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LETTERS OF BIOMEDICAL AND CLINICAL RESEARCH

Systemic syndromes of rheumatological interest with onset after COVID-19 vaccine administration: a report of 30 cases

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Dear Editor,

Mass vaccination represented the game changer for the global battle against SARS-CoV-2, an unprecedented infectious threat for the world's population. Despite the insufficient coverage of low-income countries, more than 9 billion doses of vaccine have been administered to date, providing protection for ~ 50% of the world's population. Unfortunately, the vaccination campaign is still in danger by the diffusion of fake news disseminated, mainly through the

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web, by anti-science and anti-vaccine movements, although accumulating real-life data [1] confirm the favorable safety profile already demonstrated in phase III clinical trials [2].

It is interesting to note that despite the lack of a robust literature evidence [3], the potential role of vaccines in promoting the development of autoimmunity continues to fascinate researchers. The theoretical basis of this association relies on the possibility of molecular mimicry between components of the vaccine and specific human proteins and the stimulation of aberrant immune responses by adjuvants contained in vaccines [4].

According to the World Health Organization (WHO), adverse events (AEs) after immunization are defined as "any untoward medical occurrence which follows immunization, which does not necessarily have a causal relationship with the usage of the vaccine" [5].

Regarding COVID-19 vaccines, AEs are usually mild and mainly restricted to injection site reactions. Interestingly, amongst systemic AEs, arthralgia is one of the most common [2] and only isolated cases [6–9] of inflammatory rheumatic diseases developed after COVID-19 vaccine administration have been described to date.

To contribute to shed light on this field, in December 2020, we published a web-based survey form and invited all members of the *"COVID-19 and autoimmune systemic diseases"* collaborative research group to spontaneously submit cases of systemic syndromes of rheumatological interest 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), encountered during routine clinical practice since the beginning of the vaccination campaign in January 2021. Exclusion criteria were a past history of any autoimmune or inflammatory rheumatic disease.

Using this approach, we built a series of 30 individual cases (Table 1) reported by 16 centers belonging to our research network, including 12 (40%) patients with skin vasculitis (40%), four (13.3%) with undifferentiated connective tissue diseases (CTD), two (6.7%) with Sjögren's syndrome (SjS), one (3.3%) with very early systemic sclerosis (SSc), one (3.3%) with overlap CTD (scleromyositis), two (6.7%) with atypical acrosyndrome [10], one (3.3%) with iperinflammatory syndrome, three (10%) with giant cell arteritis (GCA), two (6.7%) with Takayasu's arteritis (TAK), one (3.3%) with of small vessel vasculitis, and one (3.3%) with cryoglobulinemic vasculitis. Mean time from vaccine administration to clinical manifestations onset was 9 days (range 1–28); most patients 16 (53.3%) received the BNT162b2 vaccine.

After a median follow-up of four weeks, 21 (70%) patients achieved remission or improvement of disease activity according to clinical judgment; on the other hand, seven (23.3%) patients had ongoing active disease (one with skin vasculitis, one with undifferentiated CTD, one with scleromyositis, one with atypical acrosyndrome, one with GCA, one with small vessel vasculitis, and one with iperinflammatory syndrome), while three (10%) were lost at follow-up. Most patients (25 out of 30) were initially treated with glucocorticoids (GCs), alone or in combination with disease-modifying antirheumatic drugs (DMARDs), histamine receptor 1 antagonist (H1RA), non-steroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin (IVIG), anakinra, or vasoactive drugs.

In conclusion, despite a clear cause-effect relationship is far to be ascertained, our data suggest that systemic diseases of rheumatological interest may occasionally develop in close temporal association with COVID-19 vaccine administration. Interestingly, 15 patients (50%) developed autoantibodies, suggesting that COVID-19 vaccines may potentially elicit transient or sustained autoimmunity in selected individuals.

However, even if we assume a direct causal relationship, the overall safety of COVID-19 vaccines remains unconcerned and the benefits of vaccination largely outweigh the minimal risks associated with such potential adverse events.

Table 1 Clinical features of post-COVID-19 vaccine syndromes of rheumatological interest. Abbreviations: *aPL*, antiphospholipid antibodies; *ANA*, antinuclear antibodies; *CCA*, common carotid artery; *CPK*, creatine phosphokinase; *CTD*, connective tissue disease; *GCA*, giant cell arteritis; *GCs*, glucocorticoids; *GGO*, ground glass opacities; *HCQ*, hydroxychloroquine; *HRTC* , high-resolution computed tomography; *H1RA*, histamine receptor 1 antagonist; *IVIG*, intravenous Immunoglobulin; *MTX*, methotrexate; *NSAIDs*, non-steroidal anti-inflammatory drugs; *NVC*, nailfold videocapillaroscopy; *N/A*, not available (lost at follow-up); *PET/CT*, positron emission tomography/computed tomography; *RF*, rheumatoid factor; *RP*, Raynaud's phenomenon; *TAB*, temporal artery biopsy; *US*, ultrasonography; *18-F FDG*, 18F-fluorodeoxyglucose. *Days between vaccine administration and first symptom of rheumatological interest

Rheumatological syndrome	Gender, Age	Past COVID-19	Vaccine (days*)	Case description	Autoantibodies	Treatment	Follow-up, weeks	Patient's status
Skin vasculitis	F, 64	No	MRNA-1273 (2)	Palpable purpura of the trunk and upper and lower limbs	None	GCs	N/A	N/A
	F, 25	No	BNT162b2 (6)	Palpable purpura of the upper and lower limbs, erythematous facial rash	ANA	GCs, H1RAs	2	Remission (drug free)
	M, 53	No	BNT162b2 (7)	Palpable purpura of the upper and lower limbs	None	GCS, H1RAs	12	Remission (drug free)
	F, 31	No	BNT162b2 (7)	Urticarial vasculitis of the lower limbs, erythematous facial rash	None	GCs	6	Remission (drug free)
	F, 43	No	AZD1222 (8)	Urticarial vasculitis of the upper and lower limbs	None	GCs	4	Remission
	F, 67	No	BNT162b2 (10)	Urticarial vasculitis of the lower limbs, fever	None	GCs	8	Remission
	F, 68	No	AZD1222 (10)	Livedo reticularis of the upper and lower limbs	ANA	GCs	4	Active
	F, 25	No	MRNA-1273 (10)	Palpable purpura of the upper and lower limbs	None	GCs	3	Remission (drug free)
	F, 77	No	BNT162b2 (10)	Palpable purpura of the lower limbs, puffy hands	ANA	None	1	Remission (drug free)
	F, 47	No	BNT162b2 (15)	Palpable purpura of the lower limbs	RF	GCs	8	Remission
	F, 29	Yes	BNT162b2 (18)	Palpable purpura of the lower limbs	None	GCs	2	Remission (drug free)
	M, 38	Yes	BNT162b2 (21)	Urticarial vasculitis of the lower limbs, fever	None	GCs, H1RAs	4	Remission (drug free)
Undifferentiated CTD	F, 61	No	BNT162b2 (3)	Fever, chest pain, fatigue, arthralgia, myalgia. Laboratory and imaging studies demonstrated inflammatory pleuro-pericardial effusion with no evidence of infection or cancer. Lack of response to GCs/NSAIDs/colchicine treatment; good response to anakinra	ANA, anti-SSA	GCs, NSAIDs, colchicine, anakinra	4	Improved
	M, 50	No	AZD1222 (3)	Scarring alopecia, arthralgia of large joints, myalgia	ANA	GCs	8	Improved
	M, 45	No	BNT162b2 (5)	Chest pain, fatigue, arthralgia, myalgia. Imaging demonstrated pericardial effusion with no evidence of infection or cancer	ANA	NSAIDs	N/A	N/A
	M, 32	Yes	BNT162b2 (5)	RP with non-specific NVC abnormalities, polyarthritis of large joints, proximal myalgia with normal CPK values, sudden-onset dysphagia	ANA, anti-Jo-1	GCs, MTX	4	Active

Table 1 (continued)

Rheumatological syndrome	Gender, Age	Past COVID-19	Vaccine (days*)	Case description	Autoantibodies	Treatment	Follow-up, weeks	Patient's status
Sjögren's syndrome	F, 44	No	AZD1222 (4)	Xerostomia, xerophthalmia, dry cough, dyspnea, RP with non-specific NVC abnormalities. HRTC showed bilateral basal GGO opacities	ANA, anti-SSA	GCs	12	Improved
	F, 62	No	AZD1222 (15)	RP with non-specific NVC abnormalities, xerostomia, xerophthalmia	FR, ANA, anti-SSA	HCQ	N/A	N/A
Very early systemic sclerosis	F, 42	No	BNT162b2 (20)	RP with puffy fingers and NVC evidence of early scleroderma pattern, arthralgia, myalgia, fatigue	ANA, anti-centromere	GCs, HCQ, Felodipine	12	Improved
Overlap CTD (scleromyositis)	F, 37	No	BNT162b2 (4)	Sudden-onset muscle pain/weakness with markedly increased CPK levels, RP with NVC evidence of early scleroderma pattern	ANA, anti-Pm/Scl-75, anti-Ku, anti-RNA polymerase III, anti-fibrillarin	GCs, IVIG	1	Active
Atypical acrosyndrome	F, 41	Yes	MRNA-1273 (2)	Acrocyanosis with puffy fingers and non-specific NVC abnormalities, arthralgia, myalgia	ANA	NSAIDs, aminaphtone	4	Active
	F, 37	No	AZD1222 (28)	RP with puffy fingers and non-specific NVC abnormalities	None	NSAIDs, Felodipine	12	Remission (drug free)
Iperinflammatory syndrome	M, 16	No	BNT162b2 (2)	Pharyngodynia, intermittent erythematous skin rash, arthralgia, flexor tenosynovitis of the fingers, fever. Laboratory tests showed marked increase in inflammatory markers and neutrophil count, liver injury, and hyperferritinemia. PET/CT scan revealed accumulation of 18-FDG in axillar and inguinal lymphnodes, bone marrow, and spleen (enlarged)	None	GCs, NSAIDs	3	Active
Giant cell arteritis	M 78	No	AZD1222 (1)	Temporoparietal headache, jaw claudication, fatigue. TAB showed findings consistent with inflammation of the vessel wall and the presence of giant cells. PET/CT scan showed 18F-FDG accumulation in proximal aorta	None	GCs	3	Active
	F, 82	No	MRNA-1273 (8)	Tenderness and swelling of the right temporal artery followed by sudden-onset visual loss	None	GCs	6	Remission
	F, 67	No	AZD1222 (14)	Jaw claudication, fatigue. Temporal artery US showed the typical "halo" sign	None	GCs	6	Remission

Table 1 (continued)

Rheumatological syndrome	Gender, Age	Past COVID-19	Vaccine (days*)	Case description	Autoantibodies	Treatment	Follow-up, weeks	Patient's status
Takayasu's arteritis	F, 31	No	BNT162b2 (1)	Carotidynia, fatigue, night sweating. Doppler US of neck vessels showed diffuse thickening of right CCA; FDG PET-CT scan confirmed accumulation of 18-F FDG in right CCA and both subclavian arteries	None	GCs	8	Remission
	M, 39	No	AZD1222 (12)	Fever, fatigue, erythematous rash of the trunk. PET/CT scan showed 18-F-FDG accumulation in ascending aorta and aortic arch	None	GCs	12	Remission
Small-vessel vasculitis	M, 73	No	BNT162b2 (5)	Axonal sensorimotor polyneuropathy, moderate proteinuria, microscopic hematuria, RP with non-specific NVC abnormalities, nodular lesions, and consolidation on HRTC	RF	GCs	4	Active
Cryoglobulinemic vasculitis	F, 60	No	AZD1222 (10)	Lower limb petechiae, fever, fatigue. Laboratory test showed complement consumption and acute kidney injury with moderate proteinuria	ANA, aPL, cryoglobulins	GCs	8	Remission

Declarations

Ethics approval The study complies with the Declaration of Helsinki. Written informed consent has been obtained from the subjects involved.

Disclosures None.

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