Polymyalgia rheumatica and polymyalgia-like syndromes as adverse events following COVID-19 vaccines: working notes from a narrative review of published literature

Ciro Manzo¹, Alberto Castagna², Marco Isetta³

¹Azienda Sanitaria Locale Napoli 3 sud, Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic, Sant’Agnello, Naples, Italy
²Azienda Sanitaria Provinciale Catanzaro, Primary Care Department, Soverato, Catanzaro, Italy
³Central and North West London NHS Trust, England

Abstract

Since the 1990s, polymyalgia rheumatica (PMR) has been reported as a possible adverse event following immunization (AEFI). The aim of this narrative review is to provide an overview of PMR (and PMR-like syndromes) following the most common types of COVID-19 vaccines, namely mRNA (tozinameran and mRNA-1273) and adenovirus-vectored (ChAdOx1-S) vaccines. To date, published literature reports few cases of PMR as vaccine-linked AEFI. Yet Vigibase, the WHO pharmacovigilance database, reports a few hundred cases.

Based on these data, we address the question whether PMR/PMR-like syndromes following COVID-19 vaccines can be a true adverse or a coincidental event, and discuss its possible pathogenetic mechanisms.

Key words: polymyalgia rheumatica, narrative review, COVID-19 vaccines, adverse events following immunization.

Introduction

Polymyalgia rheumatica (PMR) is considered to be the most common inflammatory rheumatic disease occurring in older adults [1, 2]. Its onset peaks in the age group 71–80 years and its prevalence increases until the age of 90, with a slight decrease thereafter. Its annual incidence rate is estimated between 0.12 and 2.3 cases/1000 (depending on study design and population) in persons aged 50 years and older [3–7].

At present, no specific laboratory tests are available and PMR diagnosis is essentially clinical. Some criteria have been proposed [8, 9], and they may be useful in everyday clinical practice. The typical presentation of PMR involves a sudden-onset and disabling pain in both the shoulders and pelvic girdle, associated with morning stiffness lasting > 45 minutes. Pain of the neck and constitutional symptoms can be additional manifestations. Inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin 6 (IL-6) serum concentrations are usually raised at the time of diagnosis or when PMR relapses [10–13]. Finally, a fast remission following < 20 mg/day prednisone is commonly used to confirm diagnosis [14, 15].

However, atypical presentations are far from infrequent, and several conditions can mimic PMR [16–21]. For instance, it is not infrequent that some patients diagnosed at first with PMR are reclassified as having a different disease at follow-up. Additionally, normal values both of ESR and CRP at onset do not exclude diagnosis of PMR, if typical features are present and mimicking conditions are carefully excluded [22–25].

Finally, some patients with PMR-mimicking diseases can have a fast response to < 20 mg/day prednisone, but
Polymyalgia rheumatica and polymyalgia rheumatica-like syndromes following COVID-19 vaccines

Reumatologia 2022; 60/2

This response is usually transitory [14, 15]. Aetiology and pathogenesis of PMR are debated [26–28]. Polymyalgia rheumatica has been reported as an adverse event following immunization (AEFI) [29, 30].

The primary aim of our paper is to provide an overview of PMR and PMR-like syndromes following the most common types of COVID-19 vaccines, namely mRNA (tozinameran and mRNA-1273) and adenovirus-vectored (ChAdOx1-S) vaccines. Additionally, we aim to discuss whether PMR following COVID-19 vaccines could be considered a true adverse event, as well as exploring the possible pathogenetic mechanisms of this response.

Material and methods

Our review is based on a non-systematic search of PubMed and Medline (COVID interface) performed on January 18, 2022 with the following MeSH terms:

- polymyalgia rheumatica AND SARS-CoV-2 vaccines OR COVID-19 vaccines
- COVID-19 vaccination OR COVID-19 immunization
- tozinameran AND BNT162b2
- OR mRNA-1273 vaccine
- adenovirus-vectored vaccine AND ChAdOx1-S.

Concomitant or overlapping giant cell arteritis (GCA) was an exclusion criterion. Each paper's reference list was scanned for additional publications meeting this study's aims. When papers reported data partially presented in previous articles, we opted to choose the most recently published data.

Results

We found 17 case reports where isolated PMR followed immunization with COVID-19 vaccines. Thirteen of these patients received tozinameran (BNT162b2), a nucleoside-modified mRNA vaccine encoding the spike (S) protein for SARS-CoV-2 [31–35]. In Table I, we list the main features of these 13 patients.

Table I. Isolated polymyalgia rheumatica and BNT162b2 vaccine

| Patient no. | First author outcome | Year | Gender | Age | F/N | Diagnosis | US/PMR | PET-CT/PMR | Dose | Time to reaction | Suspected drug | GCs alone | Final |
|-------------|----------------------|------|--------|-----|-----|-----------|--------|------------|------|----------------|---------------|-----------|-------|
| 1           | Watad [31]           | 2020 | M      | 70  | N   | EULAR/ACR | n.r.   | n.r.       | first | 3 days         | none          | yes       | improvement |
| 2           | Manzo [32]           | 2021 | F      | 69  | N   | EULAR/ACR | yes    | yes        | first | 1 day          | none          | yes       | improvement |
| 3           | Cadiou [33]          | 2021 | M      | 71  | N   | EULAR/ACR | yes    | no         | second | n.c.           | none          | yes       | improvement |
| 4           | Osada [34]           | 2021 | F      | 80  | N   | EULAR/ACR | yes    | CT         | second | 2 days         | none          | yes       | improvement |
| 5           | Ottaviani [35]       | 2021 | F      | 74  | N   | EULAR/ACR | yes    | yes        | first | 10 days        | none          | yes       | improvement |
| 6           | Ottaviani [35]       | 2021 | F      | 70  | N   | EULAR/ACR | second | 15 days    | none          | yes       | improvement |
| 7           | Ottaviani [35]       | 2021 | F      | 74  | N   | EULAR/ACR | second | 14 days    | none          | yes       | improvement |
| 8           | Ottaviani [35]       | 2021 | F      | 77  | N   | EULAR/ACR | second | 10 days    | none          | yes       | improvement |
| 9           | Ottaviani [35]       | 2021 | F      | 78  | N   | EULAR/ACR | second | 15 days    | none          | yes       | improvement |
| 10          | Ottaviani [35]       | 2021 | F      | 73  | N   | EULAR/ACR | first  | 10 days    | none          | yes       | improvement |
| 11          | Ottaviani [35]       | 2021 | F      | 75  | N   | EULAR/ACR | second | 5 days     | none          | yes       | improvement |
| 12          | Ottaviani [35]       | 2021 | F      | 77  | N   | EULAR/ACR | second | 8 days     | none          | yes       | improvement |
| 13          | Ottaviani [35]       | 2021 | M      | 89  | F   | EULAR/ACR | third  | 10 days    | none          | yes       | improvement |

EULAR/ACR – The European League Against Rheumatism/American College of Rheumatology, 2012 classification criteria, F – flares, GCs – glucocorticosteroids, N – new onset, n.c. – not clear, n.r. – not reported, PET-CT/PMR – positron emission tomography/computed tomography suggestive for PMR, US/PMR – ultrasound findings suggestive for polymyalgia rheumatica.
Discussion

Since the early 2000s, some researchers have reported PMR as an AEFI following influenza vaccination [29, 30]. To date, PMR following immunization with influenza vaccination is the most common form of PMR as AEFI [41–44].

In line with the World Health Organization (WHO) guidelines, AEFI is “any untoward, unfavorable, or unintended medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. This adverse event may be symptom, disease, abnormal laboratory finding, unfavourable or unintended sign” [45].

The hypothesis that the link between PMR and AEFI could be an expression of the so-called “ASIA syndrome” (an autoimmune/auto-inflammatory syndrome induced by vaccine components called “adjuvants”) has been discussed [31, 46]. Indeed, some investigators proposed a previous exposure to an external stimulus and the development of some “typical” clinical manifestations (myalgia/myositis, arthralgia/arthritis, pyrexia) as major diagnostic criteria of this syndrome [46]. A genetic background mediated by some human leukocyte antigen B1 (HLA-B1) alleles is crucial [47].

According to our literature search, the onset of PMR/PMR-like syndromes following exposure to adjuvants is very uncommon. For instance, only 4 cases (3 following influenza vaccination) were reported in the 2019 version of the ASIA syndrome international registry, which listed 500 cases. Interestingly, this registry reported no new case of PMR between 2016 and 2019 [48].

Polyethylene glycol (PEG) is present in the lipid film of BNT162b2 vaccine, and is a possible culprit of anaphylaxis reactions to COVID-19 vaccines [49]. However, it is still debated whether PEG can induce an ASIA syndrome. Similarly, polysorbate 80 is an excipient used in the preparation of ChAdOx1-S vaccine whose ability to trigger an ASIA syndrome is still to be proven [50].

Based on the frequency of reported adverse reactions following COVID-19 vaccination, PMR must be considered a very rare (< 0.01%) AEFI according to the WHO guidelines [45]. Yet, the dearth of published case reports is at odds with the hundreds of PMR cases reported in Vigibase.

We recently reported the case of a 69-year-old woman who complained of PMR the day after the first dose of the BNT182b2 vaccine. After > 12 months, no different diagnosis was possible [32]. In the weeks following this report’s publication, we received about 60 emails, mostly from patients or their family members, telling us of post-COVID-19 vaccination symptoms that had been diagnosed as PMR.

However, on careful examination of available data, we could confirm PMR diagnosis only in seven of them. Seventy percent of the PMR notifiers in Vigibase were consumers, non-health professionals, and unknown.

**Table II.** Causality assessment of polymyalgia rheumatica as AEFI after COVID-19 vaccination, according to our literature search

| Causality assessment of polymyalgia rheumatica as AEFI after COVID-19 vaccination | According to our literature search |
|---|---|
| Temporal association: always present |  |
| Plausible time window: time between COVID-19 vaccine administration and onset of PMR was always short or very short |  |
| Other causes: comorbidities or drugs taken by the patients which could explain the insurgence of AEFI were excluded |  |
| Strength of the causal association: this is a very relevant point. First we proposed the hypothesis that TLR7 and TLR9 could be the common link between PMR and mRNA vaccines, able to favour over-production of inflammatory cytokines (including IL-6), in genetically predisposed individuals [32]. To date, the pathogenetic mechanisms of PMR/PMR-like syndromes following DNA vaccines is unknown |  |

AEFI – adverse events following immunization, IL-6 – interleukin 6, PMR – polymyalgia rheumatica, TLR – Toll-like receptor.
Therefore, it is more than likely that the alleged frequency of 0.022% was over-estimated [51].

The case reported by Izuka et al. [40] deserves some consideration. Indeed, the authors diagnosed PMR according to the EULAR/ACR classification criteria and found suggestive PET-CT findings, namely pathological uptake of 18-fluorodeoxyglucose at the bilateral shoulder joints, greater trochanter, interspinous bursa, and ischial tuberosity. Polymyalgia rheumatica clinical manifestations, following the mRNA-1273 vaccine, resolved within a month without GCs treatment. According to our literature search, this possibility does not occur with other types of vaccines.

A final question must be addressed. Is PMR following COVID-19 vaccines a true adverse or a coincidental event? According to the WHO guidelines, a coincidental event is “an AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety”.

These same guidelines propose a four-step process in order to assess the causality of an AEFI, namely:

1. Evaluation and assessment of the temporal association between vaccine administration and AEFI.
2. A plausible time window between vaccine administration and AEFI.
3. Exclusion of other causes such as drugs taken by the patient or comorbidities.
4. Evaluation and assessment of the causal association, based on what is currently known from the published literature [45].

In Table II, we discuss the WHO process derived from our search of published cases.

Toll-like receptors (TLRs) detect and signal within endolysosomal compartments, triggering synthesis of several cytokines essential for the innate immune response, including IL-6. Intracellular and cell surface receptors are present in the TLR family, where TLR7 and TLR9 are intracellular receptors [52]. The peripheral mononuclear blood cells of PMR patients present increased expression of TLR7 and TLR9, which resolves when PMR is in full remission [53].

In addition, an observational study performed on transcriptional signatures in whole blood of healthy volunteers documented strong activation of TLR signalling after vaccination with the BNT162b2 vaccine [54]. To the best of our knowledge, measurements of TLR7 and TLR9 levels are still lacking in patients affected by PMR following immunization with COVID-19 mRNA vaccines. Therefore, ad hoc studies are required in order to verify this hypothesis, and – in general – the strength of the causal association.

The link between COVID-19 vaccines, TLR7, TLR9, and PMR is possible only within a specific genetic profile. Therefore, the assessment of specific genetic polymorphisms (such as HLA-DRB1*04 alleles) may be the element that “closes the circle”. This hypothesized link, if confirmed, would explain why PMR is a more common AEFI when mRNA vaccines are used. Indeed, DNA vaccines usually stimulate the innate immunity through components able to favour the production of cytokines other than IL-6 [55].

Regarding point 2 (plausible time window), the time between COVID-19 vaccine administration and onset of PMR was usually very short. According to our literature search, it was 3 days in 3 patients, and < 10 days in 9 patients. Vigibase reported a 6-day median time when considering only cases reported by healthcare notifiers. In some reports we found in the published literature, PMR manifestations appeared > 20 days (45 days in one of them) after the COVID-19 vaccine [36, 37]. Could this long time window mean just a coincidence?

Conclusions

According to our literature search, published reports of PMR/PMR-like syndromes following COVID-19 vaccines are still uncommon. Some open questions need answers in order to achieve a better understanding of the relationship between COVID-19 vaccines and PMR/PMR-like syndromes.

The authors declare no conflict of interest.

References

1. Gonzalez-Gay MA, Matteson EL, Castaneda S. Polymyalgia rheumatica. Lancet 2017; 390: 1700–1712, DOI: 10.1016/S0140-6736(17)31825-1.
2. Gazitt T, Zisman Q, Gardner G. Polymyalgia rheumatica: a common disease in seniors. Curr Rheumatol Rep 2020; 22: 40, DOI: 10.1007/s11926-020-00919-2.
3. Raheel S, Shbeeib I, Crowson CA, Matteson EL. Epidemiology of polymyalgia rheumatica 2000–2014 and examination of incidence and survival trends over 45 years: a population-based study. Arthritis Care Res 2017; 69: 1282–1285, DOI: 10.1002/acr.23132.
4. Partington RJ, Muller S, Helliwell T, et al. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Ann Rheum Dis 2018; 77: 1750–1756, DOI: 10.1136/annrheumdis-2018-213883.
5. Manzo C. Incidence and prevalence of polymyalgia rheumatica (PMR): the importance of the epidemiological context. The Italian case. Med Sci (Basel) 2019; 7: 92, DOI: 10.3390/medsci7090092.
6. Gonzales-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumat-
11. Milchert M, Brzosko M. Diagnosis of polymyalgia rheumatica. Reumatismo 2018; 70: 18–22, DOI: 10.5114/reuma.2018.1048.

12. Mahmood SB, Nielson E, Padniewski J, Nasr R. Polymyalgia rheumatica with normal inflammatory indices at the time of diagnosis: can we just move a step forward? Reumatologia 2020, 58: 184–186, DOI: 10.1093/reumatology/key431.

13. Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 provisional classification criteria for the diagnosis of polymyalgia rheumatica. Reumatismo 2018, 70: 10–17, DOI: 10.1093/reumatismo/2018.1048.

14. Manzo C. The great imitator. Isr Med Assoc J 2019; 21: 627–628.

15. Manzo C, Camellino D. [Polymyalgia rheumatica: diagnostic and therapeutic issues of an apparently straightforward disease]. Recent Progress Med 2017; 108: 221–231, DOI: 10.1701/2695.27559 [Article in Italian].

16. Secco T, Uha C, Regidor M, et al. [Conditions mimicking polymyalgia rheumatica]. Reumatol Clin 2011; 7: 9–11 [Article in Spanish].

17. Manzo C. Paraneoplastic syndromes and inflammatory rheumatic diseases: not everything that glitters is gold. The case of polymyalgia rheumatica and giant cell arteritis: COVID-19 vaccine shot as a trigger? Comment on: “Can SARS-CoV-2 trigger relapse of polymyalgia rheumatica?” by Manzo et al. Joint Bone Spine 2021; 88: 105150. Joint Bone Spine 2021; 89: 105282, DOI: 10.1016/j.jbspin.2021.105282.

18. Aza R, Khassn A. Paraneoplastic rheumatoid syndromes. Curr Opin Rheumatol 2013; 25: 44–49, DOI: 10.1097/BOR.0b013e328359e780.

19. Manzo C, Natale M, Traini E. Diagnosis of polymyalgia rheumatica in primary health care: favoring and confounding factors – a cohort study. Reumatologia 2018; 56: 131–139, DOI: 10.5114/reuma.2018.76900.

20. Gonzalez-Gay MA, García-Porrúa C, Salvatori C, et al. Polymyalgia rheumatica following the administration of the Pfizer-BioNTech COVID-19 vaccine. Intern Med 2021; 61: 749–753, DOI: 10.2169/internalmedicine.8651-21.

21. Gazit T, Kibari A, Nasrallah N, et al. Polymyalgia rheumatica: the great imitator. Isr Med Assoc J 2019; 21: 627–628.

22. Manzo C, Milchert M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis: a four-point guidance. Reumatologia 2018; 56: 1–2, DOI: 10.5114/reuma.2018.74740.

23. Manzo C, Milchert M, Natale M, Brzosko M. Polymyalgia rheumatica with normal values of both erythrocyte sedimentation rate and C-reactive protein concentration at the time of diagnosis. Rheumatology (Oxford) 2019; 5: 921–923, DOI: 10.1093/rheumatology/key431.

24. Manzo C, Milchert M, Natale M, Brzosko M. Polymyalgia rheumatica with normal inflammatory indices at the time of diagnosis: can we just move a step forward? Reumatologia 2020, 58: 184–186, DOI: 10.1093/reumatology/key431.

25. Manzo C, Milchert M, Natale M, Brzosko M. Polymyalgia rheumatica without elevated baseline acute phase reactants. Clin Exp Rheumatol 2021; 39: 441.
37. Vanni E, Ciaffi J, Mancarella L, Ursini F. An unusual case of “con-jugal” polymyalgia rheumatica after SARS-CoV-2 Vaccination. Rheumatol 2021; 1: 17–21, DOI: 10.3390/rheumato100004.
38. Mettler C, Jonville-Bera AP, Grandvuillemin A, et al. Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study. Rheumatology (Oxford) 2021; 61: 865–867, DOI: 10.1093/rheumatology/keab756.
39. Ursini F, Ruscitti P, Raimondo V, et al. Spectrum of short-term inflammatory musculoskeletal manifestations after COVID-19 vaccine administration: a report of 66 cases. Ann Rheum Dis 2021; 81: 440–441, DOI: 10.1136/annrheumdis-2021-221587.
40. Izuka S, Komai T, Natsumoto B, et al. Self-limited polymyalgia rheumatica-like syndrome following mRNA-1273 SARS-CoV-2 vaccination. Intern Med 2022; 61: 903–906, DOI: 10.2169/internalmedicine.8829-21.
41. Bassendine MF, Bridge SH. Relapse of polymyalgia rheumat-ica following adjuvanted influenza vaccine: a case-based review. Eur J Rheumatol 2019; 7: 37–40, DOI: 10.5152/eurjheum.2019.19152.
42. Falletti P, Conticini E, Acciai C, et al. Polymyalgia rheumatica following infective triggers or vaccinations: a different subset of disease? Reumatologia 2020; 58: 76–80, DOI: 10.5114/reum.2020.93560.
43. World Health Organization. User manual for the revised WHO classification, second edition. WHO, Geneva 2018.
44. Borba V, Malkova A, Basantaova N, et al. Classical examples of the concept of the ASIA syndrome. Biomolecules 2020; 10: 1436, DOI: 10.3390/biom10101436.