Spectrum of short-term inflammatory musculoskeletal manifestations after COVID-19 vaccine administration: a report of 66 cases

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In the last months, mass vaccination represented the turning point of the global battle against the COVID-19 pandemic, an unprecedented challenge for physicians, healthcare professionals, health systems and pharmaceutical companies. More than 6 billion doses of vaccine have been administered to date, covering nearly 50% of the world's population. Although the vaccination campaign is still thwarted by spread of fake news disseminated by a ubiquitous anti-vaxxer movement, accumulating real-life data [1] confirm the favourable safety profile already demonstrated in phase III clinical trials [2].

Despite the lack of a steady literature evidence [3], the potential role of vaccines in promoting autoimmunity continues to intrigue many researchers. The theoretical basis of this association relies on the possible molecular mimicry between macromolecular components of the vaccine and specific human proteins and the exuberant immune response elicited by adjuvants contained in vaccines [4].

Adverse events (AEs) associated with COVID-19 vaccines are usually mild and mainly restricted to injection site reactions. Interestingly, amongst systemic AEs, arthralgia is one of the most common [2]. To the best of our knowledge, only isolated cases [5] of arthritis developed after COVID-19 vaccine administration have been described; however, in a recently published survey including 1377 participants with rheumatic diseases, 11% of the respondents reported flare requiring treatment following injection of mRNA-based vaccines [6].

The "*COVID-19 and autoimmune systemic diseases*" is a collaborative network of Italian rheumatologists, equally distributed across the country, spontaneously born in response to the COVID-19 pandemic with the aim to contribute to the advancing knowledge about COVID-19 and rheumatic diseases, by providing real-life data obtained from participating centres. To date, more than 60 rheumatologists from 40 different rheumatology clinics are affiliated to the study group.

In December 2020, we published a web-based survey form and invited all members of the study group to inform cases of inflammatory musculoskeletal manifestations (e.g., synovitis, tenosynovitis, enthesitis, inflammatory spinal pain or girdles pain/stiffness with serological evidence of inflammation) with onset within four weeks from the administration of the first or second dose of one of the COVID-19 vaccines approved in Italy (BNT162b2, mRNA-1273, AZD1222, Ad26.COV2.S), prospectively encountered during routine clinical practice since the beginning of the vaccination campaign, in January 2021, and up to August 31, 2021. Exclusion criteria were a past history of any inflammatory rheumatic disease, isolated arthralgia/myalgia without clear evidence of inflammation or vague and/or non-specific musculoskeletal complains. Written informed consent was obtained from all patients.

By using this approach, we built a case series comprising 66 individual patients reported by 16 different rheumatology centres; most of them (59%) received the BNT162b2 vaccine. The average delay between the day of the "trigger" injection (44.4% coinciding with the first dose) and arthritis onset was 11-13 days.

Stratification according to the predominant pattern of involvement at presentation (Table 1) revealed that girdles pain/stiffness with acute phase reactants elevation resembling polymyalgia rheumatica (PMR-like) was the most common (41%) clinical picture followed by oligoarthritis (32%) and polyarthritis (27%). Polyarticular and PMR-like cases were mainly symmetric (83% and 89% respectively); involvement of small joints and tenosynovitis (39%) were significantly more frequent in polyarthritic forms (61% and 39%, respectively) while

enthesitis was more common in oligoarthritic presentation (14%). Of note, two patients (one in the polyarticular and one in the oligoarticular group, respectively) had also inflammatory back pain with evidence of active sacroiliitis and/or spondylitis on magnetic resonance (MR) imaging. Detection of autoantibodies in sera was an uncommon finding; HLA-B27 status was obtained in only 21 (31.8%) patients of which one in the polyarthritis subgroup tested positive.

Most patients were treated with glucocorticoids (50-78%), non-steroidal anti-inflammatory drugs (NSAIDs) (33-52%) or analgesics (14-28%) while disease-modifying antirheumatic drugs (DMARDs) were used in five (28%) patients with polyarthritis, five (24%) patients with oligoarthritis and only three (11%) patients with PMR-like presentation.

Despite the limitation of a very short follow-up, the clinical course seemed excellent in patients with PMR-like onset with 74% achieving full remission of symptoms after two weeks; on the other hand, 67% of patients with polyarthritis had active disease after an average follow-up of six weeks.

In conclusion, despite a clear cause-effect relationship is far to be ascertained, our data suggest that inflammatory musculoskeletal symptoms may occasionally develop in close temporal association with COVID-19 vaccine administration. However, even assuming a direct causal relationship, we feel that the overall safety of COVID-19 vaccines remains unaffected and the benefits of vaccination largely outweigh the minimal risks associated with such uncommon inflammatory complications, probably reflecting a transient reactogenic response to the vaccine rather than a structured, chronic inflammatory joint disease.

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Competing Interests

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Patient and Public Involvement statement

Patients or public were not involved because the current manuscript is only the description of a case series.

Table 1. Clinical features of the patients stratified according to the pattern of presentation.

	Polyarthritis (n = 18)	**Oligoarthritis (n = 21)**	**PMR-like (n = 27)**	***p* value**
Age, years	54 ± 16	64 ± 15	67 ± 10	**0.006**
Female gender, n (%)	10 (55.6)	16 (76.2)	17 (63.0)	0.696
Past COVID-19, n (%)	2 (11.1)	1 (4.8)	0 (0.0)	0.211
Specific vaccine administered				
BNT162b2, n (%)	9 (50.0)	12 (57.1)	18 (66.7)	0.363
mRNA-1273, n (%)	0 (0.0)	1 (4.8)	2 (7.4)	0.535
AZD1222, n (%)	9 (50.0)	7 (33.3)	7 (25.9)	0.197
Ad26.COV2.S, n (%)	0 (0.0)	1 (4.8)	0 (0.0)	0.295
Vaccine-related adverse events				
None, n (%)	3 (16.7)	9 (42.9)	11 (40.7)	0.195
Pain at the injection site, n (%)	12 (66.7)	10 (47.6)	13 (48.1)	0.440
Fever, n (%)	5 (27.8)	1 (4.8)	3 (11.1)	0.112
Headache, n (%)	2 (11.1)	2 (9.5)	2 (7.4)	0.869
Fatigue, n (%)	6 (33.3)	3 (14.3)	1 (3.7)	**0.023**
Rheumatic manifestations onset after first dose, n (%)	11 (61.1)	7 (33.3)	12 (44.4)	0.322
Delay between vaccine administration and rheumatic manifestations onset, days	12 ± 9	11 ± 7	13 ± 7	0.450
Rheumatic manifestations				
Symmetrical involvement, n (%)	15 (83.3)	9 (42.9)	24 (88.9)	**0.001**
Involvement of small joints, n (%)	11 (61.1)	4 (19.0)	2 (7.4)	**< 0.001**

Tenosynovitis, n (%)	7 (38.9)	4 (19.0)	2 (7.4)	**0.029**
Enthesitis, n (%)	0 (0.0)	3 (14.3)	0 (0.0)	**0.023**
Bursitis, n (%)	1 (5.6)	1 (4.8)	0 (0.0)	0.456
Inflammatory back pain with MRI evidence of sacroiliitis or spondylitis, n (%)	1 (5.6)	1 (4.8)	0 (0.0)	0.456
Fatigue, n (%)	4 (22.2)	3 (14.3)	8 (29.6)	0.613
Laboratory features				
ESR, mm/h	51 ± 34	36 ± 25	45 ± 28	0.108
CRP, mg/dL	2.13 (1.25 – 5.20)	1.90 (0.50 – 3.61)	2.13 (1.25 – 5.20)	0.121
RF positive, n (%)*	1 (6.3)	0 (0.0)	0 (0.0)	0.255
ACPA positive, n (%)*	1 (6.3)	0 (0.0)	0 (0.0)	0.255
RF and ACPA positive, n (%)*	1 (6.3)	0 (0.0)	0 (0.0)	0.255
ANA positive, n (%)#	2 (15.4)	3 (17.6)	0 (0.0)	0.061
Treatment				
NSAIDs, n (%)	6 (33.3)	11 (52.4)	9 (33.3)	0.507
Paracetamol or opioids, n (%)	5 (27.8)	3 (14.3)	6 (22.2)	0.669
Glucocorticoids, n (%)	9 (50.0)	13 (61.9)	21 (77.8)	0.113
Methotrexate, n (%)	4 (22.2)	5 (23.8)	3 (11.1)	0.490
Sulfasalazine, n (%)	1 (5.6)	0 (0.0)	0 (0.0)	0.523
Follow-up duration, weeks	6 (2 – 8)	4 (3 – 8)	2 (1 – 5)	0.209
Outcome				
Active disease, n (%)	12 (66.7)	9 (42.9)	6 (22.2)	**0.007**
Remission, n (%)	6 (33.3)	10 (47.6)	20 (74.1)	**0.014**
N/A, n (%)	0 (0.0)	2 (9.5)	1 (3.7)	0.296

Data are expressed as mean ± standard deviation (SD) or median (25th – 75th percentile), as appropriate. P values refer to one-way analysis of variance (ANOVA) or Kruskal-Wallis H test for continuous or categorical variables, respectively.

Legend: ACPA, anti-citrullinated protein antibodies; ANA, antinuclear antibodies; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; N/A, not available; PMR, polymyalgia rheumatica; RF, rheumatoid factor.

* Information for RF/ACPA status available for 56 patients

Information for ANA status available for 48 patients