

NEW-ONSET SEROPOSITIVE RHEUMATOID ARTHRITIS FOLLOWING SARS-COV-2 INFECTION AND AFTER COVID-19 VACCINATION

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ABSTRACT

Shortly after the outbreak of atypical pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative agent of COVID-19, reports have emerged regarding the presence of immunological phenomena and autoimmune rheumatic diseases, including new-onset seropositive rheumatoid arthritis (RA). Within less than 12 months of the epidemic, the Pfizer and Moderna mRNA vaccines demonstrated an efficacy of over 95%. With the time, side effects have also been documented. This study aimed to analyze patients who were diagnosed as RA following SARS-CoV-2 infection and after vaccination against COVID-19. The major characteristics of these patients are: polyarthritis predominantly of small joints; presence of anti-citrulline protein antibody in 94% and the combination with rheumatoid factor was of 86%; serum levels of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) increased; the time interval between the viral infection or vaccination and the onset was 1 to 6 weeks; predominance in women, 77% of cases; six cases had pneumonia following SARS-CoV-2 vs 0 after COVID-19 vaccine; joint symptoms presented after the second dose in 10 (67%)/15 cases: two patients previously seronegative eventually developed seropositive RA; and there was a personal or family history of autoimmune diseases in 9 cases. Remission induction was achieved with methotrexate, with or without glucocorticoids, other disease-modifying antirheumatic drugs, and biological agents. Only 1 patient died of COVID-19. These findings show that in a limited number of cases, COVID-19 causes autoimmunity, possibly through molecular mimicry, adjuvants, or the activation of autoreactive T cells.

KEYWORDS: COVID-19; SARS-CoV-2; Rheumatoid Arthritis; Autoimmunity; COVID-19 Vaccination; Methotrexate; Anti-Citrullinated Protein Antibodies (ACPA); Rheumatoid Factor (RF).

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by symmetric polyarthritis predominantly of small joints, presence of rheumatoid factors (RF), anti-citrullinated protein antibody (ACPA), and serum levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) increased.^[1] HLA-DR molecules contribute to the

development of ACPA.^[2] The combination of RF and ACPA has greater specificity than positive RF alone in supporting the diagnosis. A connection between viral infection in RA has previously been suggested,^[3] and now severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causative agent of COVID-19, is linked to immunological phenomena, inflammatory syndromes,

and autoimmune rheumatic diseases, including seropositive RA.

The spike glycoprotein (Sgp) is the target of neutralizing antibodies, contains hexapeptides similar to peptides found in host tissue, and can elicit cross-response. Acute hyperactivity of immune responses results in autoantibodies production, inflammation, release of pro-inflammatory cytokines and acute-phase reactants, similar to those found in patients with RA. With the aim of reducing the morbidity and severity of SARS-CoV-2 infection and following the sequencing of the coronavirus genome, work began on the development of a vaccine. In less than 12 months COVID-19 immunization began. The approved messenger RNA-based vaccines encode the Sgp which is encapsulated in lipid nanoparticles (LNP's) and contain phospholipids and polyethylene glycol (PEG) to protect the mRNA and increase their water solubility and bioavailability. PEG is one of the possible causes of COVID-19 type 1-hypersensitivity reactions. COVID-19 vaccines have also been associated with immunological phenomena and autoimmune rheumatic diseases.^[4-12]

METHODS

Search Strategy

A search PubMed/Medline for case reports, case series, systemic review, and letters to the editor on de novo-seropositive rheumatoid arthritis (RA) following SARS-CoV-2 infection and after the vaccination against COVID-19. Related references and citations were also included for review and potential inclusion in the results. The search terms were: 1) de novo- seropositive RA, 2) SARS-CoV-2, 3) COVID-19 vaccine and adverse effects; 3) COVID-19 and autoimmune phenomena. The review was conducted from January 2020 to August 2026. There were no restrictions based on geographic area, language, or study design.

Selection and exclusion criteria

Patients included were those with case reports, case series, and letters to the editor on rheumatoid arthritis (RA) following SARS-CoV-2 infection and RA after COVID-19 vaccination; seropositivity for ACPA and rheumatoid factor (RF); time interval between SARS-CoV-2 infection or COVID vaccination and first symptoms ≤ 6 weeks; those who at least 1 dose received of COVID-19 vaccine; presence of acute phase reactants; and a personal or family history of autoimmune disease, treatment and outcomes. Patients with a known diagnosis of RA and those without RA biomarkers were excluded.

Data extraction

The following information was obtained from the patients: 1) age and gender; 2) information on infection and vaccination; 3) type and number of vaccine doses; 4) time interval between infection or vaccination and the onset of joint symptoms; and 5) imaging studies, 6) physical examination, immunologic tests, serum levels of

C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).

RESULTS

A total of 36 patients of seropositive RA (median age 54 years, 77% females) were identified. Table 1 shows the 21 cases of RA following SARS-CoV-2 infection: the main clinical manifestations were fever, cough, anosmia, dysgeusia, myalgia, arthritis, and pneumonia in 6 cases. The time interval between SARS-CoV-2 infection to joint symptoms onset ranged from 1 week to 6 weeks. ACPA-positive RA was present in 19 (90.4%) cases and the combination of ACPA and RF was found in 18/21 (86%) cases. One patient previously seronegative for RF experienced high serum levels (411 IU/ml) following SARS-CoV-2 infection. Inflammatory markers (CRP or ESR) were increased in 20 (96%) cases. Eight patients presented positive antinuclear antibodies (ANA) and 1 patient presented anti-peptidyl-arginine deaminase (PAD 4/2). Serum concentrations of IL-6 were elevated in 3 cases. There were 6 patients with personal or family history of autoimmune rheumatic disease. Classic HLA-DRB1 genotype was absent. Methotrexate (MTX) was used in 15 patients, alone or in combination with oral or IV glucocorticoids, as well as leflunomide, hydroxychloroquine, sulfasalazine, NSAIDs, and TNF blockers.

Table 2 shows 15 cases of RA after COVID-19 vaccination. Messenger RNA-based vaccines (Pfizer and Moderna) were used in 7 (47%) cases, followed by viral vector vaccines, Sputnik V and ChAdOx1. ACPA alone was found in 15 (100%) cases and the combination RF+ACPA was found in 12 (80%) cases. Autoimmune manifestations appeared between 1 and 30 days after vaccination. There were no cases of pneumonia. Antinuclear antibodies (ANA) were positive in 7 cases. There was a personal or familial history of autoimmune diseases in 5 cases. A 54-year-old man was seronegative for RF and ACPA before vaccination but became seropositive after vaccination (RF 1712 IU/ml and ACPA 162 U/ml). One patient presented facial and lingual edema, hypereosinophilia, and elevated IgE levels 7 days after administration of the 2nd dose of BBV152 vaccine. Although no parasites were found, the patient received albendazole, methotrexate and NSAIDs. Inflammatory markers were increased in 13/15 (87%) patients. Six (43%) patients received methotrexate with or/without oral or intravenous glucocorticoids. Anti-TNF blockers, anti-IL-6, abatacept in combination with glucocorticoids and disease-modifying antirheumatic drugs also were started. One patient died of COVID-19.

Table 1: Clinical and paraclinical characteristics of 21 patients with COVID-19 infection confirmed by PCR or anti-protein S Ab. who developed seropositive rheumatoid arthritis						
Author	Age/sex	Interval between SARS-CoV-2 and first symptoms	CRP/ESR mg/l/ mm/h	Immunologic tests	Therapy	Response
1. Ansari C et al 2020 Rheumatology	70/F	6 weeks, cough, dyspnea pneumonia (Chest CT) Fever	CRP 276 ESR 90	RF 428 ACPA 51	GC	Improved
2. Talarico et al 2020 Lancet Rheumatol Famiy history of SpA	45/M	3 weeks, symmetric arthritis anosmia, dysgeusia, myalgia fever, pericardial effusion	CRP 1,6 ESR 13	RF negativo- ACPA+	GC	Complete remission
3. Baimukhamedev C et al, Lancet Rheumatol, 2021 (RF-)	67/M	4 weeks. Fever, arthritis, pneumonia (Chest CT)	CRP 55 ESR 59	RF 411 ACPA 104	Antibiotics MTX, IV GC	Improved
4. Perrot L et al 2021 Lancet Rheumatol	60/F	25 days, arthritis, , fever pneumonia (Chest CT) US, doppler, no erosions	CRP 18.5 ESR 97 IL-6 31 pg/ml	RF 21, ACPA 76 ANA+, anti- Ro/La+ anti-PAD 4/2 +	Antibióticos MTX	Improved
5. Ben-Chatrit E et al, 2021 Clin Exp Rheumat	33/F	4 weeks, arthritis, disosmia, disgeusia	Elevated CRP. ESR	Negative RF, AAN+ ACPA 6.3 <3	MTX, GC	Improved
6. Tamborrini G 2021, Praxis	36/M	6 sweeks, arthritis, fever	Normals CRP/ESR	RF 200, ACPA 146	HCQ, ritonavir	Improved
7. Safar et al 2021, Int J Res Med Sci	41/F	4 sem. Polyarthritis, fever, dyspnea, pneumonia (Chest CT)	CRP 0.8, 20 ESR 15, 44	RF 22 <14 ACPA 22 <17	Antibióticos. HCQ MTX, IV GC oral GC, anti-TNF	Improved
8. Slouma M et al 2022 Egypt Rheumatol	72/F	8 weeks, polyarthritis sinovitis US doppler	CRP 108 ESR 95 Elevated IL-6	RF 128 ACPA 200, ANA+	GC MTX	Improved
9. Roongta R et al 2022 Ann Rheum Dis	56/F	2 weeks, arthritis	Elevated CRP, ESR	RF 131, ACPA 35	MTX	Improved
10. Deeb M et al 2022, Ir Med J	63/M	8 weeks, fever, arthritis	PCR 113 VSG 73	FR 133 ACPA 64	MTX GC	Improved
11. Fernandez-Avila et al 2022 Rev Colomb Reumatol Family hypothyroidism	44/F	18 days, arthritis, cough, ageusia, anosmia	CRP< 1 ESR 49	RF 199 ACPA 1132	MTX GC	Improved
12. Bouzid S et al 2022, Clin Case Rep Family RA	38/F	4 weeks, fever, cough, symmetric poliartthritis MRI, synovitis	PCR 4.3, ESR 13	FR 62, ACPA 237 ANA+	MTX NSAIDs	Improved
13. Oscan E et al 2022 Kastamonu Med	23/F	2 weeks, polyarthritis and myalgias	CRP 82 ESR 41	RF 116, ACPA>200	GC Leflunomide	Improved Follow-up 10 months
14. Ljilja A et al 2022 Infektol Glasn	60/M	6 weeks, poliartthritis, cough, pneumonía Fever	CRP 15 ESR 9	RF 50 ACPA 34	GC NSAIDs	Improved
15. Yadav S et al 2023 Am J Case Rep	45/F	4 weeks, polyarthritis, fever	CRP 9 IL-6, 5.6 <2	RF 120 ACPA 23	GC, MTX anti-TNF	Improved
16. Bouden S et al 2024 Mediter J Rheumatol	27/F	8 weeks, polyarthritis	CRP 53	RF 62, ACPA 192, ANA+	GC, MTX	Improved
17	55/F	2 weeks, arthritis	PCR 54	RF 45, ANA+ ACPA, no tested	GC, MTX	Improved

18 Family RA	62/F	8 weeks, arthritis	CRP 23	RF 142 ACPA 104	GC, MTX	Improved
19. De Carvalho JF et al, 2024 Mediter J Rheumatol	37/F	12 weeks, cough, fever, polyarthritis.	CRP 48	RF 68 ACPA 200, ANA+	MTX	Improved
20. Tsugura et al. Case Rep Infec Dis 2026	50/F	4 weeks, fever, pneumonia (Chest CT), arthritis	ESR 93	RF 108 ACPA 9.7	Antibiotics IV GC GC	Improved
21. Elhommosani MR et al Next Research, 2026	46/F	Polyarthritis 3 weeks	16	ACPA 71 0, ANA+	MTX	Improved
Family history of RA						
MTX, methotrexate, GC glucocorticoid, hydroxychloroquine, RF rheumatoid factor, ACPA anti-citrullinated protein antibody						
CRP C-reactive protein, ESR erythrocyte sedimentation rate, ANA, antinuclear antibodies						

Table 2: Clinical and paraclinical characteristics of patients with RA who received COVID-19 vaccine.		
Author (es)	Age/	Interval between vaccination and first symptoms
1. Baimukhamedov C, et al. 2021 Int J Rheumatol Dis	38/F	20 days after the first dose Sputnik-5, adenovirus vector vaccine). Polyarthritis
2. Watanabe T et al Front Immunol, 2022 Family RA	53/M	30 days after the 2nd dose (mARN) MRI knee synovitis
3. Yonezawa H et al Intern Med, 2022 RF/ACPA neg.	54/M	1 day after the 2nd dose mARN Polyarthritis
4. Barman B et al Indian J Rheumatol 2022	38/F	Chad0x1 After the 1st dose, arthritis
5. Abe N et al, 2022 Mayo Clin Proc Type 1 DM Hashimoto thyroiditis	77/F	Arthritis after the 1st dose mARN
6. Gang B et al. 2022, J Med Virol	60/F	10 days after the 2nd dose (ChAd0x1). Polyarthritis Astrazeneca
7. Singh R et al 2022, J Med Virol	50/F	7 days after 2nd dose BBV152 Polyarthritis Nodules
8. Nahra V et al 2022 Cureaus	74/M	10 days after the 2nd dose Pfizer (mRNA). Polyarthritis
9. Safary A et al Int Immunopharmacol 2022	85/F	7 days after the 1st dose, symmetric arthritis of small joints Sinopharm (Inactivated virus)
10	58/F	10 days after the 1st dose, symmetric arthritis, AztraZeneca (Viral vector vaccine)
11. Chang B et al. 2022	60s/F	10 days after 2nd dose ChAd0xl-S polyarthritis Astrazeneca
12. Van DerVeer et al, J Clin Rheumatol, 2023 Family lupus	36/F	After 2nd dose (mRNA) Polyarthritis
13. Type 1 DM	72/F	1 day after the 2nd dose (mRNA, Pfizer). Polyarthritis
14. Almouslem A. et al. 2024 Omen Med J hypothyroidism	32/F	2 days after the 2nd dose (mRNA, Pfizer). Polyarthritis and myalgias
15. Matsuda M et al. 2024 Immunol Med	79/F	2 days after the 2nd dose (mRNA Pfizer). Polyarthritis

DISCUSSION

This current study identified 36` cases of de novo RA following SARS-CoV-2 infection and after COVID-19 vaccination with a higher incidence in women. The presence of symmetric arthritis predominantly of small joints, inflammatory markers, high titers of ACPA and/or RF, and ≥ 6 weeks of symptoms' duration, fulfill the 2010 ACR/EULAR classification criteria for RA.^[1] In RA, autoantibodies represent a diagnostic and prognostic tool. It is well known that RF, ACPA, and anti-peptidyl arginine deiminase (PADI) 4/2 antibody (enzyme involved in the conversion of the amino acid arginine to citrulline) can be present before the clinical onset of RA.^[13-15] These findings suggest that autoantibodies were present subclinically (subclinical autoimmunity) and that

the viral infection or the COVID-19 vaccine unmasked the disease. However, upon routine examination, two patients tested negative for ACPA or rheumatoid factor up to 3 months prior to the onset of disease symptoms or vaccination, yet high titers of rheumatoid factor and ACPA were found at the time of admission.

The infection following SARS-CoV-2 or after the COVID-19 immunization, hyperactive immune response, and the molecular mimicry between viral peptides and host tissue peptides are prerequisites for the autoimmune disease triangle.^[16] The hyperactivity of the immune system and acute hyperinflammation justify treatment with NSAIDs, glucocorticoids, methotrexate, biological agents, and other disease-modifying antirheumatic drugs.

Patients with pneumonia required antibiotics. Of 36 cases, there was only one death.

CONCLUSION

This study identified 36 patients with new-onset RA who met ACR/EULAR classification criteria for RA following SARS-CoV-2 infection or COVID-19 vaccination. The mechanisms underlying this link can be explained by molecular mimicry, indirect activation of autoreactive T cells, and viral persistence—acting either alone or in combination.^[17]

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