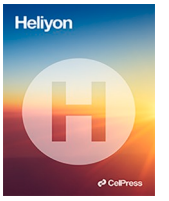
Heliyon 10 (2024) e24982

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

# Long-term rheumatoid manifestations as a consequence of COVID-19 and/or vaccination: A case report after a 2-year follow-up

Mona Sadat Larijani [a], Mohammad Banifazl [b], Afsaneh Karami [c], Amitis Ramezani [a,*]

[a] Clinical Research Department, Pasteur Institute of Iran, Tehran, Iran
[b] Iranian Society for Support of Patients with Infectious Disease, Tehran, Iran
[c] Department of Infectious Disease, Zanjan University of Medical Sciences, Zanjan, Iran

ARTICLE INFO

*Keywords:*
COVID-19
Late adverse events
Long-COVID
Vaccine
Case report

ABSTRACT

COVID-19 is now established as a multi-organ involvement disease with a broad range of manifestations. Identification of post-acute COVID-19 incidence is critical according to increasing number of late symptoms reports. Hereby, we report a case with a past history of COVID-19 who presented different manifestations including osteoarticular and neurological involvement within a long-term follow-up. The organs involvement initiated lately after primary vaccinations (with inactivated vaccine) and lasted few months without any pre-existing medical condition. However, upon the completion of the vaccine schedule and receiving a protein subunit vaccine, PastoCovac Plus, as a booster, the symptoms improved substantially and resolved, though in the reinfection episode partial, reoccurrence was recorded. This presentation can be a challenging issue owing to the fact that the majority of global population are vaccinated and also experience COVID-19 in this era and sometimes differentiation between consequences of the virus as post COVID-19 or the vaccination side effects is difficult.

## 1. Introduction

COVID-19 pandemic was firstly considered as an acute lung infection which then was proved to affect multiple organs possibly in different timetable. The infected individuals normally recover from acute symptoms, however, some people experience late events which might last for weeks or months post-acute phase known as post-COVID-19 syndrome (PCS) or long-COVID-19 [1]. The PCS could develop multiple disorders such as fatigue, myalgia, arthralgia, gastrointestinal disturbance, headache, memory loss, depression and etc. COVID-19 vaccination has had great impact on prevention of severe form of the disease and pandemic control, though it has been shown that vaccination may induce or trigger some disorders [2].

Nevertheless, the impact of vaccination against COVID-19 on persistent symptoms is less discussed [3]. It has been shown that vaccination might trigger some long-term symptoms through triggering pre-existing diseases or onset of them though the exact mechanism is yet under investigation. A probable cause could be molecular mimicry existence between synovial membrane and the virus epitopes [4,5]. The majority of vaccine inflammatory arthritis onset occur up to seven days post administration, however, they can occur later as well [6,7].

* Corresponding author. No:69, Pasteur Ave, Clinical Research Department, Pasteur Institute of Iran, Tehran, 1316943551, Iran.
*E-mail address:* amitisramezani@hotmail.com (A. Ramezani).

https://doi.org/10.1016/j.heliyon.2024.e24982
Received 17 July 2023; Received in revised form 7 October 2023; Accepted 17 January 2024
Available online 18 January 2024

Despite some reports of autoimmune manifestation after COVID-19/vaccination, the mechanism of flare up is not clear. Considering the fact that all the COVID-19 vaccine platforms include the whole inactivated viral particle or encodes its epitopic part like Spike protein, one of these components might potential effect on the autoimmune response [8].

By the successfully developed vaccine types against SARS-CoV-2 through different platforms, studies provided vaccine efficacy and also long COVID-19 symptoms improvement as well [9,10]. PastoCovac Plus is a protein subunit vaccine composing of highly immunogenic part of RBD which is approved as the booster shot for all primary vaccine doses in Iran with successful safety profile [11].

COVXIN (development name, BBV152) is a whole inactivated virus-based COVID-19 vaccine which was developed by Bharat Biotech (India).This vaccine was validated by the World Health Organization (WHO) on November 3, 2021 for emergency use. As of January 31, 2022, COVAXIN has been granted emergency use approval in 13 countries including Iran [12,13].

In this study, a full presentation of long-term rheumatoid and neurologic symptoms of a case is investigated in each episode of COVID-19 incidence and vaccination schedule.

### *1.1. Case presentation*

The informed consent was obtained from the patient for the publication regarding the image, clinical data and demographics included in the manuscript.

A 52-year-old woman with normal BMI (23.5) and no serious underlying disease except history of controlled asthma (no need to receiving medicine) and a history of routinely applying medicines including rosuvastatin (20 mg) once a day, experienced moderate severity symptoms of COVID-19 including fever, weakness, headache, fatigue and dry cough lasted for three weeks in Oct 2020 with no requirement of hospital admission. The first COVID-19 incidence was during D614G clade peak in Iran. The applied medicine included naproxen and supportive medicine during the first week. Prednisolone (5 mg, b.i.d) and Sovodok (Sofosbuvir plus Daclatasvir, per day) were applied following cough worsening by the end of the second week.

A few months after COVID-19 incidence and shortly after the second dose of vaccination (inactivated vaccine, BBV152 Baharat Biotech), some interphalangeal joint involvements, specifically at distal interphalangeal joint (DIP) of the left index finger manifested which then made a small red node and a mild joint deformity with pain progression to other finger joints (Fig. 1). This joint involvement then was followed by acute back pain (without any reasons). The acute back pain presented severely and interfered with some functions. Then, paresthesia (neurologic involvement) started at the same location of the back pain, persistently.

Moreover, she complained of morning stiffness and knee pain which were felt strongly at the beginning of the day but less irritating during the day. Finally, the multi-joint involvements tend to accumulate around the elbow. Then some supportive medicines were provided and resulted in temporary relief without complete resolution.

Later, by completion of the vaccine schedule and receiving a booster, the symptoms substantially resolved.

In the next episode, far later than the first infection, the case experienced reinfection in March 2023 during Omicron (XBB variant) peak in Iran. The symptoms including severe sore throat, cough and fever lasted one week with no need of specific care but supportive medicine. After this episode, DIP inflammation and back paresthesia reoccurred though in a milder form than the first episode. Table 1 simply presents COVID-19 course in the case.

SARS-CoV-2 PCR test was done to confirm the infection at the start of disease and the negative PCR result obtained 3 weeks post COIVD-19 initiation. SARS-CoV-2 IgG was positive against Spike protein at the same time. The laboratory tests were done to evaluate any associated factors and the tests were done three times after recovery of COVID-19. Total leucocyte count was within the normal range as 6.62 cells/μl. C-reactive protein (CRP) was also normal. To investigate the presence of rheumatologic diseases, rheumatoid factor (RF) was evaluated which was negative. Anti-cyclic citrullinated peptide (anti-CCP) antibodies, Anti-PR3 (C.A.N.C.A) and perinuclear anti-neutrophil cytoplasmic antibodies (P.A.N.C.A) were measured which all were within the normal range (Table 2). These tests were done three times during the follow-up and the last was performed in Jun 2022 and the normal values were detected each time. Table 2 presents the first laboratory tests results. Similar results were recorded in other tests too.

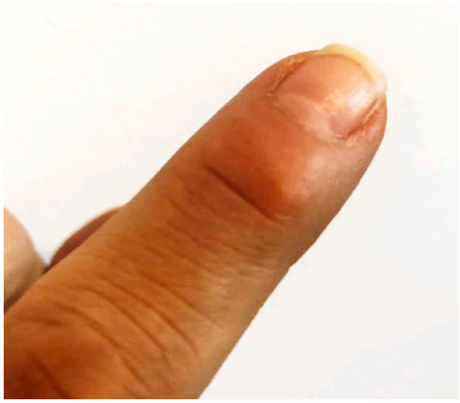


**Fig. 1.** Hebreden node at DIP of the left index finger of the case.

**Table 1**
The case trend during the long-term follow-up.

| 2020 | 2020 | 2021 | 2021 | 2021 | 2021 | 2022 | 2023 | 2023 |
|---|---|---|---|---|---|---|---|---|
| Oct 4th First COVID-19 incidence Confirmed by PCR test | Oct 25th Negative PCR test | May 22nd 1st dose of COVAXIN | Jun 19th 2nd dose of COVAXIN | Jul Neurologic and rheumatoid manifestation | Oct 25th PastoCovac booster shot | Feb Symptoms improvement | Mar 16th Reinfection Confirmed by PCR test | Apr Symptoms reoccurrence |

Lab tests during Follow-up.

**Table 2**
Laboratory features during the follow-up.

| Feature | Value | Unit | Reference Value |
|---|---|---|---|
| R.F | Negative | – | Negative |
| C.A.N.C.A[a] | 0.5 | u/ml | ≤ 18 normal |
| P.A.N.C.A[b] | 1.7 | u/ml | ≤ 18 normal |
| Anti CCP | 0.5 | u/ml | <5 normal |
| Fibrinogen | 1.16 | g/l | 2–4 g/l |
| FBS | 111 | mg/dl | 70–110 |
| Urea | 22 | mg/dl | 10–50 |
| Creatinine | 0.9 | mg/dl | male: 0.9–1.3 female: 0.6–1.1 |
| Uric Acid | 3.0 | mg/dl | male: 3.5–7.2 female: 2.6–6 |
| Cholesterol | 172 | mg/dl | up to 200 |
| Triglyceride | 70 | mg/dl | up to 200 |
| HDL | 50 | mg/dl | more than 34 |
| LDL | 108 | mg/dl | up to 130 |
| AST(SGOT) | 28 | IU/Lit | 5–40 |
| ALT(SGPT) | 33 | IU/Lit | 5–40 |
| CPK[c] | 89 | IU/Lit | 24–200 |
| Alkaline Phosphatase | 218 | IU/Lit | male:80-306 female: 64-306 |
| Quantitative CRP | 3 | Mg/l | Adult <10 |

[a] Anti-PR3.
[b] Perinuclear anti-neutrophil cytoplasmic antibodies.
[c] Creatine phosphokinase.

### *1.2. Treatment*

In order to treat the back pain, methocarbamol (t.d.s), acetaminophen (500 mg t d.s) and celecoxib 200 mg (b d) were taken for back pain. Moreover, prednisolone (5 mg, once a day) was regularly used for 1 week along with naproxen (250 mg, once a day) to treat the DIP inflammation and knee pain. Nevertheless, the applied medicines only provided temporary relief and did not result in complete resolution and these back pain and paresthesia stayed for at least 7 months.

The symptoms started to manifest one month after the second dose of COVAXIN, though the vaccine itself, led to no reactogenicity except mild topical pain. Four months post the second dose, the case got the booster shot of a different vaccine type, PastoCovac Plus, when she still was suffering from the symptoms on-and-off and the applied treatment only provided her with temporary relief.

## 2. Discussion

Following SARS-CoV-2 outbreak which eventually was managed by developed vaccination, the world has faced another crisis by progress or persistence of COVID-19 symptoms, called long-COVID. What has made this issue trickier in this era, is that the main cause of some late disorders is not easily distinguishable according to the massive immunization against the recent pandemic of people who may still develop the infection. It is to say that some complications even late could be a possible consequence of both COVID-19 infection and/or vaccination.

There have been few studies which shared rheumatology case reports as COVID-19 consequences. Here, we investigated sero-negative rheumatologic case with past history of COVID-19 who experienced different osteoarticular symptoms after vaccination.

A 39-year-old Saudi Arabian woman was reported with no underlying disease who developed pain in DIP and PIP three weeks after the infection. Similar to the presented care here, all the laboratory tests were in the normal range including RF, anti-CPP and CRP. NSAIDs application for two months led to symptoms improvement [14].

In another study, reactive arthritis was reported in a 53-year-old woman four months after COVID-19 infection. Prednisolone and also NSAIDs medicines were applied for her treatment which significantly improved the symptoms [15]. In their study the level of CRP

reported high, however, in our study the CRP level of the case was in normal range.

The mechanism through which SARS-CoV-2 might cause articular/neurological involvements, is not exactly clear. The molecular mimicry existence between synovial membrane and viral epitopes cause local inflammation or the presence of circulating immune complexes or possible viral localization on joint tissue could be assumed as possible causes [16,17].

In addition to the possibility of late COVID-19 manifestation, it has been shown that vaccination might trigger some related symptoms. The majority of vaccine inflammatory arthritis onset occur up to seven days post administration, however, they can occur later as well [18].

Some studies have proposed possible disease development of rheumatoid arthritis following COVID-19 vaccination. Firstly, it could trigger pre-existing rheumatoid manifestation. A 55-year-old male reported by Terracina et al., developed rheumatoid arthritis 12 hours after receiving the second dose of the COVID-19 vaccine. The administrated vaccine was BNT162b2 which contains mRNA encoding spike protein encapsulated in lipid nanoparticles, in addition to other stabilizing components. Thus, each component might have affected the disease [8]. Moreover, it could be an emergence of de novo disease. For instance, a new onset of rheumatoid arthritis was reported by Watanabe et al., in a 53-year-old male one month after covid-19 vaccine [19]. Pro-inflammatory cytokine responses have strong impact on autoimmune disorders development. Therefore, it is likely that COVID-19 vaccination can trigger pro-inflammatory cytokines production [20,21].

What makes our case an interesting topic to discuss is that she developed osteoarticular disorders after 2 doses of inactivated virus-based vaccine, in which both large and small joints (elbow, knee and hand fingers) were affected with no related diseases but previous history of COVID-19. Reports of autoimmune diseases like rheumatoid disorder initiation after COVID-19 vaccination are on the go, though such a wide range of symptoms is rare.

Two doses of BNT162b2 led to new-onset of rheumatoid arthritis in a case whose laboratory positive tests were in favor of the rheumatoid progress after vaccination [19].

However, the associated laboratory tests of our case was done three times with 1–2 months interval which all had negative results. Moreover, NSAID and steroid medicines led to partial improvement. This case achieved significant recovery post the protein subunit booster shot, though this spontaneous improvement could also stem from time passing.

According to the well-developed approved vaccines profiles in which inactivated, adeno virus and mRNA ones are leading, protein subunit vaccines are less discussed. Therefore, the heterologous boosting regimen in this case could have the potency to reduce the inflammation either caused by SARS-CoV-2 or COVAXIN immunization.

Taken together, a certain differentiation between COVID-19 and its vaccination is not possible in this case, the partial return of the symptoms in the reinfection time highlight post-COVID as the main cause and it is more likely to be a late onset post-CVOID-19. However, the vaccine could also be considered as a trigger of the symptoms initiation.

## 3. Conclusion

This study has the advantage of long-term follow-up of more than 2 years which presents osteoarticular and neurological presentation in each episode of COVID-19 infections and vaccinations. However, this presentation is a challenging issue due to the fact that the majority of worldwide population are vaccinated and also experienced COVID-19 infection in this era and it makes difficult differentiation post-COVID-19 from the vaccine late effects.

Furthermore, the impact of a protein subunit booster shot, PastoCovac Plus, is firstly noted. The possible impact of protein subunit vaccine against post COVID is recommended for further follow-up design with a large study population in order to understand and clarify the potential mechanisms of vaccines in prevention and/or reduction of long-COVID symptoms.

## Data availability statement

All the data are included in the manuscript.

## Ethical approval

The study was approved by Pasteur Institute of Iran Ethical committee under IR.PII.REC.1399.009 ethical code.

## Additional information

No additional information is available for this paper.

## CRediT authorship contribution statement

**Mona Sadat Larijani:** Data curation, Writing – original draft, Writing – review & editing. **Mohammad Banifazl:** Methodology, Supervision. **Afsaneh Karami:** Methodology, Validation. **Amitis Ramezani:** Conceptualization, Methodology, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We do appreciate Pasteur Institute of Iran to support this study.

## References

[1] M. Sadat Larijani, et al., Characterization of long COVID-19 manifestations and its associated factors: a prospective cohort study from Iran, Microb. Pathog. 169 (2022) 105618.
[2] M. Sadat Larijani, et al., Assessment of Long-Term Adverse Events Regarding Different COVID-19 Vaccine Regimens within an 18-month Follow-Up Study, Pathogens and Disease, 2023, p. ftad010.
[3] T.C.D.C. Nascimento, et al., Vaccination status and long COVID symptoms in patients discharged from hospital, Sci. Rep. 13 (1) (2023) 2481.
[4] J. Liu, H. Wu, S.L. Xia, New-onset arthritis following COVID-19 vaccination: a systematic review of case reports, Vaccines 11 (3) (2023).
[5] M.A. Golstein, O. Fagnart, S.D. Steinfeld, Reactive arthritis after COVID-19 vaccination: 17 cases, Rheumatology (2023) kead169.
[6] Sadat Larijani, M., et al., A landscape on disorders following different COVID-19 vaccination: a systematic review of Iranian case reports, in *Preprints*2023, Preprints..
[7] E. Lebowitz, J.S. Kim, C. Magro, Reactive arthritis following COVID-19 vaccination with BNT162b2, JAAD Case Reports 24 (2022) 108–111.
[8] K.A. Terracina, F.K. Tan, Flare of rheumatoid arthritis after COVID-19 vaccination, Lancet Rheumatol. 3 (7) (2021) e469–e470.
[9] A. Watanabe, et al., Protective effect of COVID-19 vaccination against long COVID syndrome: a systematic review and meta-analysis, Vaccine 41 (11) (2023) 1783–1790.
[10] B. Abu Hamdh, Z. Nazzal, A prospective cohort study assessing the relationship between long-COVID symptom incidence in COVID-19 patients and COVID-19 vaccination, Sci. Rep. 13 (1) (2023) 4896.
[11] A. Ramezani, et al., PastoCovac and PastoCovac Plus as protein subunit COVID-19 vaccines led to great humoral immune responses in BBIP-CorV immunized individuals, Sci. Rep. 13 (1) (2023) 8065.
[12] COVAXIN® (BBV152) – Inactivated, COVID-19 Vaccine, World Health Organization.
[13] B. Farahmand, et al., Evaluation of PastoCovac plus vaccine as a booster dose on vaccinated individuals with inactivated COVID-19 vaccine, Heliyon 9 (10) (2023) e20555.
[14] I. Jali, Reactive arthritis after COVID-19 infection, Cureus 12 (11) (2020).
[15] B.L. Hønge, M.-L.F. Hermansen, M. Storgaard, Reactive arthritis after COVID-19, BMJ Case Rep. 14 (3) (2021) e241375.
[16] M. Gasparotto, et al., Post-COVID-19 arthritis: a case report and literature review, Clin. Rheumatol. 40 (8) (2021) 3357–3362.
[17] B. Silva Andrade, et al., Long-COVID and post-COVID Health complications: an up-to-date review on clinical conditions and their possible molecular mechanisms, Viruses 13 (4) (2021) 700.
[18] S.M. Mung, et al., Inflammatory arthritis associated with COVID-19 vaccination, Cureus 15 (3) (2023) e35951.
[19] T. Watanabe, et al., Case report: new-onset rheumatoid arthritis following COVID-19 vaccination, Front. Immunol. 13 (2022) 859926.
[20] J.R. Teijaro, D.L. Farber, COVID-19 vaccines: modes of immune activation and future challenges, Nat. Rev. Immunol. 21 (4) (2021) 195–197.
[21] U. Sahin, K. Karikó, Ö. Türeci, mRNA-based therapeutics–developing a new class of drugs, Nat. Rev. Drug Discov. 13 (10) (2014) 759–780.