Infection and Drug Resistance

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CASE SERIES

Emergence of Post COVID-19 Vaccine Autoimmune Diseases: A Single Center Study

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Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) became a major concern since the announcement that it is a pandemic in early 2020. Vaccine trials were started in November 2020, and completed rapidly due to the urgency to get over the infection. Side effects to vaccines started to be reported. There were minor side effects including site of injection pain and heaviness and constitutional symptoms like fever which are considered minor. One of the rare adverse events is post vaccine new onset autoimmune diseases.

Methods: Data were obtained from one center in the eastern province of Saudi Arabia (King Fahd Hospital of University). All patient events reported occurred in the study period March 2021 to February 2022. We identified patients presenting with autoimmune diseases with exclusively new onset presentations.

Results: We identified 31 cases of immune-mediated disease: 18 females (58%); 13 males (42%). Only 4 of them (13%) had an autoimmune background before COVID-19 vaccination. The average time between vaccination and new-onset disease symptoms was 7 days. Among all the cases in our study, 7 patients (22.5%) had new-onset vasculitis, 2 cases had IgA vasculitis and 5 cases had ANCA vasculitis, 6 cases had neurological diseases (19.3%), 4 cases (12.9%) had new-onset systemic lupus erythematosus (SLE), 3 cases (9.6%) presented with new-onset inflammatory arthritis, and one had Sjogren's syndrome (3.2%).

Conclusion: Our study is unique as it is the first study to include the largest number (31 patients) of new onsets of confirmed autoimmune diseases related to Covid-19 vaccines.

Keywords: autoimmune disease, SARS CoV-2, vaccine, immune-mediated disease

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) became a major concern since the announcement that it is a pandemic in early 2020. It consumed the financial and manpower resources of healthcare systems around the globe and enforced quarantine in most countries. This led to a major breakdown of many sectors. It "drained" people financially and emotionally.[1] To date, around 8 million lost their lives. In addition, over 448 million of those who were infected with COVID-19 are still suffering from its sequelae which include long COVID and post COVID permanent lung damage.[2]

Vaccine trials were started in November 2020 and completed rapidly due to the urgency to get over the infection.[3] The first vaccine, Pfizer-BioNTech, was approved by the US Food and Drug Administration (FDA) in August 2020 and the rollout of vaccines started in December the same year. The second vaccine (Oxford-AstraZeneca) was approved by UK/European FDA shortly after.[4] Many other vaccines were developed since including the Russian Sputnik V and the Chinese Sinovac vaccines. To improve the COVID-19 pandemic situation, two different mRNA vaccines, BNT162b2 mRNA COVID-19 Pfizer-BioNTech and mRNA-1273 COVID-19 Moderna, were authorized by the US Food and Drug Administration on December 11, 2020, and December 18, 2020, respectively.[5,6]

Received: 23 October 2022
Accepted: 23 February 2023
Published: 4 March 2023

Saudi Arabia introduced strict measures to fight the pandemic early-on. This included quarantine, implementing working from home, travel restriction, mandating social distancing and wearing masks in public places and reducing the number of people in one place at a certain time.[7]

In Saudi Arabia, the rollout of vaccination for adults more than 18 years of age started in December 2020.[8] In June 2021, the rollout started for children 12 to 18 years of age and in January 2022 for children 5 to 11 years.[9–11] Up until the time this article was written, around 62 million doses were introduced to different ages, thus, 74.1% of the population received at least one dose and about 24 million (68.8%) people received the booster dose of the vaccine.[12] After that, the number of hospitalizations dropped dramatically along with the number of Intensive Care Unit (ICU) admissions and deaths, indicating that vaccines are very effective.[13,14]

Side effects to vaccines started to be reported with the increasing number of people getting vaccinated. There were minor side effects that were reported in clinical trials including site of injection pain and heaviness and constitutional symptoms like fever and fatigue which are considered minor.[15] Other side effects that were not reported in clinical trials include thrombosis and seizure.[16–19]

Many case reports were published in relation to rare side effects like cardiac arrhythmias, facial nerve palsy, and abortion.[20–22] One of the adverse events that were noticed is the exacerbation of autoimmune disorders like multiple sclerosis and post vaccine new onset autoimmune diseases.[23–26]

In this article, we report 31 patients with new onset post vaccine autoimmune diseases and a severe exacerbation of an existing disease including patients with connective tissue disorders, vasculitis, and neurologic diseases. To our knowledge, this is the largest cohort of patients reported in the literature and the first in Saudi Arabia and the Gulf countries.

Methods

This study was reported according to the "Case Reports" (CARE) guidelines.[27] Verbal and written consent were obtained from all patients for the use of anonymized data. Data were obtained from one center in the eastern province of Saudi Arabia (King Fahd Hospital of University). All patient events reported occurred in the study period March 2021 to February 2022. We identified patients presenting with autoimmune diseases, especially rheumatic diseases, including new presentations and disease relapses.

Inclusion Criteria

1. Patients who presented with new onset of autoimmune diseases who received COVID-19 vaccine 2 to 28 days prior to their first complaint.
2. Patients 14 years of age and older.

Exclusion Criteria

1. Patients less than 14 years of age.
2. Patients who developed symptoms of autoimmune diseases more than 28 days after receiving the last dose of the vaccine.

Data Collection Method

Data were collected from medical records utilizing data collection sheet which includes:

- Bio-data with items such as: age, gender and weight.
- The underlying autoimmune disease.
- Medical history including the clinical presentation and comorbidities.
- Important investigations that confirm the diagnosis.
- Course of the autoimmune disease.
- Severity of the post vaccine condition: the grading was as follows: mild: skin and tissue injury; moderate: injury to internal organs such as kidney; severe or life threatening: respiratory failure and cardiac failure.

Data Management and Analysis

The data were analyzed using SPSS v21. Both parametric and non-parametric tests were conducted. Data were assessed for assumptions of normality with a Kolmogorov–Smirnov test. Two-tailed *t*-test and Chi-squared tests or a Fisher's exact test were used where indicated.

We evaluated the causality of the adverse events following immunization (AEFI) after COVID-19 vaccination based on the WHO guidelines, which propose a comprehensive four-step analytical and algorithmic diagramming process. Even though the WHO instrument has been criticized, currently, there are no valid and reliable alternatives.[28] All possible "other causes" that could explain the insurgence of the AEFI, excluding the etiopathological role of the vaccine, were initially considered. After validating Immune Mediated Disease (IMD) diagnosis, and excluding non-vaccination related causalities, biological plausibility and temporal compatibility between the immunization and the occurrence of the AEFI were assessed. To ensure a reliable assessment of AEFIs, a multi-disciplinary evaluation was performed, involving different specialists, ranging from immunologists, rheumatologists, internal medicine doctors and epidemiologists, as recommended by the WHO guidelines. We also followed the appropriate guidelines for Guillain-Barré syndrome (GBS)[29] and peripheral neuropathy (small fiber disease).[30]

Ethical Approval

King Fahad Hospital of the university is the hospital of Imam Abdulrahman Bin Faisal University. So, this study's ethical approval was issued by the ethics committee of the institutional review board (IRB), Imam Abdulrahman Bin Faisal (IRB-2022-01-311). The study complies with the declaration of Helsinki.

Results

We identified 31 cases of immune-mediated disease (IMD) (18 Females (58%); 13 males (42%)); mean age 34.6. Only 4 of them (13%) had an autoimmune background before COVID-19 vaccination. In 27 patients (87%) there was no autoimmune disease background and patients presented with new-onset disease (Table 1). Twenty-nine (93.5%), one

Table 1 Demographics and Characteristics of Patients

Parameter	Value (31 New Onset)
Sex	
- Female	18 (58%)
- Male	13 (42%)
Age	
- Mean	34.6
- Median	37
Pre-vaccine Autoimmune/rheumatic disease	
- None	27 (87%)
- Present	4 (13%)
Type of vaccine	
- Pfizer	29 (93.6%)
- Moderna	1 (3.2%)
- Oxford	1 (3.2%)
- Others	0
Doses of vaccine received	
- 1	8 (25.8%)
- 2	18 (58.1%)
- 3	5 (16.1%)

(*Continued*)

Table 1 (Continued).

Parameter	Value (31 New Onset)
Days from vaccine to symptoms	
- After 1st dose	Median of 7 days [3–21 days]
- After 2nd dose	Median of 14 days [2–25 days]
- After booster	Median of 19 days [17–22 days]
New Onset Disease	
- Vasculitis	7 (22.6%)
- Neuro	6 (19.4%)
- Thyroid	3 (9.7%)
- SLE	4 (12.9%)
- Gastro	3 (9.7%)
- Inflammatory arthritis	3 (9.7%)
- Idiopathic inflammatory myopathy (IIM)	2 (6.4%)
- Cardiology (Myocarditis)	1(3.2%)
- Hematology	1(3.2%)
- Sjogren's	1 (3.2%)
Severity of the post vaccine disease	
- Mild	5 (16.1%)
- Moderate	18 (58.1%)
- Severe	8 (25.8)
Treatment	
- Pulse steroid	10 (17.5%)
- Oral steroid	15 (26.3%)
- HCQ	8 (14%)
- Rituximab	4 (7%)
- MMF	2 (3.5%)
- Imuran	5 (8.7%)
- No medications	
- ICU	1 (1.8%)
- Intubation	1 (1.8%)
- IVIG	5 (8.8%)
- Dialysis	3 (5.3%)
- PLEX	3 (5.3%)
Response to 1st line treatment	
- Responsive	21 (67.8%)
- Partially responsive	5 (16.1%)
- Unresponsive	4 (12.9%)
- Death	1 (3.2%)

(3.2%), and one (3.2%) received Pfizer, Moderna, and Oxford vaccines, respectively. Eight cases (25.8%) received one dose of the vaccine, eighteen cases (58%) received two doses, and only five cases (16.1%) completed all three doses of COVID-19 vaccine.

The average time between vaccination and new-onset disease symptoms was median of 7 days (3–21) in those who developed IMD after the first dose), median of 14 days (2–25) in those after the second dose, and a median of 19 days (17–22) in those after receiving the third dose, with most cases occurring after the second dose (54%).

Among all the cases in our study, 7 patients (22.5%) had new-onset vasculitis, 2 cases had IgA vasculitis and 5 cases had ANCA vasculitis, only one of them had a background of autoimmune disease (Hashimoto thyroiditis). We reported

Table 2 New Onset Disease

#	Sex, Age	Nationality	Comorbid Diseases	Type of Vaccine	# of doses	Days from Vaccine to Symptoms	Type and Sx of AI Disease	Relevant Lab Tests	Therapy	Response to Rx	Do you Feel the Vaccine Triggered the Onset of Disease	Can the Reaction be Explained by Comorbidities or Medications
1	Female 22 y/o	Saudi	No	Pfizer	2	5 days after the first dose and worsened 2 days after the 2nd dose	SLE: Fever, fatigue, arthritis, malar rash, pleuritic, lupus nephritis	ANA 1280, DsDNA, smith, SSA, low C3 and C4, 2.5 g proteinuria, WBC 2.9 (lymphopenia), elevated ESR Kidney biopsy: class 4 lupus nephritis	Pulse steroid then 1mg/kg then taper. HCQ 400 mg OD Cellcept 1.5g BD Lisinopril 10 mg	Responsive	yes	No (Found to have high TPO and TG Ab)
2	Female 37 y/o	Philippines	Treated old TB ITP (dx 10 yrs prior with negative Abs, plt normal since 2015)	Pfizer	2	3 days after the first dose, worsened after 7 days from the second dose	SLE: malar rash, arthralgia, mouth ulcers, pleuritis	ANA 1280, smith, SSA, SSB Elevated ESR and CRP	Prednisolone 20 with tapering HCQ 400mg OD AZA 50mg OD	Partial response for which AZA was added	yes	Yes
3	Female 25 y/o	Saudi	No	Pfizer	2	3 days after the 2nd dose	SLE: Subacute cutaneous lupus, fever, lymphadenopathy, arthralgia	ANA 1280, DsDNA, SSA	Steroid HCQ AZA	Partial response	yes	No
4	Female 33 y/o	Saudi	No	Pfizer	2	20 days after the 2nd dose	SLE: arthritis of small hand joints, fever, fatigue	ANA 1280, DsDNA, Smith, low C3 and C4	HCQ 300 Prednisolone 20	Responsive	yes	No
5	Female 45 y/o	Saudi	No	Pfizer	2	10 days after the second dose	Thyroiditis: severe neck pain and tenderness	High ESR Nuclear study: scintigraphy features of thyroiditis mostly Dequarvain (low uptake) TSH high T4 low TPO and TG + (prior to vaccine was –)	NSAIDs for the pain Levothyroxine 50 mcg	Responsive	yes	No

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https://doi.org/10.2147/IDR.S394602 DovePress

Table 2 (Continued).

#	Sex, Age	Nationality	Comorbid Diseases	Type of Vaccine	# of doses	Days from Vaccine to Symptoms	Type and Sx of AI Disease	Relevant Lab Tests	Therapy	Response to Rx	Do you Feel the Vaccine Triggered the Onset of Disease	Can the Reaction be Explained by Comorbidities or Medications
6	Female 46 y/o	Philippines	No	Pfizer	2	14 days after the 2nd dose	Grave's disease: Fever and neck pain	Nuclear study: Diffuse hyper-functioning thyroiditis TRAb: + TSH low FT4 high		Responsive	yes	No
7	Male 37	Saudi	No	Pfizer	3	17 days after the third dose	Grave's disease: Palpitation	Nuclear study: Diffuse hyper-functioning thyroiditis TRAb: + TSH low FT4 high		Responsive	yes	No
8	Male 29 y/o	Saudi	No	Pfizer	2	4 days after the 2nd dose	IgA vasculitis: Skin rash, Lower limb edema	Kidney biopsy: IgA nephritis Biopsy skin: LCV with IgA	Prednisolone Cellcept	Relapse after tapering of steroid so started cellcept	yes	No
9	Male 33 y/o	Saudi	Chewing tobacco 4–5 times daily for the last 4 years	Pfizer	3	2 days after the second dose worsened after the 3rd dose	IgA vasculitis: hypertension, hematuria, decrease in urine output	Kidney biopsy: IgA nephropathy, global glomerulosclerosis RFT: high BUN and Creatinine	Steroid ≫ no response Dialysis	Unresponsive Needed dialysis	yes	No
10	Female 18 y/o	Saudi	No	Pfizer	2	7 days after the 1st dose and increased 3 days after the 2nd dose	Antisynthetase: Proximal and bulbar weakness, mechanic's hands, arthritis	ANA 1280, Jo-1 Ab CPK: high	Prednisolone IVIG: 3 doses HCQ: 200 mg Rituximab	Responsive	yes	No (her grandmother has rheumatoid arthritis and father has hypothyroidism)
11	Female 46 y/o	Saudi	No	Pfizer	2	14 days after the 2nd dose	Dermatomyositis: proximal muscle weakness, dysphagia, skin rash,	ANA 1280 CPK high	Pulse steroid followed by oral 1mg/kg with tapering. AZA 50mg OD	Partial response	Yes	No

12	Male 18 y/o	Saudi	No	Pfizer	2	7 days after the 2nd dose	Ulcerative colitis: abdominal pain, bloody diarrhea and vomiting	Fecal calprotectin 1000, Endoscopy: severe colitis, ulcerative colitis with biopsy: active colitis with crypt abscess, with no granuloma CT: inflammatory colitis	Methylprednisolone 40 IV OD, Pnetasa 500 mg po TID, azathioprine 100 mg PO OD	Responsive	Yes	No
13	Male 21 y/o	Saudi	No	Pfizer	2	15 days after the 2nd dose	AI pancreatitis: Epigastric abdominal pain and vomiting	Lipase: 504 ANA 160 MRI pancreas and MRCP: bulky with loss of lobulation with fat stranding	Methylprednisolone 40 mg IV then tapering Prednisolone	Responsive	Yes	No
14	Male 16 y/o	Saudi	No	Pfizer	1	10 days after the 1st dose	AI hepatitis	Elevated ALT and AST Elevated GGTP and ALP ANA+ Anti smooth muscle Antibody +ve	Steroid AZA	Responsive	Yes	No
15	Female 34 y/o	Indian	No	Pfizer	1	7 days after the 1st dose	ANCA vasculitis GPA: pulmonary hemorrhage, hematuria, renal impairment Kidney biopsy: crescentic pauci-immune glomerulonephritis	ANCA, PR3	Pulse steroid then 1mg/kg Plasma exchange (7) Rituximab	Responsive	yes	No
16	Female 61 y/o	Saudi	No	Pfizer	2	25 days after the second dose	ANCA vasculitis (GPA): microscopic hematuria, ESRD, fatigability	ANCA, PR3 Kidney biopsy: crescentic pauci-immune GN Elevated ESR and CRP	Pulse steroid Plasma exchange Cyclophosphamide ICU Intubaion Dialysis	Unresponsive Death	yes	No
17	Female 46 y/o	Saudi	No	Pfizer	2	9 days after the 2nd dose	ANCA vasculitis (GPA): pulmonary hemorrhage, hearing loss, sinusitis, RPGN	ANCA, PR3 Kidney biopsy: pauci-immune crescentic GN	Pulse steroid then prednisolone Rituximab	Responsive	yes	No

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https://doi.org/10.2147/IDR.S394602

Table 2 (Continued).

#	Sex, Age	Nationality	Comorbid Diseases	Type of Vaccine	# of doses	Days from Vaccine to Symptoms	Type and Sx of AI Disease	Relevant Lab Tests	Therapy	Response to Rx	Do you Feel the Vaccine Triggered the Onset of Disease	Can the Reaction be Explained by Comorbidities or Medications
18	Female 46 y/o	Indian	Hypothyroidism	Pfizer	1	5 days after the 1st dose	ANCA vasculitis (GPA): sinusitis, bilateral otitis media with hearing impairment	ANCA, PR3 Kidney biopsy: crescentic pauci-immune glomerulonephritis Elevated ESR and CRP	Pulse steroid then oral 1mg/kg with tapering Cyclophosphamide	Responsive	yes	No
19	Male 47 y/o	Indian	No	Pfizer	1	20 days after the 1st dose	ANCA vasculitis (MPO): macroscopic hematuria, sinusitis, presented with uremic symptoms	ANCA, MPO Kidney biopsy: crescentic pauci-immune GN	Pulse steroid followed by 1mg/kg oral Dialysis	Unresponsive	yes	No
20	Male 38 y/o	Saudi	No	Pfizer	2	10 days after 2nd dose	AMAN ataxia, weakness bradykinesia and late onset seizures	Ganglioside GD1a (IgG, IgM), Voltage gated calcium channel, MRI brain: normal. MRI spine evidence of diffuse enhancing nerve roots of conus medularis and Cuda equina LP: albumin cytogenic dissociation	IVIg, 2 courses of plasmapheresis (total of 10 sessions)	Unresponsive	yes	No
21	Male 55 y/o	Saudi	Type 1 Diabetes	Pfizer	2	14 days after 2nd dose	Central demyelination Bickerstaff encephalitis Headache, change in sensorium, ataxia	Multiple hyperintensitis involving left thalamus, pons and medulla oblingata CSF: mild pleocytosis with negative culture and PCR	IVIg, steroids and PLEX	Unresponsive	yes	No
22	Male 27 y/o	Saudi	No	Pfizer	1	21 days after	Myasthenia gravis: ptosis, diplopia, generalized weakness Upper limb > Lower limb	Positive acetylcholine antibodies RNS: decremental response	IVIg, PLEX, pyridostagmine with immunomodulation therapy	Recovered	yes	No

23	Male 36	Saudi	No	Pfizer	2	21 days after 2nd dose	GBS: Lower limb parasthsethsia, ascending weakness, urinary retention	Albuminocytogenic dissociation MRI Lumbar spine: enhancement of cuada equina. NCS: prolonged F-wave	PLEX	Partial response	yes	No
24	Male 38 y/o	Saudi	No	Pfizer	1	18 days after	Peripheral neuropathy: painful Lower limb sensory changes > upper limb	NCS: normal MRI brain and spine: normal	Oral prednisolone and gabapentin	Recovered	yes	No
25	Female 54 y/o	Saudi	No	Oxford	1	3 days after	Meningeal headache: occipital headache, nausea, vomiting	MRI brain and spine: normal MRV: normal CSF: normal	Oral steroid (0.5 mg/kg)	Recovered	yes	No
26	Female 16 y/o	Saudi	No	Pfizer	2	14 days after the 2nd dose	Inflammatory arthritis	ANA 640	HCQ 400 mg	Responsive	yes	No (She has positive TPO ant TG Ab)
27	Female 17 y/o	Saudi	T1M	Pfizer	1	10 days after the 1st dose	Seronegative Inflammatory arthritis	Elevated ESR and CRP ANA 1280 -ve DsDNA, Smith, RNP, SSA and SSP	HCQ 400 mg	Responsive	yes	No (She has T1DM and has positive TPO ant TG Ab)
28	Female 29 y/o	Saudi	No	Pfizer	2		Seronegative inflammatory arthritis	Elevated ESR and CRP	Steroid	Responsive	yes	No
29	Male 43 y/o	Philippines	Ex-smoker	Moderna	3	22 days after the 3rd dose	Myocarditis: New onset heart failure: shortness of breath, orthopnea and PND	ECHO: severe reduced Left ventricular function Ejection fraction 20% with mild dilated left ventricles. ECG sinus tachycardia, Rt axis deviation and inverted T wave in anterior leads with interventricular delay in conduction suggesting possibility of myopathy	IV diuretics and ant-failure medications	Responsive	yes	No (has family history of cardiac disease (father))

(*Continued*)

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Table 2 (Continued).

#	Sex, Age	Nationality	Comorbid Diseases	Type of Vaccine	# of doses	Days from Vaccine to Symptoms	Type and Sx of AI Disease	Relevant Lab Tests	Therapy	Response to Rx	Do you Feel the Vaccine Triggered the Onset of Disease	Can the Reaction be Explained by Comorbidities or Medications
30	Female 16 y/o	Saudi	No	Pfizer	3	2 days after the second dose	Autoimmune hemolytic anemia	+ DCT High LDH and indirect bilirubin Low Hgb and haptoglobin	Pulse steroid 5 days followed by PO 1 mg/kg IVIg Rituximab	Responsive	Yes	No
31	Female 44 y/o	Philippines	No	Pfizer	3	20 days after the second dose	Sjogren's Syndrome: Polyarthritis Parotid swelling and sicca symptoms	ANA 1280 SSA + RF +	HCQ Symptomatic treatment	Responsive	Yes	No

Abbreviations: ANA, Antinuclear Antibodies; DsDNA, Double Stranded DNA; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; Plt, Platelets; SSA, Anti-Sjogren's Syndrome; TB, Tuberculosis; ITP, Idiopathic Thrombocytopenia Purpura; SLE, Systemic Lupus Erythematosus; HCQ, Hydroxychloroquine; AZA, Azathioprine; TRAb, Thyrotropin receptor antibodies; TSH, Thyroid Stimulating Hormone; TPO, Thyroid peroxidase; TG, Thyroglobulin; IV, Intravenous; OD, Once Daily; MPO, Myeloperoxidase; LCV, Leukocytoclastic vasculitis; RFT, Renal Function Test; CPK, Creatine Phosphokinase; RNP, Ribonucleoprotein; ANCA, Antineutrophil Cytoplasmic Antibodies; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; CSF, Cerebrospinal Fluid; ALT, Alanine Transaminase; AST, Aspartate Aminotransferase; GGTP, Gamma-glutamyltranspeptidase; ALP, Alkaline Phosphatase; MRCP, Magnetic Resonance Cholangiopancreatography; PR3, Proteinase 3; DCT, Direct Coombs Test; ICU, Intensive Care Unit; AMAN, Acute Motor Axonal Neuropathy; GPA, Granulomatosis with polyangiitis; ESRD, End Stage Renal Disease; PLEX, Plasma Exchange; IVIg, Intravenous Immune Globulin; RPGN, Rapidly Progressive Glomerulonephritis; LDH, Lactate Dehydrogenase Enzyme; ECG, Electrocardiogram; ECHO, Echocardiogram; PND, Paroxysmal Nocturnal Dyspnea.

six cases of neurological diseases (19.3%) ranging from mild peripheral neuropathy to more severe diseases including, central demyelination Bickerstaff encephalitis, myasthenia gravis, meningeal headache, acute motor axonal neuropathy, and Guillain-Barre syndrome.

Three cases of thyroid disease (9.6%) were noted, two of them were in the form of Graves' disease with a positive thyrotropin receptor antibody (TRAb) and one case of thyroiditis with low uptake thyroid scan and positive Thyroid peroxidase (TPO) and Triglyceride (TG) that was negative prior to COVID-19 vaccine.

As for rheumatological diseases, there were 4 cases (12.9%) of new-onset systemic lupus erythematosus (SLE), only one case with a previous history of autoimmune disease (immune thrombocytopenic purpura). Three cases (9.6%) presented with new-onset inflammatory arthritis, one case with a previous history of type 1 diabetes (DM), in all three cases arthritis was the only presentation without extra-articular features. An additional two cases of idiopathic inflammatory myopathy (6.5%) were observed, one case with antisynthetase syndrome and the other one with dermatomyositis. A single case of Sjogren's syndrome (3.2%) was reported after the second dose of the vaccine with good response to symptomatic treatment.

Moreover, 3 cases of gastroenterology diseases (9.6%) were reported in a medically free young male. First case was ulcerative colitis that was confirmed by biopsy. Second case was autoimmune hepatitis with elevated liver enzymes and positive antinuclear antibody (ANA) and Anti smooth muscle antibody (ASMA). Third case was autoimmune pancreatitis with high level of pancreatic enzymes and positive ANA.

We observed one case of myocarditis (3.2%) with new onset heart failure in a patient with significant family history of cardiac disease. Patient responded well to diuretic and anti-heart failure medications. An additional case of autoimmune hemolytic anemia (3.2%) was noted in a healthy young female who responded well to the treatment. For more information regarding demographics and characteristics of patients refer to Table 1.

Individual cases are summarized in Table 2.

Discussion

COVID-19 virus manifestations are not limited to the respiratory system but can cause extra-pulmonary manifestations affecting multiple systems including the gastrointestinal, cardiovascular, and nervous systems. It can also affect the kidneys causing proteinuria, acute kidney injury and some end up on dialysis.[31,32]

Over the past two decades, questions were raised about the safety of vaccines and especially the relation between the vaccine and the development of autoimmune diseases. The most commonly reported vaccines associated with autoimmune disease were Measles, Mumps, and Rubella (MMR) and hepatitis B vaccines.[32]

The relationship between vaccines and autoimmune reaction is well-known in the literature, many theories have been postulated, and one important theory is related to molecular mimicry, which is the same mechanism in which the virus triggers autoimmune process and may contribute to the development of autoimmune diseases. The development of autoimmune disease following vaccines is attributed to the cross-reactivity that results from a lack of tolerogenic effect. Clonal expansion of T cells and B cells upon exposure to the antigen is the key for immune tolerance, however, genetic and environmental factors can affect the immune tolerance as well.[33] Perhaps it is the same mechanism through which most autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) develop.

There have been multiple reported cases linking the COVID-19 vaccine, including mRNA and adenovirus vector vaccines, with the development of new-onset AID, such as reactive arthritis, autoimmune hepatitis, SLE, vasculitis, immune thrombotic thrombocytopenia, transverse myelitis, and multiple sclerosis.[34,35] In our study we identified 31 cases of immune-mediated disease.

Raviv et al reported a case of newly diagnosed SLE in a male patient with no underlying medical condition who presented 2 days after receiving the SARS-CoV-2 Pfizer-BioNTech mRNA vaccine with skin rash and arthralgia who improved with hydroxychloroquine and topical treatment.[36] Another case was published by Nune et al who described a young Caucasian male who was investigated for fever, arthralgia, and lymphadenopathy which developed 2 weeks after getting the Pfizer-BioNTech SARS-CoV-2 vaccine and was found to have SLE.[37] These findings support our study in which we reported 4 cases (12.9%) who developed new-onset systemic lupus erythematosus (SLE), only one case with a previous history of autoimmune disease (immune thrombocytopenic purpura). Other reports indicated that SLE can be

exacerbated by SARS CoV vaccines. The largest study of mRNA vaccines and whether they exacerbate or cause new onset of inflammatory disorders included 27 patients from different centers in 3 countries. Of those, 2 were known to have underlying SLE who had exacerbation after receiving the mRNA SARS CoV vaccine.[37] The severity of exacerbation and organs affected cannot be predicted.[38] In our study the first case had the first onset of symptoms 4 days after the 1st dose and worsened 2nd day after 2nd dose. The second case had new onset of symptoms 3 days after the first dose and worsened 7 days after the 2nd dose. The third case had new onset 3 days after the 2nd dose and the final case developed new symptoms 20 days after the 2nd dose. The severity of exacerbation in our case was moderate.

Many case reports suggested that COVID-19 vaccines could be a potential trigger for Immunoglobulin A Nephropathy (IgAN). Nakatani et al reported the first case of IgAN in a 47-year-old male with a background of hypertension and hyperuricemia who developed skin lesions in the lower extremity after receiving the first dose COVID-19 vaccine and his symptoms were exacerbated 15 days after the second dose. Another case of confirmed IgAN was also reported for a 94-year-old male who presented, 10 days after the second dose of COVID-19 vaccination, with purpuric skin rash, proteinuria and microscopic hematuria.[39] Other cases of new onset IgA vasculitis without kidney involvement after receiving the BNT162b2 mRNA COVID-19 vaccine, the RNA 1273 COVID-19 vaccine, and the Oxford-AstraZeneca COVID19 vaccine were also reported in the literature.[40–43] In our study we reported 2 cases of new onset IgA vasculitis in the form of nephritis and IgA nephropathy. One of these 2 cases needed dialysis. Several reports described reactivation of IgAN 24 hours after COVID-19 vaccination.[44,45] In our study our 2 patients developed the condition 2 days after 2nd dose and 4 days after 3rd dose respectively.

Many cases of new onset ANCA-associated vasculitis after COVID-19 vaccination have been reported in the literature. Acute kidney injury (AKI) and microscopic hematuria were the main clinical presentations in most of the reported cases. However other manifestations like macroscopic hematuria and hemoptysis were also noted.[46–51] Patients had different clinical outcomes ranging from improvement and partial clinical response to End Stage Renal Disease (ESRD) requiring dialysis.[52] In our study 5 cases developed ANCA vasculitis and only one of them had a background of autoimmune disease (Hashimoto's thyroiditis). Two patients required dialysis and one patient had ESRD that led to death.

Weintraub et al reported a case series of 3 patients who developed Graves' disease days to weeks after being vaccinated against SARS-CoV-2; Pfizer-BioNTech in two patients and Moderna in the third patient.[53] The same observation was reported by Liu et al but in a Chinese female with a long-standing history of hypothyroidism who presented with diffuse goiter and thyrotoxicosis symptoms five weeks following the second dose of COVID-19 vaccine.[54] Additionally, several recently published reports have highlighted the relation of SARS-CoV-2 vaccination and subacute thyroiditis (SAT), also termed De Quervain's thyroiditis.[55] Furthermore, Oyibo described the development of SAT in a 55-year-old female who received adenovirus-vectored vaccination for COVID-19 3 weeks prior.[56] Three cases of thyroid disease (9.6%) were noted, two of them were in the form of Graves' disease with a positive thyrotropin receptor antibody (TRAb) and one case of thyroiditis with positive TPO and TG and low uptake thyroid scan that was negative prior to COVID-19 vaccine.

Since the emergence of COVID-19 and the development of various vaccines, a number of hypotheses have been suggested to describe the response of Inflammatory Bowel Disease (IBD) patients to vaccinations, however, the potential of these vaccines to induce onset of IBD has not been reported in the literature.[57,58] To explore rates of IBD exacerbation after administration of COVID-19 vaccines, a cross-sectional study was carried out in Germany on 781 vaccinated IBD patients. The authors concluded that there was no increase in rates of exacerbation symptoms, including abdominal pain and rectal bleeding, among Crohn's disease (CD) and Ulcerative Colitis (UC) patients after receiving various available COVID vaccines.[59] Another study, but prospective observational cohort in design, was conducted on 3316 individuals with IBD who had at least one dose of SARS-CoV-2 vaccine. Rate of exacerbation attributed to vaccination was 2.1% among 71 participants of whom 48 received Pfizer-BioNTech, 22 had Moderna, and one received Johnson & Johnson vaccines.[60] In our study there was one case of ulcerative colitis that was confirmed by biopsy.

In our study there was one case of autoimmune hepatitis with elevated liver enzymes and positive antinuclear antibody (ANA) and Anti smooth muscle antibody (ASMA). This finding is consistent with other studies.[61–64] The first case of autoimmune hepatitis caused by COVID vaccination was described by Bril et al who had her first dose of

PfizerBioNTech vaccine and, shortly after, developed pruritus, jaundice along with choluria and then was found to have AIH upon investigation.[61] Several case reports since then were published to further portray the possible association between SARS-CoV-2 vaccines and AIH.[62,63] Erard et al, for instance, shared their experience in diagnosing three patients with AIH, days following exposure to COVID-19 vaccines' components.[64] The ability of COVID-19 vaccines to exacerbate a pre-existing AIH was also illustrated in the literature by several authors.[65,66]

As with any vaccine, the molecular mimicry and the formation of autoantibodies that attack either central or peripheral nervous system is a very common post vaccination phenomenon. The neurological manifestation of this entity includes acute disseminated encephalomyelitis, neuro-myelitis optica spectrum disorder, transverse myelitis, and Guillain-Barré syndrome. Cao et al reported a young lady who presented 2 weeks after receiving the vaccine, initially she had gastro-enteritis like symptoms. MRI and CSF were obtained and confirmed the diagnosis of acute disseminated encephalomyelitis (ADEM).[67] In addition, there are reported cases with similar diagnosis in Turkey, Bangladesh, USA, Italy, and Germany with mean duration of symptoms onset 9–16 days and associated with different SARS-COV2 vaccinations, and all cases improved with methylprednisolone treatment.[68–70] Peripheral demyelination secondary to molecular mimicry such as Guillain-Barré syndrome (GBS) has been reported worldwide with different types of vaccination and all SARS-COV2 vaccinations subtypes. The clinical presentations which consist of ascending weakness, paraesthesia and cranial nerve palsies and respiratory involvement have been variable and the outcome varies from complete recovery to death. There have been almost 61 reported cases of GBS all-over the globe, most of them occurred after the first dose of the vaccine.[71–74] In our study six cases of neurological diseases (19.3%) were reported ranging from mild peripheral neuropathy to more severe diseases including, central demyelination, encephalitis, myasthenia gravis, meningeal headache, and Guillain-Barre syndrome.

Deep molecular characterization techniques have been used in the past to investigate the severity of COVID-19. Both molecular and virology approaches, such as virus isolation and diagnostic tests, are used to study the disease entity of viral infection. It is possible to characterize SARS-CoV-2 utilizing molecular methods. According to Zhou et al[75] SARS-CoV-2 is responsible for an outbreak of respiratory illnesses in humans. Infected patients' bronchoalveolar lavage fluid was used by Zhang et al[76] to extract the viral sample, which was then characterized using RT-PCR with degenerate primers and probes made for SARS-CoV-2 detection. However, no studies have been conducted on vaccine related autoimmune response. In order to develop an efficient COVID-19 vaccination approach with a low risk of side effects, the new clinical studies should focus on understanding the impact of BNT162b2 immunization on groups of various autoimmune problem patients.

Conclusion

In conclusion, our study is unique as it is, as far as the authors know at the time of writing, the first case series which includes the largest number of new onsets of confirmed autoimmune disease related to Covid-19 vaccines.

Abbreviation

SARS CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease; SLE, systemic lupus erythematosus; ANCA, antineutrophil cytoplasmic antibodies; FDA, US Food and Drug Administration; IDA, immune mediated disease; ICU, Intensive Care Unit; AEFI, adverse events following immunization; GBS, Guillain-Barré syndrome; TPO, thyroid peroxidase; TRAb, thyrotropin receptor antibody; TG, triglyceride; ITP, immune thrombocytopenic purpura; ASMA, anti smooth muscle antibody; MMR, Measles, Mumps, and Rubella; AKI, acute kidney injury; ESRD, end stage renal disease; SAT, subacute thyroiditis; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ADEM, acute disseminated encephalomyelitis.

Data Sharing Statement

The analyzed datasets used in this study and all analysis output reports are available upon reasonable request from the corresponding author. The data do not contain any identifiable data, and the confidentiality of the included patients is fully maintained.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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