

Case Report

An Unusual Case of “Conjugal” Polymyalgia Rheumatica after SARS-CoV-2 Vaccination

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Abstract: The rare occurrence of polymyalgia rheumatica (PMR) in married couples has been reported in the literature. Susceptibility to PMR is contributed by genetic and environmental factors and cases of PMR developing after influenza vaccine have also been described, in a debated phenomenon known as ‘ASIA’ syndrome. We report the case of two cohabitating married patients developing PMR few weeks after the first dose of ChAdOx1-S SARS-CoV-2 vaccine. Both patients presented with typical symptoms suggestive of PMR. Laboratory findings and ultrasound examination confirmed the diagnosis. Glucocorticoid therapy led to rapid improvement of symptoms. Anti-receptor-binding domain IgG titre was tested and, eight weeks after vaccination, both patients showed no antibody response. It has been suggested that vaccines might trigger autoimmune or inflammatory states in predisposed individuals and various hypotheses have been made regarding the pathogenesis of PMR. Although the causative effect of vaccines cannot be determined, the close temporal correlation observed in our case supports the potential role of environmental factors in triggering the onset of PMR. However, the literature indicates that post-COVID19 vaccination immune-mediated or inflammatory adverse events are extremely rare and vaccination should be encouraged since the benefit largely outweighs possible risks.

Keywords: polymyalgia rheumatica; COVID-19; vaccine; ASIA syndrome; couple



Citation: Vanni, E.; Ciaffi, J.; Mancarella, L.; Ursini, F. An Unusual Case of “Conjugal” Polymyalgia Rheumatica after SARS-CoV-2 Vaccination. *Rheumato* **2021**, *1*, 17–21. <https://doi.org/10.3390/rheumato1010004>

Academic Editor: Bruce M. Rothschild

Received: 21 October 2021

Accepted: 15 November 2021

Published: 30 November 2021

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1. Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disorder characterized by severe bilateral muscle pain, usually in the neck, shoulders and pelvic girdles, associated with prolonged morning stiffness. Additionally, constitutional symptoms such as fatigue and malaise may also be present. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often raised. PMR affects almost exclusively adults older than 50 years and a geographical gradient with incidence increasing from southern to northern countries has been proposed [1]. In a considerable proportion of patients, PMR can be associated with giant cell arteritis (GCA), a large vessel vasculitis. Rapid improvement of symptoms is obtained with glucocorticoid therapy, but relapses are common when the dose is tapered [2]. Susceptibility to PMR is contributed by genetic and environmental factors, with seasonal variations and geographical trends in incidence supporting the hypothesis of infectious triggers [3].

Even if the occurrence of PMR affecting both members of an unrelated and cohabitating married couple is rare, previous cases have been described in the literature [4–11]. The almost simultaneous onset of these cases supports the hypothesis that common exposure to an unknown environmental risk factor could be partially responsible for the development of the disease. Additionally, several cases of familial aggregation of both PMR and GCA have been described, including four siblings and a genetically unrelated husband within the same family [12,13]. In both studies, the hypothesis was that environmental triggers, probably of infectious origin, had contributed to the synchronous disease onset.

Furthermore, rare cases of PMR developing after influenza vaccine have been described [14], suggesting a role of vaccines in promoting autoimmunity and inflammation in susceptible individuals, in a debated phenomenon described by Shoenfeld et al. as ‘ASIA’ syndrome (autoimmune/inflammatory syndrome induced by adjuvants) [15]. Moreover, a disease flare and a new case of PMR have recently been reported after BNT162b2 SARS-CoV-2 vaccine (Comirnaty, Pfizer-BioNTech) [16]. Here, we report the case of two unrelated and cohabitating married patients developing PMR after the first dose of ChAdOx1-S SARS-CoV-2 vaccine (Vaxzevria, Oxford-AstraZeneca).

2. Case Presentation

A 68-year-old Caucasian man presented to our rheumatology outpatient clinic in June 2021. The patient had been well until two weeks before, when bilateral shoulder pain developed. After a few days, he started to complain about morning stiffness and fatigue. Treatment with non-steroidal anti-inflammatory drugs was ineffective. The patient was then visited by his primary care physician and referred to the rheumatology clinic for further evaluation. The patient had a BMI of 27.2 kg/m² and was employed in an insurance company. He had quit smoking 10 years earlier, and he consumed 8–10 alcoholic drinks per week. The patient’s medical history included systemic hypertension, impaired glucose tolerance and gastroesophageal reflux disease. Medications included ramipril, hydrochlorothiazide, metformin and omeprazole. He reported an allergy to amoxicillin, which had caused a rash. Physical examination was notable for the limited and painful range of motion of the upper limbs, with swelling of the right shoulder. A shoulder ultrasound was performed, revealing bilateral inflammation, with left biceps tenosynovitis and large right subacromial-subdeltoid bursitis (Figure 1A,B). Acute phase reactants were elevated, with ESR 57 mm/h (reference value, <32 mm/h) and CRP 7.5 mg/dL (reference value, <0.5 mg/dL). Rheumatoid factor (RF), antinuclear antibodies (ANA) and anticyclic citrullinated peptide antibodies (ACPA) were negative. A diagnosis of PMR was made. There were no signs or symptoms of GCA and the patient denied jaw claudication, scalp tenderness and headache. Treatment with prednisone was initiated. At the four-week follow-up visit, symptoms had dramatically improved but, curiously, the patient reported that his wife had developed similar complaints.

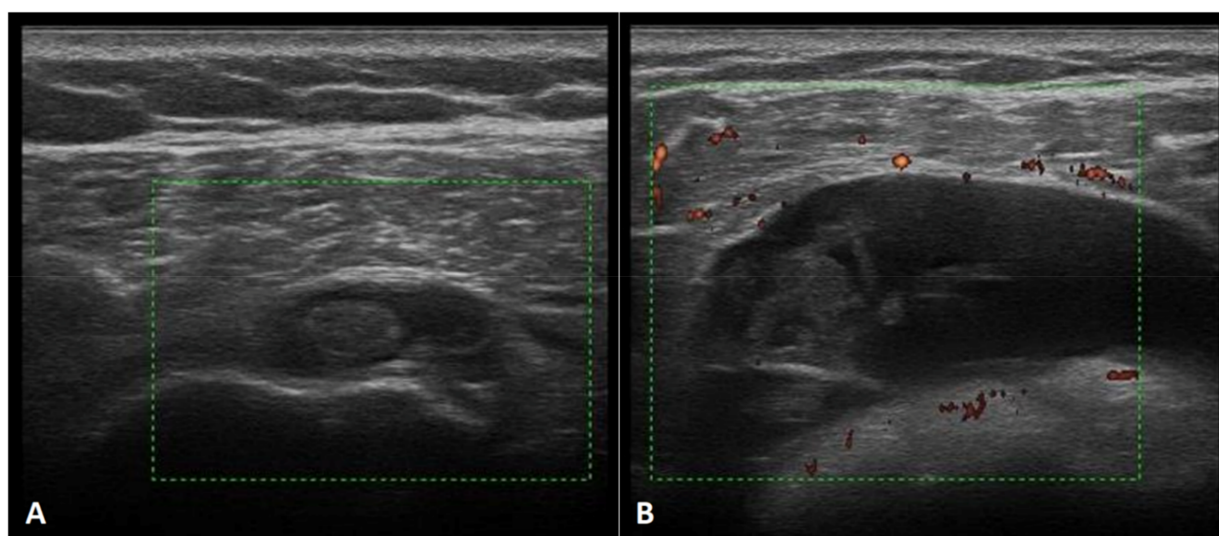


Figure 1. (A): transverse scan over the left shoulder showing tenosynovitis of the long head of the biceps tendon. (B): longitudinal scan over the right shoulder showing large effusion of the subacromial-subdeltoid bursa with synovial hypertrophy and positive Power-Doppler signal.

The wife, a 66-year-old Caucasian woman, had a BMI of 24.6 kg/m² and was employed as a high-school teacher. She did not smoke cigarettes or drink alcohol. Her medical

history was notable for dyslipidaemia and osteoporosis. Medications included simvastatin, alendronate, vitamin D and calcium supplements. There were no known adverse reactions to medications. The patient reported shoulder and neck pain associated with prolonged morning stiffness. The symptom started to develop one week before the current evaluation. Physical examination revealed a limited range of motion of the upper limbs but, in this case, ultrasound did not show inflammatory findings. Laboratory investigations showed raised ESR of 71 mm/h (reference value < 32 mm/h) and CRP of 9.7 mg/dL (reference value < 0.5 mg/dL). RF, ANA and ACPA were negative. Signs or symptoms of GCA were absent. A diagnosis of PMR was made. In both cases, the 2012 European League Against Rheumatism/American College of Rheumatology Provisional Classification Criteria were fulfilled [17]. Again, treatment with prednisone was highly effective and symptoms were fully controlled within two weeks.

The couple, married for nearly 40 years, did not have any blood relation, had always lived in the same city, had not travelled in the last two years and denied previous exposure to infectious agents, including SARS-CoV-2. No significant changes in their daily activities were reported. However, both had received the first dose of ChAdOx1-S SARS-CoV-2 vaccine (Vaxzevria, Oxford-AstraZeneca) in May. Strikingly, the wife had received the injection right after her husband in the same room, from the same batch and, presumably, from the same vial. Husband and wife developed symptoms suggestive of PMR, respectively, 20 and 45 days after the vaccination. In consideration of the recent onset of PMR and of the ongoing glucocorticoid therapy, the couple was advised to delay the second dose of vaccine. At time of writing this report, 23 weeks after the first vaccination, PMR was in remission and the patients were tapering prednisone. They had not yet received the second dose, with the aim of scheduling it after discontinuation of glucocorticoid therapy.

Interestingly, the anti-receptor-binding domain IgG titre was tested through chemiluminescent immunoassay (CLIA) eight weeks after vaccination and both patients showed no antibody response. The husband had a titre of 13.08 BAU/mL and the wife of 18.75 BAU/mL (positive > 21.8 BAU/mL).

3. Discussion

Previous reports of PMR in married couples described in the literature suggested the potential role of environmental factors in the pathogenesis of the disease. Although the exact triggers have not yet been clearly identified, various hypotheses have been made. For instance, the possible influence of specific infectious agents such as *Mycoplasma pneumoniae*, Parvovirus B19, *Chlamydia pneumoniae*, human parainfluenza type I virus and herpesvirus, has been suggested, mainly based on epidemiological evidence [1,3]. We could not identify any infectious or environmental trigger in the two married patients and we cannot exclude that the almost simultaneous onset of PMR symptoms occurred accidentally. It should also be highlighted that in our case we observed a merely temporal association between SARS-CoV-2 vaccination and development of PMR. The available data do not allow to draw any conclusions about a causal relationship between the two events.

However, previous studies assumed the possible association between PMR and vaccination. According to Shoenfeld et al. [15], adjuvants may be responsible for inducing post-vaccination adverse events such as myalgia, arthritis, neuronal damage, fatigue, encephalitis and vasculitis, in the so-called 'ASIA' syndrome. ASIA syndrome is a spectrum of presumably immune-mediated diseases secondary to exposure to an adjuvant, associated with an individual genetic predisposition. A review published in 2012 described 21 cases of healthy subjects who developed GCA/PMR within 3 months of influenza vaccination and the possible role of both genetic predisposition and adjuvants was pointed out [18]. A similar case of a female patient presenting a significant relapse of PMR after adjuvanted influenza vaccination has also been reported [14].

According to Watad et al. [19], despite being an extremely rare event, the link between vaccination and onset of autoimmune/autoinflammatory diseases has a solid basis. The authors analysed 500 cases underlining the fact that adjuvants that stimulate innate immune

components mostly lead to autoinflammatory disorders, such as GCA, PMR and Crohn's disease, whereas adjuvants that activate the adaptive immune system are more often responsible for autoimmune diseases, such as undifferentiated connective tissue disease (UCTD) and Sjögren's syndrome. Data also suggested that exposure to influenza vaccination was more often linked to autoinflammatory diseases, while autoimmune diseases were significantly associated with Hepatitis B Virus (HBV) vaccine.

SARS-CoV-2 vaccines, however, are different from previous vaccines and a key role is played by the intrinsic adjuvanticity of vaccine mRNA or DNA. Although data are still limited, a first series of immune-mediated disease flares or new-onset disease temporally associated with SARS-CoV-2 vaccination has been described [16], including various diseases such as inflammatory arthritis, Behcet's disease and systemic lupus erythematosus (SLE). Among these, one new case of PMR was reported 3 days after receiving the first dose of BNT162b2 SARS-CoV-2 vaccine (Comirnaty, Pfizer-BioNTech), which rapidly responded to steroid therapy with immediate symptom improvement. Furthermore, cases of subacute thyroiditis and of Graves' disease as part of ASIA syndrome in patients receiving different COVID-19 vaccines have been reported [20–24]. Nevertheless, it is important to emphasize that vaccine immune-mediated adverse events remain extremely rare and should not discourage vaccination, as the benefit largely outweighs possible risks.

4. Conclusions

In conclusion, we observed an unusual case of “conjugal” PMR developed in a close temporal relationship with SARS-CoV-2 vaccination. Although in our case a causative role of the vaccine on symptoms' onset cannot be ascertained, the available literature supports the hypothesis that vaccines might alter the delicate balance of immune homeostasis and trigger autoimmune or inflammatory states in predisposed individuals. The mechanisms behind post-vaccine PMR are still unknown but, at least in our case, these are not associated with the presence of adjuvant components and not apparently related to the immunogenicity of the vaccine measured by quantitative antibody assays.

Author Contributions: Conceptualization, J.C., L.M. and F.U.; methodology, E.V.; validation, J.C. and F.U.; investigation, E.V. and L.M.; resources, E.V.; data curation, L.M.; writing—original draft preparation, E.V. and J.C.; writing—review and editing, E.V., J.C., L.M. and F.U.; supervision, F.U.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study because not required by our Institution for case reports.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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