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Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review

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ARTICLE INFO

Keywords:
Autoimmunity
COVID-19
SARS-CoV-2
Vaccines

ABSTRACT

Autoimmunity linked to COVID-19 immunization has been recorded throughout the pandemic. Herein we present six new patients who experienced relapses of previous autoimmune disease (AD) or developed a new autoimmune or autoinflammatory condition following vaccination. In addition, we documented additional cases through a systematic review of the literature up to August 1st, 2022, in which 464 studies (928 cases) were included. The majority of patients (53.6%) were women, with a median age of 48 years (IQR: 34 to 66). The median period between immunization and the start of symptoms was eight days (IQR: 3 to 14). New-onset conditions were observed in 81.5% (n: 756) of the cases. The most common diseases associated with new-onset events following vaccination were immune thrombocytopenia, myocarditis, and Guillain-Barré syndrome. In contrast, immune thrombocytopenia, psoriasis, IgA nephropathy, and systemic lupus erythematosus were the most common illnesses associated with relapsing episodes (18.5%, n: 172). The first dosage was linked with new-onset events (69.8% vs. 59.3%, P = 0.0100), whereas the second dose was related to relapsing disease (29.5% vs. 59.3%, P = 0.0159). New-onset conditions and relapsing diseases were more common in women (51.5% and 62.9%, respectively; P = 0.0081). The groups were evenly balanced in age. No deaths were recorded after the disease relapsed, while 4.7% of patients with new-onset conditions died (P = 0.0013). In conclusion, there may be an association between COVID-19 vaccination and autoimmune and inflammatory diseases. Some ADs seem to be more common than others. Vaccines and SARS-CoV-2 may induce autoimmunity through similar mechanisms. Large, well-controlled studies are warranted to validate this relationship and assess additional variables such as genetic and other environmental factors.

1. Introduction

The world witnessed a major infectious disease that first emerged in the Chinese city of Wuhan in 2019, an illness known as Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It quickly spread worldwide and was declared a pandemic within a few months. On August 6, 2022, the Johns Hopkins University Center for Systems Science and Engineering reported 583,840,223 cases, with 6,417,401 deaths [1].

The clinical spectrum of COVID-19 ranges from the absence of symptoms to the presence of severe pneumonia, associated with a hyperinflammatory state, which causes multiorgan failure [2,3]. The most severe disease cases are related to an increase in the production of inflammatory cytokines (i.e., cytokine storm) [4,5]. Because of the disease’s fast spread and the lack of effective therapies, attempts were made worldwide to find vaccines to reduce the disease’s severity and mortality. To date, 12,002,790,796 dosages have been administrated [1].
Table 1
Characteristics of six new cases of post-COVID vaccine autoimmune or inflammatory diseases.

| Disease                          | Age (years) | Sex | Type of vaccine | Clinical manifestations of autoimmune disease | Diagnostic tests | Symptoms onset after vaccination (days) | Comment and outcome                                                                                                                                                                                                                                    |
|----------------------------------|-------------|-----|-----------------|-----------------------------------------------|------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Autoimmune Disease flare post-COVID vaccine | 56          | F   | Pfizer          | Loss of visual acuity of the left eye          | Ocular ultrasound: left eye retrobulbar optic neuritis | 6 days after 1st dose | In 2004, she was diagnosed with optic neuritis and received treatment with methylprednisolone. Since, she continued with progressive loss of vision, 6 cycles of cyclophosphamide were administered, and subsequently received mycophenolate for 2 years with adequate control of the disease. After the first dose of the vaccine, she once again developed loss of visual acuity. A month later she was diagnosed with an optic neuritis flare. At this instance, she received methylprednisolone (1 g/d) for 5 days, but since the symptoms persisted, plasmapheresis therapy was given for 5 days. Ambulatory management with prednisolone (10 mg/d) was prescribed. Since then, the patient’s visual disturbances have improved slowly. Since 2017, patient presents with bilateral symmetrical arthralgias in hands associated with morning stiffness, but never consulted neither received immunomodulatory therapy. After vaccination, the pain was sharply increased so she went to the emergency room where therapy with methylprednisolone (250 mg/d) for 3 days was initiated and ambulatory management with methotrexate (25 mg weekly), chloroquine (150 mg) and prednisolone was given. In a follow up consult, the patient presented modulation of her symptoms. |
| Optic neuritis flare             | 56          | F   | Pfizer          | Loss of visual acuity of the left eye          | Ocular ultrasound: left eye retrobulbar optic neuritis | 6 days after 1st dose | In 2004, she was diagnosed with optic neuritis and received treatment with methylprednisolone. Since, she continued with progressive loss of vision, 6 cycles of cyclophosphamide were administered, and subsequently received mycophenolate for 2 years with adequate control of the disease. After the first dose of the vaccine, she once again developed loss of visual acuity. A month later she was diagnosed with an optic neuritis flare. At this instance, she received methylprednisolone (1 g/d) for 5 days, but since the symptoms persisted, plasmapheresis therapy was given for 5 days. Ambulatory management with prednisolone (10 mg/d) was prescribed. Since then, the patient’s visual disturbances have improved slowly. Since 2017, patient presents with bilateral symmetrical arthralgias in hands associated with morning stiffness, but never consulted neither received immunomodulatory therapy. After vaccination, the pain was sharply increased so she went to the emergency room where therapy with methylprednisolone (250 mg/d) for 3 days was initiated and ambulatory management with methotrexate (25 mg weekly), chloroquine (150 mg) and prednisolone was given. In a follow up consult, the patient presented modulation of her symptoms. |
| Rheumatoid arthritis flare       | 47          | F   | Jansen          | Arthralgia and arthritis in 2, 3 and 4 bilateral metacarpophalangeal and proximal interphalangeal joints Right knee synovitis | C-reactive protein 6.74 mg/L Erythrocyte sedimentation rate 40 mm/h | 8 days after vaccination | Since 2017, patient presents with bilateral symmetrical arthralgias in hands associated with morning stiffness, but never consulted neither received immunomodulatory therapy. After vaccination, the pain was sharply increased so she went to the emergency room where therapy with methylprednisolone (250 mg/d) for 3 days was initiated and ambulatory management with methotrexate (25 mg weekly), chloroquine (150 mg) and prednisolone was given. In a follow up consult, the patient presented modulation of her symptoms. |
| Autoimmune Disease post-COVID vaccine | 69          | F   | Pfizer          | Jaundice Abdominal pain Choluria             | Hyperbilirubinemia (6.49 mg/dl) with direct bilirubin predominance (5.71 mg/dl) Elevated transaminases GOT: 559 U/L GPT:339 U/L Anti-smooth muscle antibodies 57.4 (Positive) Elevated IgG (3342 mg/dl) | 150 days after 2nd dose | After diagnosis, treatment with methylprednisolone (500 mg/d) for 5 days was initiated, and ambulatory treatment with azathioprine (50 mg twice a day) and tapering prednisolone of 10 mg per week was prescribed. In a follow up control in January 2022, patient clinical condition had resolved. |
| Autoimmune hepatitis             | 69          | F   | Pfizer          | Jaundice Abdominal pain Choluria             | Hyperbilirubinemia (6.49 mg/dl) with direct bilirubin predominance (5.71 mg/dl) Elevated transaminases GOT: 559 U/L GPT:339 U/L Anti-smooth muscle antibodies 57.4 (Positive) Elevated IgG (3342 mg/dl) | 150 days after 2nd dose | After diagnosis, treatment with methylprednisolone (500 mg/d) for 5 days was initiated, and ambulatory treatment with azathioprine (50 mg twice a day) and tapering prednisolone of 10 mg per week was prescribed. In a follow up control in January 2022, patient clinical condition had resolved. |
| Other disease post-COVID vaccine | 53          | F   | Pfizer          | Erythematos painful plaques of different sizes scattered on 4 extremities (See Fig. 1) Fever Malaise | Skin biopsy (See Fig. 1) C-reactive protein 89.77 mg/L. White cells count 10.690/L Neutrophils 93.4% Peripheral blood smear without alterations Chest and abdominal CT scan within normal ranges. No visceral masses | 72 days after 2nd dose | After diagnosis, treatment with methylprednisolone (500 mg/d) for 3 days was initiated for 3 days which caused resolution of the skin lesions |
| Sweet Syndrome                   | 53          | F   | Pfizer          | Erythematos painful plaques of different sizes scattered on 4 extremities (See Fig. 1) Fever Malaise | Skin biopsy (See Fig. 1) C-reactive protein 89.77 mg/L. White cells count 10.690/L Neutrophils 93.4% Peripheral blood smear without alterations Chest and abdominal CT scan within normal ranges. No visceral masses | 72 days after 2nd dose | After diagnosis, treatment with methylprednisolone (500 mg/d) for 3 days was initiated for 3 days which caused resolution of the skin lesions |
| Urticarial Vasculitis            | 56          | F   | Sinovac         | Erythematos lesions, with a pale center, pruritic, distributed on trunk and extremities (See Fig. 2) | Skin biopsy. (See Fig. 2) | 1 day after 2nd dose | After the appearance of the skin lesions treatment with loratadine and methylprednisolone (500 mg/d) was initiated for 3 days which caused improvement of the symptoms At first treatment with topic betamethasone and loratadine was initiated. Since there was no clinical improvement, methylprednisolone (500 mg/d) for 3 days, was established with which she presented resolution of her symptoms |
| Leukocytoclastic vasculitis      | 54          | F   | Pfizer          | Erythematos lesions, with irregular borders in lower extremities (See Fig. 3) | Skin biopsy (See Fig. 3) | 8 days after 2nd dose | After the appearance of the skin lesions treatment with loratadine and methylprednisolone (500 mg/d) was initiated for 3 days which caused improvement of the symptoms At first treatment with topic betamethasone and loratadine was initiated. Since there was no clinical improvement, methylprednisolone (500 mg/d) for 3 days, was established with which she presented resolution of her symptoms |

GOT: Glutamic-oxaloacetic transaminase, GPT: Glutamic-pyruvate-transaminase, IgG: Immunoglobulin G, M: Male, F: Female.
Over 200 vaccines against COVID-19 are currently being produced, with many already in clinical testing [6]. The main types include viral vector vaccines (Oxford/AstraZeneca, Sputnik V), genetic vaccines using messenger ribonucleic acid (mRNA) (Moderna and Pfizer/BioNTech), and inactivated vaccines (Sinovac, Sinopharm, Bharat Biotech Covaxin).

Vaccines save millions of lives each year, improving the quality of life. Vaccines have had great success over the last two centuries, but they are not free of side effects, including latent and overt autoimmunity via various pathways [7,8]. Although widespread vaccination against COVID-19 has reduced disease severity and mortality, vaccine-related adverse events such as autoimmune and autoinflammatory diseases have been documented. These include thrombotic thrombocytopenia, myocarditis, Guillain-Barré syndrome (GBS), demyelinating disorders, and systemic lupus erythematosus (SLE), among others [9–15]. We present six new patients who experienced relapses of autoimmune diseases (AD) or developed a new autoimmune or autoinflammatory disease following vaccination. In addition, we document the main cases of autoimmunity and autoinflammatory conditions associated with the COVID-19 vaccine in a systematic review. Finally, we discuss the possible hypotheses underlying this phenomenon based on the evidence gathered.

2. Materials and methods

2.1. Information sources and search strategy

A systematic literature review was conducted up to August 1st, 2022. The search was performed in PUBMED. We searched using the terms: ((((((((((((((((((( (((Thyroiditis, Autoimmune)[Mesh]) OR “Hashimoto Disease”[Mesh]) OR “Graves’ Disease”[Mesh]) OR “Arthritis, Rheumatoid”[Mesh]) OR ”Sjogren’s Syndrome”[Mesh]) OR “Sarcoidosis”[Mesh]) OR “Diabetes Mellitus, Type 1”[Mesh]) OR “Multiple Sclerosis”[Mesh]) OR “Scleroderma, Systemic”[Mesh]) OR “Guillain-Barre Syndrome”[Mesh]) OR “Myasthenia Gravis”[Mesh]) OR “Hepatitis, Autoimmune”[Mesh]) OR “Liver Cirrhosis, Biliary”[Mesh]) OR “Cholangitis, Sclerosing”[Mesh]) OR “Crohn Disease”[Mesh]) OR “Colitis, Ulcerative”[Mesh]) OR “Anemia, Pernicious”[Mesh]) OR “Anemia, Hemolytic”[Mesh]) OR “Anemia, Hemolytic, Autoimmune”[Mesh]) OR “Purpura, Thrombocytopenic, Idiopathic”[Mesh]) OR “Celiac Disease”[Mesh]) OR “Vitiligo”[Mesh]) OR “Pemphigoid, Bullous”[Mesh]) OR “Dermatomyositis”[Mesh]) OR “Polymyositis”[Mesh]) OR “Kawasaki Disease” OR “Lupus Erythematosus, Systemic”[Mesh]) OR “Addison Disease”[Mesh]) OR “Primary
biliary cholangitis” OR “Vasculitis”[Mesh]) OR “Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis”[Mesh]) OR “Systemic Vasculitis”[Mesh]) OR “Vasculitis, Leukocytoclastic, Cutaneous”[Mesh]) OR “Granulomatosis with Polyangiitis”[Mesh]) OR “Takayasu Arteritis”[Mesh]) OR “Giant Cell Arteritis”[Mesh]) OR “Thromboangiitis Obliterans”[Mesh]) OR “Mucocutaneous Lymph Node Syndrome”[Mesh]) OR “Polyarteritis Nodosa”[Mesh]) OR “Churg-Strauss Syndrome”[Mesh]) OR “IgA Vasculitis”[Mesh]) OR “Microscopic Polyangiitis”[Mesh]) OR “Antiphospholipid Syndrome”[Mesh]) AND “COVID-19 Vaccines”[Mesh]) OR “ChAdOx1 nCoV-19”[Mesh]) OR “2019-nCoV Vaccine mRNA-1273”[Mesh]) OR “BNT162 Vaccine”[Mesh]) OR “Ad26COVS1”[Mesh] OR SARS-CoV-2 vaccines). Additionally, a manual search was carried out through the articles referenced in the included studies to expand the number of articles.

2.2. Eligibility criteria

The articles included in this study described patients with autoimmunity, or inflammatory diseases, associated with a history of vaccination against COVID-19. Case reports and case series were included. Only articles in English or Spanish were included. Cases that did not report the population of interest and those reports that did not specify the type of vaccine were excluded.

2.3. Study selection and data extraction process

The eligibility assessment was made by two reviewers, who independently reviewed all the articles selected in the initial search. The two reviewers extracted information related to sociodemographic data, type of disease, clinical characteristics, laboratory data, histopathological data, type of vaccine received, treatment received, and response to treatment. Any differences were resolved by consensus. The PRISMA guidelines for reporting in systematic reviews were used during the selection and data analysis phases [16].

2.4. Statistical analysis

Studies reporting individual data of patients were included in the analysis. Univariate descriptive statistics were performed. Categorical variables were analyzed using frequencies, and continuous quantitative variables were expressed in the median and interquartile range (IQR). Fisher’s exact or Mann-Whitney U tests were used to explore differences between new-onset and relapsing autoimmune/autoinflammatory conditions. The significance level of the study was set to 0.05. Statistical analyses were done using R software version 4.0.2.
3. Results

3.1. Case reports

Six patients attending the post-COVID unit at the Clínica del Occidente in Bogota, Colombia, who presented autoimmunity or auto-inflammatory disease after receiving the SARS-CoV-2 vaccine are described in Table 1. Two patients showed disease relapse after vaccination (none of them were on immunomodulatory management at the moment for vaccination since they were on disease remission). One patient debuted with the disease after vaccination, and three developed other inflammatory manifestations. The images of the clinical findings and histopathological findings of these three cases are shown in Figs. 1–3.

3.2. Search results

A total of 16,949 manuscripts were found through the main search. After duplication, 15,968 were obtained. Then, 421 articles remained after the title and abstract review. In the selection phase, 46 studies were excluded. After that, additional 85 articles were identified from other resources. Finally, 464 studies were included for qualitative and quantitative analysis [11], [17–467] (Fig. 4).

3.3. Systematic review of case reports

A total of 928 reports were obtained, each with its own data set. Most of them were women (488/910, 53.6%), with a median age of 48 (IQR: 34 to 66). The median period between immunization and the start of symptoms was eight days (IQR: 3 to 14). After immunization, the most common side effect was a new onset condition (756/928, or 81.5%). About 22.5% of new-onset and 21.5% of relapsing illness cases were reported in the United States (Fig. 5).

Following vaccination, the most commonly reported diseases associated with new-onset events were immune thrombocytopenia, GBS, and myocarditis (Fig. 6) (Table 2). Immune thrombocytopenia, psoriasis, IgA nephropathy, and SLE, on the other hand, were the most commonly reported illnesses associated with relapsing episodes (Fig. 6). Both occurrences were widely linked to the mRNA-1273 SARS-CoV-2 vaccine, which was followed by Sinovac-CoronaVac and ChAdOx1 nCoV-19 vaccine (AZD1222) (Fig. 7). The first dosage was linked with new-onset events (69.8% vs. 59.3%, P = 0.0100). In contrast, the second

Fig. 3. Leukocytoclastic vasculitis. A. Skin lesions appeared 19 days after the vaccination. Erythematous macular lesions with irregular borders in the lower extremities. B. Skin biopsy histological findings. In the superficial and deep dermis perivascular infiltration of neutrophils with leukocytoclasis, extravasated erythrocytes and capillary wall damage with some oedema X40.
dose was associated with relapsing disease (29.5% vs. 39.5%, \( P = 0.0159 \)). Few new-onset or relapsing events were reported after booster dose (0.7% vs. 1.2% respectively, \( P = 0.6216 \)). New-onset conditions and relapsing disease were more common in women (51.5% and 62.9%, respectively; \( P = 0.0081 \)). The groups were evenly balanced in age (\( P = 0.7851 \)). No deaths were recorded after the disease relapsed, while 4.7% (35/920) of patients with new-onset conditions died (\( P = 0.0013 \)).

4. Discussion

The pandemic’s influence has boosted vaccine development, allowing them to be manufactured in record time. As a result, many vaccines with unique and promising modes of action have been developed. However, the quick deployment has raised several issues, including their safety, which could be linked to the dose given and the age of the patients (occurring before 55 years of age in most cases) [468].

We report six new patients who had autoimmune and autoinflammatory diseases, either for the first time or as a relapse. As revealed in the systematic review, these adverse effects have been previously reported in the literature. The most common diseases linked to immunization were thrombocytopenia, myocarditis, GBS, nephropathy, and thyroid disorders. It is remarkable since some of these diseases are usually triggered by infections and other vaccines [469–471]. It suggests similar immunopathogenic mechanisms between vaccines and infectious agents as triggering factors of ADs. This hypothesis could be supported through the anti-idiotype immune response, which shows that antibodies against a specific antigen can trigger the production of second particular antibodies against the first ones [472]. Surprisingly, the second antibodies may be capable of binding to receptors that the initial antigen may attach to. This is significant since many autoimmune or autoinflammatory reactions elicited by COVID-19 vaccinations have previously been reported with vaccines whose principal immunopathogenic mechanism is the anti-idiotype immune response [473,474].

SARS-CoV-2 might trigger ADs [475] through different mechanisms, including molecular mimicry [476,477]. Several studies have demonstrated that the history of past infections can alter the reactogenicity of mRNA vaccines through a cross-reactivity mechanism [468]. However, greater reactogenicity may confer higher protection but could generate more adverse events. Remarkably, patients with ADs are not at increased risk of adverse events associated with vaccination [478], possibly due to the effect of immunomodulatory drugs on vaccine immunogenicity.

Although RNA-based vaccines focus on synthesizing antigens that facilitate immunogenicity [479], the mRNA may bind to pattern recognition receptors (PRRs) in the cytosol or on the endosomes before
translation. This binding is accomplished through Toll-like receptors (TLR), 8,7 or 3 in endosomes, or through melanoma differentiation-associated protein 5 (MDA5) or retinoic acid-inducible gene I (RIG-I) in the cytosol. As a consequence, the activation of inflammatory cascades associated with the activation of the type I interferon (IFN-\(\text{I}\)) and transcription of the nuclear factor (NF)-kB occurs [480].

These signaling pathways have been extensively studied in different ADs, which can be triggered by the antigenic effect of inadequately eliminated nucleic acids, generating an immune system activation [481, 482]. A very high IFN-I response could negatively influence mRNA translation, affecting vaccine efficacy [483]. In addition, it has been described that an increase in the effect of IFN-I can trigger a loss of immune tolerance [483].

Some of the side effects of adenoviral vaccines have been linked to variations of the spike (S) protein, which attaches to endothelial cells in blood vessels via the angiotensin-converting enzyme 2 (ACE2), causing COVID-19-like disorders [484].

The main autoimmune phenomena correspond to vaccine-induced immune thrombotic thrombocytopenia (VITT). Several studies have documented the presence of platelet-activating antibodies directed against platelet factor 4 (PF4), like Heparin-associated thrombocytopenia, which is characterized by the presence of antibodies against the heparin/(PF4) complex, generating thrombocytopenia and thrombosis due to platelet activation. It occurs due to the binding of PF4 with endothelial cells and platelets, facilitating platelet aggregation and thrombus formation [485]. PF4 platelet activation by these antibodies occurs through Fc\(\gamma\)RIIa [336]. The similarity between thrombocytopenia induced by heparins and SARS-CoV-2 vaccines is striking [486, 487]. Patients with thrombocytopenia after ChAdOx1 nCov-19 IgG antibodies against PF4 have been described [488]. PF4 can interact with the double-stranded DNA of the vaccine vector. The PF4/DNA vector
Fig. 6. Distribution of the main documented diseases after COVID-19 vaccination.
Table 2 (continued)

| Demographic characteristics | New onset (n: 756) | Relapsing (n: 172) | P value |
|-----------------------------|-------------------|-------------------|---------|
| Polyarteritis nodosa        | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Immune complex vasculitis   | 1 (0.1%)          | 1 (0.6%)          | 0.3365  |
| Kawasaki Disease            | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Temporal arteritis like disease | 2 (0.3%)    | 0 (0.0%)          | 1.0000  |
| Lofgren syndrome            | 3 (0.4%)          | 0 (0.0%)          | 1.0000  |
| Erythema nodosum            | 3 (0.4%)          | 1 (0.6%)          | 0.5602  |
| Neurosarcoidis              | 1 (0.1%)          | 1 (0.6%)          | 0.2565  |
| Macrophage activation syndrome | 1 (0.1%)    | 0 (0.0%)          | 1.0000  |
| Hypereosinophilic syndrome  | 1 (0.1%)          | 1 (0.6%)          | 0.3365  |
| Hemophagocytic lymphohistiocytosis | 7 (0.9%) | 0 (0.0%) | 0.3599 |
| Fever of unknown origin     | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Multisystem inflammatory syndrome | 7 (0.9%) | 0 (0.0%) | 0.3599 |
| Systemic sclerosis          | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Vitiligo                    | 3 (0.4%)          | 0 (0.0%)          | 1.0000  |
| Dermatomyositis             | 5 (0.7%)          | 1 (0.6%)          | 1.0000  |
| Psoriasis                   | 3 (0.4%)          | 22 (12.8%)        | < 1e-04 |
| Bullous pemphigoid          | 23 (3.0%)         | 4 (2.3%)          | 0.8029  |
| Pemphigus vulgaris          | 7 (0.9%)          | 1 (0.6%)          | 1.0000  |
| Pemphigus foliaceus         | 1 (0.1%)          | 0 (0.0%)          | 1.0000  |
| Acute dysidriotic ecema     | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Stevens Johnson syndrome    | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Linear IgA bullous dermatosis | 2 (0.3%)     | 0 (0.0%)          | 1.0000  |
| Chilblain like lesions      | 3 (0.4%)          | 0 (0.0%)          | 1.0000  |
| Sweet syndrome              | 4 (0.5%)          | 0 (0.0%)          | 1.0000  |
| Lichen planus               | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Pigmented purpuric dermatosis | 2 (0.3%)   | 0 (0.0%)          | 1.0000  |
| Exanthenomatous pustulosus  | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Sarcodeiosis                | 2 (0.3%)          | 0 (0.0%)          | 1.0000  |
| Laboratory characteristics  |                   |                   |         |
| Elevated D Dimer            | 95 (15.5%)        | 1 (0.7%)          | < 1e-04 |
| CSF albuminocytological dissociation | 48 (7.8%) | 1 (0.7%) | 0.0003 |
| Thrombocytopenia            | 225 (36.2%)       | 23 (23.2%)        | 0.0032  |
| Proteinuria                 | 53 (8.7%)         | 24 (16.1%)        | 0.0098  |
| Haematuria                  | 40 (6.5%)         | 20 (13.4%)        | 0.0098  |
| Gadolinium enhancement of the myocardium pericardium | 35 (5.7%) | 0 (0.0%) | 0.0007 |
| Diffuse ST elevations       | 28 (4.6%)         | 1 (0.7%)          | 0.0285  |
| Elevated troponin           | 69 (11.3%)        | 1 (0.7%)          | < 1e-04 |
| Subepicardial enhancement   | 21 (3.4%)         | 0 (0.0%)          | 0.0212  |
| Clinical characteristics    |                   |                   |         |
| Arthralgia arthritis        | 32 (5.2%)         | 17 (11.3%)        | 0.0092  |
| Headache                    | 39 (6.4%)         | 3 (2.0%)          | 0.0432  |
| Parathresia                 | 33 (5.3%)         | 1 (0.7%)          | 0.0975  |
| Weakness                    | 70 (11.1%)        | 5 (3.3%)          | 0.0020  |
| Pleurisy                    | 6 (1.0%)          | 7 (4.6%)          | 0.0845  |
| Treatment                  |                   |                   |         |
| Corticosteroids             | 400 (61.5%)       | 112 (65.1%)       | 0.0039  |
| Anticoagulants/antiaggregants | 77 (10.2%)  | 0 (0.0%)          | < 1e-04 |
| IV immunoglobulins          | 160 (21.2%)       | 18 (10.5%)        | 0.0009  |
| Transfusion of blood products: platelet | 56 (7.4%) | 2 (2.9%) | 0.3899 |
| NSAIDs                      | 61 (8.1%)         | 6 (3.5%)          | 0.0341  |
| Cyclosporine                | 3 (0.4%)          | 4 (2.3%)          | 0.0251  |
| Diuretics/ACE inhibitor/calcium channel blocker/beta blocker/ angiotensin II receptor antagonist | 49 (6.5%) | 3 (1.7%) | 0.0153 |
| Tacrolimus                  | 2 (0.3%)          | 3 (1.7%)          | 0.0468  |
| Ixekizumab                  | 0 (0.0%)          | 2 (1.2%)          | 0.0342  |
| Clinical outcomes           |                   |                   |         |
| Good response               | 342 (47.4%)       | 81 (47.4%)        | 0.7339  |
| Resistance                  | 236 (31.5%)       | 57 (33.3%)        | 0.6500  |
| Relapse                     | 30 (4.7%)         | 1 (0.6%)          | 0.1515  |
| Death                       | 35 (4.7%)         | 0 (0.0%)          | 0.0013  |
| IQR: Interquartile range, ANCA: Antineutrophil cytoplasmic antibody, CSF: cerebrospinal fluid, PP4: Platelet factor 4, NSAIDs: Non-steroidal anti-inflammatory drugs, ACE: Angiotensin-converting enzyme. |
complex is taken up by antigen-presenting cells, later facilitating the production of antibodies against PF4 [489]. A recent study showed the structure of ChAdOx1/AZD-1222, evidencing a strong electronegative potential in the ChAdOx1 viral capsid, facilitating its binding with proteins such as PF4 [490].

Recently, the association between VITT and neutrophil activation was studied. It can occur through different signaling pathways and could be facilitated by NETosis and platelet activation [491]. Another mechanism that could explain the presence of VITT may be related to the activation of the NF-κB pathway. Plasminogen activator inhibitor-1 (PAI-1) plays a relevant role in thrombotic events. It has been described that the presence of TNF alpha can promote an increase in serum concentrations of PAI 1 in sepsis. In addition, nuclear translocation of NF-κB in monocytes has been described, increasing the expression of tissue factor (TF) and increasing the expression of thrombin expression [492]. Besides being produced in monocytes, it is also expressed in the endothelium [493]. Due to the direct effect of NF-κB on monocytes, the production of cytokines, such as interleukin 1β, can generate procoagulant states [494,495].

5. Conclusions

There is likely an association between COVID-19 vaccination and autoimmune and inflammatory diseases. Some ADs seem to be more common than others. The mechanisms of autoimmunity induction by COVID-19 vaccines and SARS-CoV-2 infection may be similar. Large, well-controlled studies are warranted to validate this relationship and assess additional variables such as genetic and environmental influences. Further detailed studies focusing on mechanisms, including molecular mimicry and bystander activation, will be essential to explain these rare events. Noteworthy, these rare events should not deter the use of this and other necessary vaccinations.

Funding

This study was supported by Universidad del Rosario (grant ABN011) and LifeFactors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

None.

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