In a study indicating an association between COVID-19 vaccine and R-IMID, the mean duration from COVID-19 vaccination to R-IMID onset was 10.6 days [7]. The temporal relationship between COVID-19 vaccination and R-IMID has been discussed because of the short interval of AAV onset following COVID-19 vaccination [8]. Another study reported that the median time to AAV onset after COVID-19 vaccination was significantly shorter than that of other drug-induced AAV (14 days vs 9 months) [14]. Nune et al [7] noted that the cases of new onset of R-IMID following COVID-19 vaccination were notably under-reported from an African region, with the opinion that this was due to the relatively low COVID-19 vaccination coverage in the African region. However, the molecular mechanisms involved in the immunological response and AAV development following COVID-19 vaccination remain unclear. COVID-19 mRNA vaccine has been suggested to activate the inflammasome pathway recognized by Toll-like receptors [15]. Furthermore, the subtype of Toll-like receptors activated by the COVID-19 vaccine has been found to be Toll-like receptor 2 [16]. However, the timeline for AAV activation after COVID-19 vaccination is inconsistent [8]. The variations in the onset of vasculitis make it difficult to understand the pathogenesis of AAV.

A case series of AAV following COVID-19 vaccination included cases of bilateral or unilateral sensorineural hearing loss and tinnitus that were diagnosed as otitis media [12]. However, the hearing loss in those cases may be attributed to OMAAV. Nonspecific symptoms of AAV are prone to be masked by patients, as the symptoms are not considered important. Consequently, the diagnosis of AAV can be delayed [6]. New-onset hearing loss and otitis media unresponsive to tympanic ventilation tube placement or antimicrobial treatment should be considered as possible indications for OMAAV. As COVID-19 vaccination can trigger the development of AAV, a history of COVID-19 vaccination would be useful for diagnosing OMAAV.

Conclusions

We reported a case of a woman who developed OMAAV following COVID-19 mRNA vaccination. However, an association

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

between the development of AAV and COVID-19 vaccination remains unclear. The pathogenesis of AAV following COVID-19 vaccination has not been resolved either. Nevertheless, we collected several reports of AAV with hearing loss or otitis media that developed after COVID-19 vaccination. Since our knowledge of autoimmune disease developing after COVID-19 vaccination is still in the accumulation phase, it is relevant to amass such case reports and use them for assistance in diagnosis in the future.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

Department and Institution Where Work Was Done

Department of Internal Medicine, Saitama Citizens Medical Center, Saitama, Japan.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Cheng H, Peng Z, Luo W, et al. Efficacy and safety of COVID-19 vaccines in phase III trials: A meta-analysis. Vaccines (Basel). 2021;9:582
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603-15
3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403-16
4. Theodorou DJ, Theodorou SJ, Axiotis A, et al. COVID-19 vaccine-related myositis. QJM. 2021;114:424-25
5. Pollard AJ, Bijker EM. A guide to vaccinology: From basic principles to new developments. Nat Rev Immunol. 2020;21:83-100
6. Molnár A, Studinger P, Ledó N. Diagnostic and therapeutic approach in ANCA-associated glomerulonephritis: A review on management strategies. Front Med. 2022;9:884188
7. Nune A, Durkowski V, Pillay SS, et al. New-onset rheumatic immune-mediated inflammatory diseases following SARS-CoV-2 vaccinations until May 2023: A systematic review. Vaccines (Basel). 2023;11:1571
8. Chen CC, Chen HY, Lu CC, Lin SH. Case Report: Anti-neutrophil cytoplasmic antibody-associated vasculitis with acute renal failure and pulmonary hemorrhage may occur after COVID-19 vaccination. Front Med. 2021;8:765447
9. Harabuchi Y, Kishibe K, Tateyama K, et al. Clinical features and treatment outcomes of otitis media with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV): A retrospective analysis of 235 patients from a nationwide survey in Japan. Mod Rheumatol. 2017;27:87-94
10. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382:622-31
11. Kim Y, Kang J, Lee SG, et al. COVID-19 vaccination-related small vessel vasculitis with multiorgan involvement. Z Rheumatol. 2022;81:509-12
12. Thammathiwat T, Banjongjit A, Iampenkhae K, et al. ANCA associated glomerulonephritis following SARS-CoV-2 vaccination: A case series and systematic review. Vaccines (Basel). 2023;11:983
13. Shirai T, Suzuki J, Kuniyoshi S, Tanno Y, Fujii H. Granulomatosis with polyangiitis following Pfizer-BioNTech COVID-19 vaccination. Mod Rheumatol Case Rep. 2023;7:127-29
14. Deshayes S, Dolladille C, Dumont A, et al. A worldwide pharmacoepidemiological update of drug-associated anca-associated vasculitis at the time of targeted therapies. Ann Rheum Dis. 2021;80:270
15. Teijaro JR, Farber DL. COVID-19 vaccines: Modes of immune activation and future challenges. Nat Rev Immunol. 2021;21:195-97
16. Kumar N, Admane N, Kumari A, et al. Cytotoxic T-lymphocyte elicited vaccine against SARS-CoV-2 employing immunoinformatics framework. Sci Rep. 2021;11:7653

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]