



Autoimmune post-COVID vaccine syndromes: does the spectrum of autoimmune/inflammatory syndrome expand?

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Abstract

To date, around 60% of the world population has been protected by vaccines against SARS-CoV-2, significantly reducing the devastating effect of the pandemic and restoring social economic activity through mass vaccination. Multiple studies have demonstrated the effectiveness and safety of vaccines against COVID-19 in healthy populations, in people with risk factors, in people with or without SARS-CoV-2 infection, and in immunocompromised people. According to the criteria for post-vaccine adverse events established by the World Health Organization, a minority of individuals may develop adverse events, including autoimmune syndromes. The exact mechanisms for the development of these autoimmune syndromes are under study, and to date, a cause-effect relationship has not been established. Many of these autoimmune syndromes meet sufficient criteria for the diagnosis of Adjuvant-Induced Autoimmune Syndrome (ASIA syndrome). The descriptions of these autoimmune syndromes open new perspectives to the knowledge of the complex relationship between the host, its immune system, with the new vaccines and the development of new-onset autoimmune syndromes. Fortunately, most of these autoimmune syndromes are easily controlled with steroids and other immunomodulatory medications and are short-lived. Rheumatologists must be alert to the development of these autoimmune syndromes, and investigate the relationship between autoimmune/inflammatory symptoms and vaccination time, and assess their therapeutic response.

Keywords Adverse event vaccine · Autoimmunity · Autoimmune diseases · Autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) · COVID-19 vaccine.

Vaccines, autoimmunity, and autoimmune syndromes

Vaccines represent one of the most critical advances in medicine and are the most effective method to prevent morbidity and mortality associated with infections. However, unlike antimicrobial agents used to treat infected persons, vaccines are applied to healthy subjects to prevent infections; therefore, adverse effects acquire great relevance [1]. Nevertheless, adverse effects do not outweigh the indisputable advantages vaccines offer to humanity by preventing diseases that constitute a significant economic, social, and familial burden. In this manner, informing individuals, families, and communities of the characteristics of vaccines makes the risk–benefit of each of the vaccines more familiar, doubtlessly contributing to the population’s health [2].

Vaccination campaigns against COVID-19 began one year ago. At present, more than 4.6 billion persons, about 59% of the world population, on the planet have received one or more doses [3]. The efficacy of COVID-19 vaccines has

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recently been analyzed through a meta-analysis from August to October 2021 compared to outcomes by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. According to the study, the effectiveness of the COVID-19 vaccine in terms of COVID-19-related hospitalization, admission to the intensive care unit, and death was 89.1%, 97.4%, and 99.0%, respectively. The effectiveness of COVID-19 vaccines in the general population aged ≥ 16 years, the elderly, and healthcare workers was 86.1%, 83.8%, and 95.3%, respectively. The COVID-19 vaccines are highly protective against SARS-CoV-2-related diseases in real-world settings [4]. Moreover, a recent meta-analysis aimed at assessing the short-term effectiveness of COVID-19 vaccines among immunocompromised patients (solid organ transplant, malignant diseases, and inflammatory rheumatic diseases) was conducted. The results of this study indicated that COVID-19 messenger RNA (mRNA) vaccines were effective against symptomatic COVID-19 among immunocompromised patients but had lower vaccine effectiveness compared with the controls. Therefore, the discord between antibody production and protection against symptomatic COVID-19 must be investigated [5].

In 2011, Shoenfeld et al. [6] proposed the autoimmune/inflammatory syndrome induced by adjuvant (ASIA), which included four entities: siliconosis, the Gulf War syndrome (GWS), the macrophagic myofasciitis (MMF) syndrome, and post-vaccination phenomena. The four shared similar signs and symptoms alongside a previous exposure to adjuvants. More than one decade has passed since the initial description of ASIA, and the clinical manifestations have expanded. For instance, a recent study of 500 patients obtained from the ASIA International Registry found that 69% of the enrollees had well-defined immune diseases. After exposure to adjuvants, polygenic autoimmune disorders were significantly higher than autoinflammatory disorders. While connective tissue diseases were mainly linked to exposure to the hepatitis B virus vaccine. Polygenic autoinflammatory disorders were significantly associated with exposure to the influenza vaccination. Autoimmune syndromes following vaccination are rare and are reported under the umbrella of ASIA. However, the benefit of vaccines outweighs their autoimmune adverse effects [7]. The seasonal influenza vaccine is widely recommended for persons over 50 years. A recent study found that 358 patients with giant cell arteritis and polymyalgia rheumatica (GCA/PMR) were recruited since 2002; 10 (2.8%) of these qualified for post-influenza GCA/PMR vaccination. Patients with the post-influenza vaccination GCA/PMR had the DRB1*13:01 haplotype more frequently than those with familial GCA/PMR or with GCA/PMR without a known trigger. It is of interest that the post-influenza vaccination GCA/PMR generally appeared to be self-limited. Therefore, the genetic study must be confirmed with a more significant number of patients. The post-influenza

vaccination GCA/PMR may be part of the spectrum of ASIA [8]. In 2012, another researchers reported 10 GCA/PMR cases that met ASIA criteria for the post-influenza vaccine [9]. From the description of ASIA in 2011 to the year 2020, more than 4400 patients were described as fulfilling the ASIA criteria. Such patients were shown to possess a great diversity of clinical manifestations, ranging from minor to severe life-threatening cases, which may constitute a real public health problem [10–12]. Loss of immunological tolerance in patients with ASIA is evident by the presence of autoantibodies and clinical and immunological recovery after removing the agent that stimulates the innate and adaptive immune response [13]. This interaction between vaccine compounds, silicone implantation, drugs, infections, metals, and the immune system occurs in genetically predisposed individuals (*HLA-DRB1* and *PTPN22* genes), perhaps leading to the development of sarcoidosis, Sjögren's syndrome, undifferentiated connective tissue disease, and the silicone implant incompatibility syndrome, which share the characteristics of ASIA [10].

Post-COVID-19 vaccine autoimmune syndromes

The World Health Organization definition of a post-vaccine adverse event is as follows: any untoward medical occurrence that follows immunization, which does not necessarily have a causal relationship with the usage of the vaccine [14]. According to the cited definition, a minority of individuals may develop adverse effects, including autoimmune syndromes, after applying a vaccine. The central hypothesis proposed to explain the development of these autoimmune syndromes is molecular mimicry. According to this hypothesis, the antigen administered with the vaccine, denominated adjuvants (aluminum salts, virosomes, oil-in-water emulsions, immune modulatory complexes, squalene, montanide, lipovant, and xenobiotic adjuvants) entertain structural similarities with self-antigens. Another mechanism is the activation of “innocent bystanders,” leading to autoreactive T cells, polyclonal activation, and epitope spreading; however, the pathogenic mechanisms behind the correlation between vaccines and autoimmune diseases are not yet present fully elucidated [15].

As of January 2021, SARS-CoV-2 vaccines were authorized for emergency use in Europe, North America, South America, Australia, and Asia, with priority for vaccination of the elderly and clinically vulnerable individuals [16]. The first two approved mRNA vaccines included BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). In addition, the ChAdOx1 (AstraZeneca vaccine), a recombinant adenoviral vector that encodes the spike protein antigen of SARS-CoV-2, was approved by British and European authorities

[17, 18]. A few months following the vaccination campaign, in April 2021, Schultz et al. [19] reported five patients who presented with venous thrombosis and thrombocytopenia between 7 and 10 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. The patients had high titers of antibodies to platelet factor 4-polyanion complexes, but none had previous exposure to heparin. The final diagnosis was vaccine-induced immune thrombotic thrombocytopenia (VITT), a newly introduced entity related to COVID-19 vaccines [20]. Later, various autoimmune syndromes have been described, such as severe autoimmune thrombocytopenia associated with anti-SSA/Ro antibodies and hypocomplementemia [21]. Neurological autoimmune diseases following vaccinations have also been described. Twenty-one diagnosed cases (new-onset, $n=17$, flares $n=4$) diagnosed a median of 11 days (range, 3–23 days) following SARS-CoV-2 vaccinations (BNT162b2 $n=12$, ChAdOx1 $n=8$, mRNA-1273 $n=1$) were identified. Cases included VITT with cerebral venous sinus thrombosis ($n=3$), central nervous system demyelinating diseases ($n=8$), inflammatory peripheral neuropathies ($n=4$), myositis ($n=3$), myasthenia ($n=1$), limbic encephalitis ($n=1$), and giant cell arteritis ($n=1$). Patients were predominantly female (ratio 3.2:1), and median age at diagnosis was 50 years (range, 22–86 years) [22].

The first systematic review of the literature on new-onset autoimmune syndromes after the COVID-19 vaccine was published in December 2021 [23]. In this study, 276 published cases were identified. The mainstream cases corresponded to Guillain-Barré syndrome (151 patients) followed by vaccine-induced thrombotic thrombocytopenia (93 cases). Less frequent cases, such as autoimmune liver diseases (eight cases), immune thrombocytopenic purpura (seven cases), IgA nephropathy (five), autoimmune polyarthritis (two), rheumatoid arthritis (two), Graves' disease (four), or systemic lupus erythematosus (three), have been reported as well. Multicenter studies have been carried out to continue informing the scientific community, in addition to informing on the indisputable advantages of vaccines against COVID-19 in groups of patients who presented autoimmune syndromes shortly after applying the first or second dose of the vaccine. In Italy [24], 71 patients with a previous diagnosis of cryoglobulinemia were recruited as follows: infection-cured hepatitis C virus (HCV)-related mixed cryoglobulinemia (MC), either uncomplicated (HCV-MC, $n=50$) or complicated by low-grade non-Hodgkin lymphoma (MC-NHL, $n=8$), or essential MC (EMC, $n=13$). Of these patients, eight were excluded due to previous relapses, and six of the remaining 63 patients (9.5%) with stable MC had bona fide vaccination-related flares. Flares were more frequent in patients with EMC than HCV-cured HCV-MC or MC-NHL. China demonstrated disease flare after inactivated COVID-19 vaccination in patients with

autoimmune rheumatic diseases (ARD). This study involved 1507 patients with ARD, including 614 with systemic lupus erythematosus (SLE), 434 with rheumatoid arthritis (RA), 122 Behcet's disease (BD), 76 psoriatic arthritis/psoriasis (PsA/PsO), and 74 with primary Sjögren's syndrome (pSS). Overall, 158 patients (10.5%) among the study participants experienced disease flare after vaccination, and no fatal flare occurred, indicating the excellent tolerability of inactivated COVID-19 vaccines in the population with ARD [25]. Additionally, a large real-world study supported by the European League Against Rheumatism (EULAR) COVID-19 database (83% mRNA vaccines) was conducted. The study included 5121 participants, vaccine-related adverse events were observed in 37% of patients, and flare was reported in 4.4% of patients with rheumatic diseases [26]. From January 2021 to Aug 31, 2021, a study group reported cases of musculoskeletal inflammatory manifestations including synovitis, tenosynovitis, enthesitis, inflammatory spinal pain or girdles, and pain/stiffness with serological evidence of inflammation appearing within 4 weeks of the administration of the first or second dose of one of the COVID-19 vaccines (BNT162b2, mRNA-1273, ChAdOx1, d26.COV2.S). A total of 66 patients met the inclusion criteria and presented polymyalgia rheumatica (PMR-like) (41%), oligoarthritis (32%), and polyarthritis (27%). It is noteworthy that two patients (one in the polyarticular group and one in the oligoarticular group, respectively) also had inflammatory back pain with active sacroiliitis and spondylitis on MRI. Autoantibodies comprised a rare finding, and HLA-B27 was positive in 31.8% of patients [27].

Recently, several cases were published of ARD that developed shortly after application of the anti-COVID-19 vaccine. Oskay et al. [28] described the acute onset of eruptive skin disorder in a 77-year-old male patient after the third dose of the CoronaVac vaccination. After 72 h, he experienced intestinal symptoms including bloody diarrhea and abdominal pain. Dermatologic examination revealed diffuse palpable, tender, non-blanching violaceous coalescent macules, and patches on the thighs, calves, feet, and hands. There also were bullous hemorrhagic lesions distributed bilaterally on the extensor sides of the lower legs and feet. Skin biopsy was compatible with small-vessel leukocytoclastic vasculitis (LCV). Antinuclear antibodies and anti-PM-SCI antibodies were positive. Liang et al. [29] described the case of a 62-year-old Asian female who presented bilateral lower-limb non-blanching petechial rash 7 days after the first dose of the ChAdOx1 vaccine. The symptoms included headache, myalgia, and arthralgias. CRP was elevated (<5). Antinuclear antibodies (1:80 speckled) were positive, with depressed C4 complement and positive rheumatoid factor (169 IU/mL [<20]). Skin biopsy was consistent with LCV along with C3 and fibrinogen deposition in the superficial dermal vessels.

These two cases, and other cases of vasculitis, and autoimmune syndromes after the administration of COVID-19 vaccines described, suggest an association between an “adjuvant” of these vaccines and the development of such autoimmune syndromes in genetically and immunologically predisposed individuals. In this context, and to explain autoimmune disease flares and new-onset disease following COVID-19 vaccination, the participation of age-associated B cells (ABC) in the immune response triggered by the SARS-CoV-2 vaccine has been proposed. These ABC cells (CD11c + T-bet +), or double negative (DN) in humans, expand with age in healthy individuals, and are increased early in autoimmune diseases such as SLE, and infections. The cells are characterized by generating immunoglobulin G, increasing antigen presentation to T cells and germinal center formation. Another characteristic of these ABC cells lies in their role in triggering a hyper response when stimulated with Toll-like receptors 7 (TLR7) signaling, capable of generating autoreactive antibody-secreting plasmablasts. mRNA/DNA SARS-CoV-2 vaccines use TLR7/8 and TLR9 agonists as “adjuvants,” which may stimulate the subgroup of ABC, to form autoantibodies and post-vaccine autoimmune syndromes [30, 31]. The activation of TLR7 and TLR9 can lead to the production of interferon I, an essential cytokine for the development of SLE and other ARD [32]. There are other candidate B-lymphocyte stimulators, such as anti-spike antibodies developed after exposure to the SARS-CoV-2 virus and that stimulate the production of anti-idiotypic antibodies after the anti-COVID vaccine. Lipid nanoparticles or other components of the vaccine have been proposed [33]. However, the exact mechanisms behind post-COVID-19 vaccine autoimmune syndromes remain to be established.

Does the spectrum of the autoimmune/inflammatory syndrome expand?

Many of the autoimmune syndromes mentioned earlier that appeared following COVID-19 vaccination meet sufficient criteria for the diagnosis of ASIA [6, 34–38]:

Major criteria

- 1) Exposure to an external stimulus (COVID-19 vaccine). Average number of days-of-onset of symptoms after applying the COVID-19 vaccine is short and ranges from 8 days to 3 weeks [23]. In our experience and that of other researchers [19, 28, 31], in the majority of cases of ASIA, symptoms occur within 2–5 days after application of the COVID-19 vaccine.
- 2) The appearance of “typical” clinical manifestation. Many of these patients develop acute clinical pictures

with manifestations of autoimmune diseases, including vasculitis, arthritis, SLE, and neurological syndromes.

- 3) Removal of the inciting agent induces improvement. Fortunately, autoimmune syndromes induced or triggered by the COVID-19 vaccine are rare, short-lived, and respond to steroidal and other symptomatic treatments, therefore having a good prognosis [23].

One aspect of the discussion is whether to continue the application of subsequent vaccinations for patients who develop autoimmune manifestations after the first dose of the vaccine. A recent study suggests that in some cases, such as VITT, administering a second dose, regardless of the vaccine received against COVID-19, did not cause any adverse events [39]. The absence of relapse after the second dose suggests that, in some cases, the autoimmune syndrome is not related to components of the vaccine such as spike protein.

Minor criteria

The appearance of autoantibodies or antibodies directed at the suspected adjuvant. Multiple organ-specific [34] and non-organ-specific autoantibodies [31] have been described in patients with autoimmune syndromes associated with COVID-19 vaccines. The simultaneous presence of anti-neutrophil cytoplasmic autoantibody-mediated glomerulonephritis and anti-glomerular basement membrane after COVID-19 vaccination in a patient without prior kidney injury has recently been described [40].

During the period from May 2021 to December 2021, 36 patients referred to hospitals in Mexico City were diagnosed with ASIA after vaccination with different types of COVID-19 vaccines (Table 1).

Multiple evidences suggest the existence of a new syndrome called “post-COVID syndrome,” “long COVID,” and “chronic COVID-19,” characterized by “nonspecific” symptoms and signs such as encephalomyelitis/chronic fatigue syndrome (ME/CFS) like, severe fatigue, sleep disorders, cognitive impairments, and different manifestations of autonomic dysfunction. The autoimmunity to the autonomic nervous system may explain the diversity of the clinical manifestations. The persistence of these symptoms is not caused by the persistence of the infection. In this regard, it has been proposed that the spike protein could damage the endothelium in an animal model, that it could disrupt an in vitro model of the blood–brain barrier (BBB), and that it can cross the BBB resulting in perivascular inflammation. These findings suggest an involvement of immune-related dysfunction in the development of post-COVID syndrome, and have led to the proposal of immunomodulatory treatments in conjunction with vaccination against COVID-19 in patients with long-term COVID-19 [41, 42].

Table 1 Autoimmune/ autoinflammatory syndrome (ASIA) induced by COVID-19 vaccine *N* = 36

Autoimmune disease	Number of patients	Vaccines	Autoantibodies
Neurologic			
Guillain-Barré syndrome	10	Sinovac 1 Sputnik 1 AstraZeneca 8	ANA = 1 Anti Ro = 2 RF = 3
Optical neuromyelitis	5	Sputnik 2 AstraZeneca 1 Moderna 1 Pfizer 1	AQP4 = 2
Transverse myelitis	4	Sputnik 1 AstraZeneca 3	ANA = 1 Anti Ro = 1
Autoimmune encephalitis	3	AstraZeneca 2 Moderna 1	Anti NMD = 2 Anti GABA = 1
Sensory neuropathy	2	Johnson & Johnson 1 AstraZeneca 1	ANA = 1
Rheumatologic			
Kawasaki vasculitis	2	AstraZeneca 2	ANA = 1 Anti Ro = 1 Coombs = 1
Polyarthritis autoimmune RA	2	AstraZeneca 2	RF = 1
ANCA-associated vasculitis	1	Pfizer 1	ANCA = 1
Endocrinologic			
Graves' disease	2	Pfizer 2	Anti TSI = 1 ANA = 1
Subacute thyroiditis	2	Sputnik 1 AstraZeneca 1	Anti TPO = 2
Hematologic			
Vaccine-induced immune thrombocytopenia	3	AstraZeneca 2 Pfizer 1	IgM aCL

ANA, antinuclear antibodies; RF, rheumatoid factor; Anti AQP4, ; Anti-Aquaporin 4 antibody, Anti NMDA, *N*-methyl-D-aspartate; Anti GABA, gamma-aminobutyric acid; TSI, thyroid-stimulating immunoglobulin; Anti TPO, antithyroid peroxidase; IgM aCL, IgM anti cardiolipin antibodies

Conclusion

- 1) Even though a cause-effect relationship cannot be established for now, the autoimmune syndromes have been observed after the administration of the COVID-19 vaccines.
- 2) Despite the increasing number of reports regarding autoimmune syndromes following vaccination against COVID-19, the incidence is very low, and the benefits of vaccines overcome such rarity.
- 3) The association between the COVID-19 vaccines and the autoimmune syndromes described open the doors to further investigate the complex relationship between the components of the vaccine and the innate and adaptive immune response.
- 4) The autoimmune syndromes observed in some individuals following COVID-19 vaccines expand the diagnosis of ASIA.

Declarations

Disclosures None.

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