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Autoimmune phenomena following SARS-CoV-2 vaccination

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ABSTRACT

Vaccines represent an attractive possible solution to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. Widespread vaccine distribution has yet to occur in most countries, partially due to public concerns regarding possible side effects. While studies indicate the vaccine is exceptionally safe, rare systemic side effects remain possible. In Israel, where a large percentage of the population has been rapidly vaccinated, such adverse events may be more apparent. We report a series of patients presenting with de-novo or flares of existing autoimmune conditions associated with the Pfizer BNT162b2 mRNA SARS-CoV-2 vaccine. All patients were assessed in our tertiary care center in Israel and had no history of previous SARS-COV-2 infection. We observed that while immune phenomena may occur following vaccination, they usually follow a mild course and require modest therapy. We briefly expound on the theoretical background of vaccine related autoimmunity and explore future research prospects.

1. Introduction

Vaccines as triggers of autoimmunity is a controversial subject. Many vaccine related immunological adverse events have been described; for example, evidence for an increased risk of Guillain-Barre syndrome following Influenza vaccine, an association between systemic lupus erythematosus and the papilloma vaccine, and episodes of immune demyelination after hepatitis B vaccine were all previously suggested [1,2]. Although direct causation is debatable, the association is plausible.

Detecting immunological adverse reactions to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is of great public and scientific interest. This is especially the case for the mRNA-based vaccines available, the first mRNA-based vaccines entering mass use.

By March 2021, more than half of the adult (>16 years) population in Israel had been vaccinated with at least one dose of the BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine (BioNTech and Pfizer). Studies suggest significant efficacy in preventing COVID-19 and reducing disease severity. This tremendous vaccination rate provides an opportunity to detect rare adverse events not reported in the original trial [3]. Here, we present eight cases of autoimmune phenomena following COVID-19 vaccination, suggesting a possible association between these novel vaccines and autoimmunity.

2. Methods

All patients have been treated during the first 3 months of 2021 by

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; CRP, C-reactive protein, ANA: antinuclear antibody; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; ED, emergency department; FMF, familial Mediterranean fever; ESR, erythrocyte sedimentation rate; AF, atrial fibrillation; ECG, electrocardiography; TTE, transthoracic echocardiogram; NSAIDs, non-steroidal anti-inflammatory drugs; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; CT, computed tomography; NLRP3, NLR pyrin domain containing 3; TLR, toll-like receptor; MHC, Major histocompatibility complex.

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the contributing authors under the auspices of Hadassah Ein Kerem medical center in Jerusalem, Israel. They have all been treated according to their condition and all testing was done by clinical judgement only. All patient interactions were done under strict adherence to the Hadassah ethical code. To protect patient privacy, we have omitted all details which may identify the patients.

3. Case presentations

Herein, we describe the cases we find to be most informative on post-vaccine immune phenomena. Pertinent details are repeated in table, and several similar cases are summarized in table form only (Table 1). All references to vaccine refer to the BNT162B2 mRNA vaccine.

3.1. Symmetric polyarthritis

A 49-year-old male (patient #1) presented with a 2-day history of bilateral hand pain, swelling, and stiffness. His complaints appeared three days after receiving the first dose of the vaccine. His medical history was notable for dyslipidemia, non-alcoholic fatty liver disease, and active smoking. Physical examination revealed prominent symmetrical arthritis in the metacarpophalangeal and proximal interphalangeal joints. No history of gout, psoriasis, inflammatory bowel disease or recent infection was elicited. Blood tests showed slightly elevated C-reactive protein (CRP). Antinuclear antibody (ANA), Rheumatoid factor (RF), and parvovirus IgM, tested immediately following the acute symptoms, were negative. Anti-citrullinated protein antibody (ACPA) was mildly elevated. Hand radiographs and chest X-ray were unremarkable.

While the acute development of symptoms in proximity to vaccination argue against a diagnosis of rheumatoid arthritis, the distribution pattern and ACPA positivity support the diagnosis. Autoimmune polyarthritis, possibly representing early rheumatoid arthritis, induced or triggered by the vaccine, was diagnosed. Therapy with prednisone 10 mg brought immediate relief. Upon gradual steroid tapering over a period of 8 weeks, polyarthralgia reappeared, necessitating the commencement of methotrexate therapy.

3.2. Left eye panuveitis as a manifestation of Behçet's disease flare

A 28-year-old male patient (patient #2) presented with a 2-day history of left eye pain, redness, and blurred vision. His symptoms

Table 1
Patient Characteristics, Treatment and Outcome.

Patient number, age, and sex	Autoimmune phenomenon	Time between vaccination and symptom onset	Vaccine dose	Relevant investigations	Treatment(outcome in parenthesis)
1, 49 y/o, Male	Symmetric polyarthritis	3 days	First (Second uneventful under prednisone 10 mg)	• CRP 1.3 mg/dL • Hand radiographs and CXR: Normal • ANA, RF, and parvovirus IgM: Negative • ACPA: Positive	Prednisone 10 mg per day (Resolution of symptoms). Flared upon gradual tapering over 8 weeks, thus methotrexate was added
2, 28 y/o, Male	Left eye panuveitis (Exacerbation of Behçet's disease)	10 days	First (Second uneventful under prednisone 40 mg)	• Ophthalmologic evaluation • WBC count 12,100/μL, CRP 6 mg/dL, ESR 40 mm/hr • Previously, ANA, RF, c-ANCA, and p-ANCA: Negative	Topical corticosteroids, IV corticosteroids, azathioprine (Resolution of symptoms and normalization of WBC count and CRP levels)
3, 34 y/o, Male	Pericarditis (Recurrence)	1 day	First (Second uneventful under prophylactic NSAIDs)	• WBC count 11,300/μL, CRP 2.75 mg/dL • ECG: Known lateral wall T-wave inversions. • TTE: Mild pericardial effusion • Previously, ANA and RF: Negative	NSAIDs and colchicine (Resolution of symptoms and normalization of WBC count and CRP levels)
4, 60 y/o, Male	Temporal arteritis-like disease	3 days	First (Second uneventful under prednisone 15 mg)	• CRP 8.7 mg/dL, ESR 48 mm/hr • Temporal US and brain CT angiography: Unremarkable • Ophthalmologic evaluation: No AION	Prednisone 20 mg per day (Resolution of symptoms)
5, 60 y/o, Male	FUO	A few hours	Second (First uneventful)	• CRP 29 mg/dL, ESR 70 mm/hr • Negative blood cultures. Negative serology for Brucella, Ricketsia typhi, Coxiella Burnetti , cytomegalovirus, HIV, and Syphilis • Negative PCR for SARS-COV-2 • ANA, RF, c-ANCA, and p-ANCA: Negative • Whole body CT scan –no pathology Temporal US- negative	No specific treatment(Spontaneous clinical resolution; repeat CRP within 2 days declined to 12.4 mg/dL)
6, 37 y/o, Female	Oligoarthritis	3 weeks	Second (First uneventful)	• CRP 0.7 mg/dL	NSAIDs (Resolution of symptoms)
7, 37 y/o, Male	Pericarditis (new-onset)	10 days	First (Second uneventful)	• CRP 0.8 mg/dL • ECG: Normal • TTE: Mild pericardial effusion	NSAIDs and colchicine (Resolution of symptoms)
8, 22 y/oMale	Myocarditis	2 weeks	Second (First uneventful)	• WBC count 12,700/μL, CRP 1.4 mg/dL, Troponin 103 ng/L, CPK 2380 U/L • Negative PCR for SARS-COV-2 • ECG: Diffuse ST elevations and PR depressions • TTE: Unremarkable	NSAIDs and colchicine (Resolution of symptoms and normalization of WBC count, CRP, CPK, and troponin levels)

Abbreviations: (reference range where relevant): ACPA, anti-citrullinated protein antibodies; AION, anterior ischemic optic neuropathy; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibody; c-ANCA, cytoplasmic ANCA; CRP, C-reactive protein (0–0.5 mg/dL); CT, computed tomography; CXR, chest X-ray; CMV, cytomegalovirus; ECG, electrocardiograph; ESR, erythrocyte sedimentation rate (0–20 mm/hr); FUO, fever of unknown origin; HIV, human immunodeficiency virus; NSAIDs, non-steroidal anti-inflammatory drugs; p-ANCA, perinuclear ANCA; PCR, polymerase chain reaction; RF, rheumatoid factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTE, transthoracic echocardiography; US, ultrasound; WBC, white blood cells(3.79–10.33 cells/μL; y/o, year-old; CPK creatine phosphokinase (46–161 U/L)

began 10 days after receiving the first dose of the vaccine. The patient's medical record was notable for Behçet's disease, diagnosed four years earlier, manifesting with oral aphthous ulcers, pericarditis, and erythema nodosum. Familial Mediterranean fever (FMF) was previously ruled out, in the absence of typical episodes of fever and abdominal pain. During the preceding months, the disease was quiescent, being maintained on colchicine therapy, 0.5 mg twice daily.

Blood tests showed leukocytosis and elevated CRP and erythrocyte sedimentation rate (ESR). Ophthalmologic evaluation revealed severe left eye panuveitis compatible with Behçet uveitis, probably vaccine induced. No other systemic signs of disease activity were present. Pulse intravenous methylprednisolone (1 g/day for 5 days) was instituted in addition to intensive topical steroid therapy. Oral corticosteroids were subsequently introduced with azathioprine. There was remarkable clinical recovery, with resolution of leukocytosis and decline in CRP levels.

3.3. Pericarditis (Recurrence)

A 34-year-old male (patient #3) presented with pleuritic chest pain one day after receiving the first dose of the vaccine. This was followed shortly by an episode of symptomatic atrial fibrillation (AF). The patient's medical history was notable for recurrent pericarditis, appearing two years earlier, and a single, brief episode of AF, attributed to stress. The absence of episodes of fever and abdominal pain ruled out a diagnosis of FMF. The patient was well-controlled on colchicine therapy, with the last pericarditis flare occurring 15 months pre-vaccination. Current symptoms resembled the well-known previous inflammatory events.

Blood tests showed mild leukocytosis and elevated CRP; cardiac biomarkers were unremarkable. Electrocardiography (ECG) revealed lateral wall T-wave inversions, known from previous episodes. Transthoracic echocardiography (TTE) showed a mild pericardial effusion.

A flare of pericarditis was suspected. As the disease was completely quiescent in the previous months, an association with the vaccine was considered. The patient was started on a course of non-steroidal anti-inflammatory drugs (NSAIDs) and underwent successful pharmacologic cardioversion. Therapy with NSAIDs was continued, with resolution of symptoms and normalization of the leukocyte count and CRP levels.

3.4. Temporal arteritis-like disease

A 60-year-old male (patient #4) presented with a 3-day history of frontotemporal headaches, accompanied by diffuse arthralgia, general weakness, and blurred vision. No fever or jaw claudication were present. The patient's medical record was notable for metabolic syndrome and gout.

While physical examination was normal, blood tests revealed elevated CRP and ESR. The combination of frontotemporal headaches, blurred vision, diffuse arthralgia, general weakness, and elevated inflammatory markers raised suspicion of temporal arteritis. Neurological evaluation was normal, and head computed tomography (CT) angiography showed no ischemic lesions. Ophthalmologic examination and temporal ultrasonography were unremarkable.

Upon thorough history taking, the patient mentioned that his complaints started three days following the first dose of the vaccine. A vaccine-related syndrome resembling temporal arteritis was suspected, owing to the suggestive clinical picture. Therapy with prednisone 20 mg per day led to immediate clinical improvement.

3.5. Fever of unknown origin (FUO)

A 60-year-old male (patient #5) presented with a 2-week history of malaise and high-grade fever, progressing to diffuse arthralgia, myalgia, frontal headache, throat pain, and bilateral hand swelling. A generalized pruritic rash was also present. The patient's complaints began several hours after receiving the second dose of the vaccine. His medical record was unremarkable.

Physical examination revealed bilateral shoulder tenderness, pitting edema on the dorsal aspect of the hands, and remnants of an urticarial rash on the flexor surface of the arms. Blood tests showed elevated CRP and ESR; creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), thyroid function tests, and ferritin levels were normal. A broad microbiologic workup was negative, including blood cultures, serologies for Brucella, Coxiella Burnetti, Cytomegalovirus, and human immunodeficiency virus (HIV), as well as a nasopharyngeal PCR for SARS-CoV-2. Whole-body CT scan and temporal ultrasonography were normal.

Since a thorough investigation revealed no evident etiology, a post-vaccine immune syndrome was suspected. The patient improved clinically over several days without specific intervention, paralleling a decline in CRP levels.

4. Discussion

COVID-19 has wreaked global havoc economically and politically and has had a far-reaching impact on worldwide health. Countries and persons have had to radically change their way of life. Across the globe, people yearn for a return to normalcy. While ongoing studies attempt to fill the physician's armamentarium with effective drugs, they are far from the panacea that will allow restoration of normal life. Vaccines carry the potential benefit of reducing disease transmission and disease severity a-priori. This is especially true if they can protect at-risk populations from severe disease and the attendant burden on health systems.

In Israel, where health management organizations with electronic health records serve virtually the entire population, distribution of vaccines has been managed with striking rapidity and completeness. Procuring the Pfizer BNT162b2 2-dose mRNA vaccine, Israel has to date vaccinated over 5 million persons with both vaccine doses. This represents a substantial percentage of the qualifying population and approaches 60% of the total 9.2 million persons population. Real life results concerning vaccine efficacy in Israel have been recently published in peer-reviewed journals [4,5], and results match up to those presented in clinical trials. Despite the success of the Israeli vaccine drive, it has not gone without skeptics. Specifically, concern has been garnered regarding the relatively novel technology of mRNA vaccines and has persisted despite concerted efforts from government and private organizations to refute misinformation and provide assurance regarding vaccine safety.

While the vaccine appears to be effective and safe, side effects have been observed. Most side effects have been mild and associated with short-term reactions to the vaccine, including injection site reactions, fever and flu-like symptoms [3]. A small fraction of vaccinated persons nonetheless had more severe autoimmune manifestations following the first or second vaccines doses. While the benefits of vaccination far outweigh the risks in the vast majority of cases, it is prudent to be acquainted with possible autoimmune phenomena observed in the post-vaccine period.

The manifestation drawing the most attention in the post-vaccination period is myocarditis, especially those rare reports of severe myocarditis. Mild cases of perimyocarditis, such as the ones presented herein, are likely more common. The true added incidence of these conditions is hard to assess at the present time.

In our series, a trend of acute inflammation, usually poorly localized and involving joints, predominates. Persons suffering from previous auto-inflammatory diseases seem more likely to suffer exacerbations following vaccination. Most of the cases herein presented have had a benign course requiring little or no specific treatment and enjoyed a prompt resolution. True, chronic autoimmune diseases usually display a gradual onset, with distinct autoantibodies, sometimes preceding clinical disease by years [6]. The majority of these cases are thus unlikely to represent the onset of a chronic disease but immune epiphenomena

following vaccination. Some have nonetheless gone on to manifest prolonged symptoms in patterns appropriate for diagnosis of a chronic autoimmune disease or have had clear-cut exacerbations of known diseases.

The mechanisms of immune activation underlying these events are unknown, but we may draw on previous experience and pre-clinical data.

Exacerbation of inflammatory or autoimmune conditions following infection is not a new concept and has been suggested and demonstrated in different settings [7–9]. As the vaccine exerts its protective action by eliciting an inflammatory immune response, this could be channeled to initiate or exacerbate hyperinflammatory changes in certain vulnerable settings.

Some vaccine adjuvants – the substances lending immunogenicity to the vaccine – have been noted to act via induction and activation of the NLR pyrin domain containing 3 (NLRP3) inflammasome [10]. mRNA vaccines, BNT162b2 included, exhibit a property of self-adjuvantation, the mRNA acting as both antigen and adjuvant. They are recognized by endosomal toll-like receptors (TLRs) and cytosolic inflammasome components (MDA5,RIG-I,NOD2 and PKR), inciting inflammation and immunity [11]. In murine models, lipid nanoparticles in the SARS-CoV-2 mRNA vaccines have been demonstrated to trigger inflammatory reactions by several mechanisms, including the NLRP3 inflammasome, acting as an impromptu adjuvant and possibly accentuating inflammation [12]. It is interesting, then, to note that the NLRP3 inflammasome has been shown to varying degrees to be involved in the pathogenesis of inflammation in pericarditis, rheumatoid arthritis, and arteritis [13–15].

An alternative explanation may depend on the exact molecular makeup of SARS-CoV-2, partially shared by the protein expressed after mRNA translation. COVID-19 has been known to sometimes cause myocarditis and pericarditis[16,17]. These manifestations have also been associated with the vaccine – and have not been largely associated with other vaccines. It is possible that certain self-antigens, expressed more widely in the myopericardium, share a structural similarity with the S protein. These antigens may then trigger an immune response targeted at these antigens. Notably, molecular mimicry has been suggested as a mechanism in COVID-19 related immune phenomena, where viral proteins have elicited immune cross-reactivity with human tissue [18,19]. This cross reactivity is dependent on environmental factors and genetic predisposition, such as immune tolerance deficit following aberrant major histocompatibility complex (MHC) class ll antigen presentation to autoreactive T cells [2].

Finally, the adjuvant theory, or bystander effect, states that immune activation stems from the presence of an exposed autoantigen in the setting of a pro-inflammatory or pathogenic context. Exact characterization of the immune response triggered by the BNT162b2 has not, to our knowledge, been completely elaborated. Intracellular mRNA or the translated fragment of the SARS-CoV-2 spike protein may trigger components aimed at detecting danger associated molecular patterns, such as TLRs. Activation of TLR7 and TLR8 especially, and downstream signaling via type I interferon production, has been suggested as the driving mechanism [20]. The spike protein fragment, itself likely to be inherently immunogenic [21], may be translocated to the plasma membrane. The context of a xenoprotein embedded in the plasma membrane of a cell in which TLRs and similar proteins have become activated, may trigger an immune response aimed at components of the cell. Similar effects have been implicated in viral infection [22].

Whether any of these theories are true and whether a single theory explains all instances of post-vaccine autoimmunity remains unknown. As different vaccines will permeate different nations, data will accumulate, and comparisons will become possible. Future vaccines may be further refined and less prone to cause side effects, or we will be more able to determine who is at greater risk of developing side effects. Alternatively, sober future analysis may reveal no added burden of autoimmune manifestations occurs in the post-vaccine period.

Our study has several limitations. The preliminary nature of our report necessarily lends itself to biases including salience bias of post-vaccine presentations and selection bias of patients seeking medical attention more often post-vaccination. With over 5 million persons vaccinated in Israel in the preceding months and over a million yearly visits to the Hadassah medical centers, these events are likely exceedingly rare. As a case-series study, the lack of a control group further disallows definitive statements. We nonetheless believe our report may be of value to clinicians, especially those treating patients with established autoimmune or autoinflammatory disease, in this nascent era of COVID-19 vaccines.

CRediT authorship contribution statement

Yuval Ishay: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Ariel Kenig:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Tehila Tsemach-Toren:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Radgonde Amer:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Limor Rubin:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Yoav Hershkovitz:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing. **Fadi Kharouf:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Investigation, Supervision, Validation, Writing - review & editing.

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.

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