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Case Series

Case Series of Rare Complications Associated with COVID-19 Vaccination

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ABSTRACT

Vaccines against SARS-CoV-2 infection have been hailed the biggest victory in the battle to control the pandemic. The safety of these vaccines has been the topic of much debate, particularly in the media. Overwhelmingly the data suggests they are safe. Around 6% of patients will develop mild to moderate symptoms for a few days. We present a case series of four patients who developed extremely rare complications in association with vaccination with recombinant Astra Zeneca SARS-CoV-2 vaccine namely Acute Inflammatory Demyelinating Polyneuropathy, Eosinophilic granulomatosis with polyangiitis and Multisystem Inflammatory Syndrome. As illustrated by these four cases, mass vaccination is not without risk and the receiving physician should be aware of these potential complications as well as other autoimmune mediated systemic illnesses, when assessing patients post vaccine. As mass vaccination programs continue worldwide, it is likely more cases demonstrating such complications will emerge.

Keywords: Vaccination; COVID-19; Eosinophilic Granulomatosis Polyangiitis (EGPA); Guillain-Barre Syndrome (GBS)

INTRODUCTION

Vaccines against SARS-CoV-2 infection have been hailed the biggest victory in the battle to control the pandemic. The safety of these vaccines has been the topic of much debate, particularly in the media. Overwhelmingly the data suggests they are safe. Around 6% of patients will develop mild to moderate symptoms for a few days. The most commonly reported of these are headache, localised swelling, fever, fatigue and myalgia [1]. Severe adverse events related to vaccines are rare, although recent reports in the literature demonstrate severe adverse events in a small number of individuals. Severe allergic reactions (1 in 100,000) from hives to anaphylaxis have been reported in association with Pfizer-BioNTech m-RNA SARS-CoV-2 [2]. The risk of thromboembolism following the AstraZeneca-Oxford SARS-CoV-2 vaccine has been the subject of much debate recently [3]. In April 2021, the MHRA reported seven deaths in the 18 million adults who had been vaccinated at that point [4]. More rare adverse events include peripheral neuropathy, EGPA and MIS-a have recently been more reported. We present a case series of four patients who developed extremely rare complications in association with vaccination with recombinant Astra Zeneca SARS-CoV-2 vaccine namely Acute Inflammatory Demyelinating Polyneuropathy, Eosinophilic granulomatosis with polyangiitis and Multisystem Inflammatory Syndrome [5].

CASE PRESENTATION

This case series describes the presentation, investigations, progress and outcome of these four patients. All of these patients tested negative for SARS-CoV-2 by reverse transcription Polymerase Chain Reaction (PCR) of nasopharyngeal swabs. In addition, of note, none reported previous infection with SARS-CoV-2.

Case: 1

A 54-year-old Caucasian male with a background of historic alcohol, depression and current smoker. Six days prior to presentation and three weeks after first dose of AstraZeneca recombinant vaccine, he noted bilateral paraesthesia and tingling of both fingers and toes. This was followed by gradual leg weakness and cramping of thighs precipitating several falls. Two days prior to admission, the weakness progressed such that he was able only to crawl to the bathroom. After developing paraesthesia of the tongue and dyspnoea, he present to the local primary care centre where urgent referral for medical opinion was made. On admission, the patient was afebrile, cognitively intact with no evidence of bladder or bowel dysfunction. On examination, there was increased tone bilaterally, with altered sensation to light touch throughout the lower limbs, power deficit to 4/5 MRC scale and absent reflexes. There was no respiratory compromise with normal oxygen saturations and peak flow measurements. The patient did complain of dysphagia

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and after assessment by speech and language therapy, was noted to give an impaired swallow and restricted to level four diet and fluids. Admission biochemistry including inflammatory markers, calcium, B12 and folate were all-normal, in Table 1. Given the historic alcohol excess, the patient was treated with IV vitamin b and c therapy (Pabrinex) and a lumbar puncture performed. The CSF fluid demonstrated significantly raised protein count but normal glucose and cell count. Viral PCR was negative but presence of oligo clonal bands in the CSF suggested a diagnosis of probable AIDP. This was later confirmed by neurophysiology studies. The patient was treated with five days of Intra Venous Immunoglobulin (IVIG) resulting in marked improvement. After a period of intensive rehabilitation under the physiotherapy team, the patient made a full recovery and was discharged home with neurology follow up.

Case: 2

A 61-year-old non-smoking Caucasian male with past medical history limited to asthma, nasal polyps, folate deficiency and previous renal colic. Presented to our centre on the 19th of May 2021 with four weeks of progressive, symmetrical distal muscle weakness and paraesthesia starting 24 hours after a second dose of recombinant Astra Zeneca SARS-CoV-2 vaccine. Admission was precipitated by 48 hours of worsening facial and lower limb swelling.

On admission, the patient was noted to have symmetrical distal peripheral neuropathy affecting all modalities but no bulbar signs. Admission bloods were notable for a raised CRP, ESR and marked eosinophilia. There were no respiratory signs and urine dip was negative for protein and blood. CT and MR imaging of head as well analysis of cerebrospinal fluid were all normal. Electromagnetic studies confirmed symmetrical changes in the distal lower limb and patchy changes in the upper limbs keeping with mononeuritis multiplex.

Blood results for this patient are listed in Table 1. Of note, the patient had strongly positive titres of MPO antibodies but negative titres for PR3 AB(s), rheumatoid factor, and ANA.

Several criteria for eGPA (formally known as Churg-Strauss Syndrome) have been developed with the most popular being that developed by the American College of Rheumatology, in Table 2. Here the presence of four of the six features outlined clinches the diagnosis of eGPA. Interestingly our patient was diagnosed with asthma as an adult in his 30s and had been troubled with nasal polyps for the last ten years. He went on to develop mononeuritis multiplex (leading to admission) and demonstrated significant eosinophilia on differential white blood cell count.

The patient was commenced on high dose oral steroid prednisolone 60 mg OD and PPI but continued to deteriorate. A decision was made to treat with cyclophosphamide at a dose of 15 mg per kg, and taper steroids gradually. This resulted in marked improvement in the patient's symptoms and normalisation of eosinophil count.

After a period of observation the patient was discharged with on-going vasculitis team follow up. He is currently being maintained on an intravenous course of cyclophosphamide as an outpatient (CYCLOPS regime) and on most recent review unfortunately, remains wheelchair bound.

Case: 3

A previously fit and well 44 year old Caucasian female was admitted to our centre 13 days after first dose of the recombinant AstraZeneca SARS-CoV-2 vaccine on the 14th of April 2021. The primary symptoms were fatigue, myalgia and dyspnoea. The only past medical history was of well-controlled ulcerative colitis, on oral Mesalazine, and previous pelvic inflammatory disease. She initially presented to her general practitioner with these symptoms but when routine blood samples revealed a raised CRP at 501 and a white cell count of 27.4 with neutrophils of 25.1, she was referred urgently to secondary care, in Table 3. An initial diagnosis of left community acquired pneumonia was made based on chest X-ray and CT imaging showing an enlarged heart, left sided pleural effusion with consolidation and a small pericardial effusion. The patient was commenced intravenous amoxicillin and oral clarithromycin as per local guidelines. Given the discovery of a pericardial effusion, an echocardiogram was arranged alongside Cardiology review (Table 4). Of note, the patient had no peripheral oedema or finger clubbing. Echocardiogram revealed a small rim of pericardial fluid with normal valves and ventricular function. The pericardial effusion was thought to be reactive.

Table 1: Blood results for this patient.

Case 2	Admission CRP	Peak CRP	CRP on discharge	Esr	Admission Eosinophil count	Eosinophil count post steroid
	116	144	46	44	15.72×10^9 ($0.02\text{-}0.5 \times 10^9$)	0.42×10^9
ANCA Screen	p-ANCA				MPO AB (S) (<3.5 IU/ml negative)	PR3 AB (S) (<2.0 IU/ml)
	p-ANCA Strongly Positive				>135.0 IU/ml	0.7 IU/ml

Note: CRP: C-Reactive Protein; MPO: Myeloperoxidase; PR3 AB: Proteinase Antibody; ANCA : Antineutrophil Cytoplasmic Antibodies.

Table 2: American College of Rheumatology Criteria for eGPA est 1990.

Rheumatology Criteria for eGPA
Asthma (a history of wheezing or the finding of diffuse high pitched wheeze on expiration)
Eosinophilia >10 percent on differential of white blood cell count
Mononeuropathy (including multiplex) or polyneuropathy
Migratory or transient pulmonary opacities detected radiographically
Paranasal sinus abnormality
Biopsy confirmed evidence of eosinophil accumulation in extravascular areas.
Four of the six criteria needed for diagnosis with sensivity of 85% and a specificity of 99.7%.

Table 3: Primary symptoms on pelvic inflammatory diseases.

	Admission CRP	Peak CRP	Discharge CRP	Peak Esr	D-dimer	Ferritin
Case three	506	556	19	119	3181	26916
Case four	466	492	24	52	3368	>40000

Table 4: Indicators of rheumatoid factor, Respiration and Myeloperoxidase.

Case 3	Rheumatoid factor <20 (neg)	Mpo ab(s) 0.4 (<3.5 iu/ml)	Pr3 ab(s) 0.24 (0.15-0.57)	Ana titres (negative)
Complement Levels	C3 2.00 (0.83-1.93)	C4 0.2 (0.15-0.57)		

Despite adequate antibiotic treatment and intravenous fluid resuscitation, the patient's condition continued to worsen with recurrent pyrexia and a further rise in inflammatory markers after initial improvement. Serial blood cultures, sputum samples, pleural aspirate and an atypical screen were all negative. Given the patient's history of UC, steroid therapy was also initiated but again CT imaging of the abdomen revealed no evidence of active colitis. Finally after an MRI spine that ruled out discitis, the patient was transferred to the tertiary Infectious Diseases Unit for further assessment. There it was noted that the patient had an ESR of 119 and a significantly raised ferritin. Interestingly the patient tested negative for other important antibodies including RF, ANA, MPO and PR3. At this point it was agreed that the patient had a likely inflammatory process driving the clinically picture, rather than infectious. However, a haematological condition still needed to be excluded. Therefore, all antibiotics were stopped and a bone marrow aspirate was obtained. This demonstrated reactive changes only and the patient was commenced on IV methylprednisolone 500 mg once daily. Initiation of high dose steroid resulted in marked improvement in symptoms with the pyrexia settling and blood results normalising. Given the response, a diagnosis of adult MIS was made with features of Still's disease. An Interleukin 1 receptor antagonist, Anakinra was added to the treatment plan and after a period of observation, the patient discharged. Most recent review in the outpatient setting confirms the patient to be stable on this combination.

Case: 4

A 50-year-old non-smoking Caucasian male with a past medical history of lumbar discectomy. Six days prior to presentation, he developed myalgia, fevers, lethargy and a sore throat. This was treated by Penicillin V in the community to no improvement. 24 hours prior to admission, the patient developed severe left sided pleuritic chest pain. The patient had received his first dose of the Astra Zeneca vaccine exactly two weeks prior to hospital admission. On presentation, he was febrile, tachycardic with significantly raised inflammatory markers (CRP of 466 and WCC of 10.5) and troponin level of 660 and a D-dimer of 3668. On ECG, the patient was noted to be in new atrial fibrillation and chest X-ray showed left lower lobe consolidation. Given the nature of chest pain a CTPA was organised, which demonstrated no PE but bibasal inflammatory change. Blood and sputum cultures sent prior to administration of broad-spectrum antibiotics and fluid therapy. Despite IV antibiotic therapy, the patient continued to have intermittent significant episodes of pyrexia above 39 degrees Celsius and recurrent AF with rapid ventricular response. This was managed with IV amiodarone therapy. A CT CAP was obtained to rule out intraabdominal or pelvic course of infection and this revealed mild splenomegaly. An inpatient echocardiogram was also performed and this did not reveal any vegetation or ventricular dysfunction but a degree of pericardial fluid. This was thought to be likely myopericarditis secondary to another inflammatory or infectious cause. After discussion with the local ID unit, antibiotics were stopped and a period of observation commenced. During this period, the patient continued to have significant temperature spikes with accompanying malaise. Despite multiple cultures, no organisms were isolated although a pro-calcitonin level obtained on specialist advice came back significantly raised at 10.3 g/decilitre. The patient went onto develop a widespread petechial rash covering both chest and back. At this point he was commenced on IV ceftriaxone to cover for meningococcal septicaemia and a vasculitis screen was sent. This screen was positive for raised ESR and ferritin but negative for ANCA and other autoantibodies, in Table 5. After a process of exclusion, a diagnosis Multisystem Inflammatory Disorder with some features of Adult Onset Still's disease was made. Diagnostic criteria for this new disorder are still developing but the main features are outlined below, in Table 6. Also below is the most commonly used diagnostic criteria of Adult Onset Still's Disease (Table 7).

Table 5: Exclusion criteria of a diagnosis multisystem inflammatory disorder.

Case 4	Rheumatoid factor <20 (neg)	Mpo ab(s) 0.4 (<3.5 iu/ml)	Pr3 ab(s) <0.2 (0.15-0.57)	ACNA titres (negative)
Complement Levels	C3 1.33 (0.83-1.93)	C4 0.21 (0.15-0.57)		

Table 6: Multisystem Inflammatory Disorder with some features of adult onset still's diseases.

Multisystem Inflammatory Syndrome–Adults
Acute COVID-19 symptoms
Persistent pyrexia
Shock, persistent hypotension
CRP elevation
ESR elevation

Ferritin elevation
D-dimer elevation
Ferritin elevation
Reduced LVEF

Note: LVEF : Left Ventricular Ejection Fraction.

Table 7: A diagnostic criterion of adult onset still diseases.

Yamaguchi's Criteria [5]		
Five or more criteria are required. Two or more criteria must be major		
Major Criteria	Minor Criteria	Exclusion Criteria
Fever >39°C lasting > 7	Sore throat	Infection
Arthralgia or arthritis for 14 days or longer	Hepatomegaly or splenomegaly	Malignancies
Typical rash	Lymphadenopathy	Other rheumatic disease
WBC count>10,000/μL	Abnormal aminotransferases	
Negative RF and Anti-nuclear antibody		

For this patient, a treatment regime of IV methylprednisolone accompanied by Interleukin 1 antagonist Anakinra was commenced. After five days of therapy, the fevers and myalgia settled along with an improvement in blood tests and the patient was discharged. An outpatient PET scan was arranged and this confirmed reactive inflammatory changes.

RESULTS AND DISCUSSION

The Certain cerebrovascular conditions such as acute disseminated encephalomyelitis and transverse myelitis associated with SARS-CoV-2 are documented in the literature [6]. Peripheral manifestations such as GBS and its variants have also been reported [7]. Although the link between them poorly understood [8]. Historically, GBS has been associated with other vaccines, most notably the rabies vaccine [9]. Early formulations of these vaccines were derived from neural tissue and linked to higher rates of GBS. These formulations tend to be less expensive and so are more commonly used in Asian, African and South American countries [10]. The pathophysiology of GBS post vaccination is poorly understood with molecular mimicry being one theory. This proposes that environmental exposure, either infection or vaccination, creates an immune response that results in destruction of native peripheral nerve architecture, namely the myelin sheath [11].

According to VAERS (Vaccine Associated Event Reporting System) vaccine associated GBS is characterised as GBS occurring within six weeks of vaccination [12]. GBS associated with SARS-CoV-2 typically occurs 11-20 days after initial infective symptoms [13]. In our patient, symptoms arose roughly three weeks after initial vaccination. This correlates with the time frame upon which maximal immune response to vaccine would be anticipated.

Eosinophillic Granulomatosis Polyangitis (EGPA) is a type of vasculitis that affects small and medium sized blood vessels often but not limited to, the pulmonary tissue [14]. It is well known that infections bacterial and viral can trigger GPA [15]. There have been a few reports of the occurrence of EGPA in association with COVID-19 [16]. And one report in the literature at the time of writing, of anca-associated vasculitis occurring post Pfizer-BioNTech COVID-19 mRNA vaccination. In this case the patient developed rhabdomyolysis and crescentic glomerulonephritis two weeks after a second dose of Pfizer BioNTech COVID-19 mRNA vaccine. While the mechanisms by which this occurred are yet to be fully understood, one theory is an autoimmune response driven by neutrophils post exposure to mRNA [17]. Rhabdomyolysis, as described in the latter case, has been previously associated with vaccination, namely the Influenza vaccine [18,19]. Interestingly, emerging evidence suggests COVID-19 mRNA vaccine can cause myositis at injection site [20].

European colleagues reported the first cases of a hyper inflammatory syndrome in children with features similar to Kawasaki disease and toxic shock syndrome [21]. These children presented usually in shock with significantly raised inflammatory markers. Gastrointestinal symptoms, rashes and fevers being the other predominant features. Since then, Multisystem Inflammatory Syndrome (MIS-a), in associated with SARS-CoV-2 has been well documented in the paediatric population [22-24].

There is a growing body of evidence that this also occurs in the adult population with several case reports in the literature [25-27]. Two of our patients in the case series demonstrated several features of MIS-a with persistent fever, elevated inflammatory markers, cardiac dysfunction and hypotension. The interval between vaccination and onset of symptoms was roughly two weeks for our patients [28]. This is similar to other described cases of MIS-a in associated with SARS-CoV-2 infection where symptoms develop four-twenty days after positive PCR test. Earlier this year the first reported case of vaccine associated MIS-a was published [28]. This patient in this case demonstrated many parallels to our cohort with predominant features being persistent pyrexia, raised inflammatory markers, hypotension and skin rash. Important differences to highlight are, the patient in that case report was vaccinated with fizer-BioNTech m-RNA SARS-CoV-2 vaccine and symptoms developed just two days after vaccination. The treatment however, was similar to that received in our cohort-namely supportive measures, high dose intravenous methylprednisolone and immunomodulatory drugs. In addition, another study published this year reports similar delayed hypersensitivity reactions to the Moderna m-RNA SARS Cov-2 vaccines in twelve previously healthy individuals [29]. This emphasises the importance being aware of such reactions when treating patients presenting with multiorgan dysfunction post vaccination.

Additionally, the striking similiarities between Adult Onset Stills' disease and MIS-a beg the question, could MIS-a be a variant of Stills' disease. Alternatively, do both represent a spectrum of multisystem inflammatory processes yet to be fully understood?

The mechanisms by which SARS-CoV-2 infection causes MIS-a and MIS-c are still to be elucidated, with immune system dysregulation and cytokine storm causing multiorgan dysfunction, thought to be critical [30]. It is likely the pathophysiology for MIS-a associated with vaccination is similar in susceptible individuals

For the astute physician, it is critical therefore, to consider the diagnosis of MIS-a in patients presenting acutely unwell post vaccination. Our case series demonstrates the great variety of symptoms with which patients' may present and raise awareness of these important albeit rare, complications. Early suspicion would lead to more timely diagnosis and a reduction in the morbidity associated with these conditions.

CONCLUSION

The As illustrated by these four cases, mass vaccination is not without risk and the receiving physician should be aware of these potential complications as well as other autoimmune mediated systemic illnesses, when assessing patients post vaccine. As mass vaccination programmes continue worldwide, it is likely more cases demonstrating such complications will emerge. Having said that, we would like to emphasise that such side effects are extremely rare and vaccines overall, are overwhelmingly safe.

KEY LEARNING POINTS

1. Always consider demyelinating pathology in patients presenting with acute motor or sensory disturbance post vaccination.

2. Consider alternate diagnoses' for patients presenting with persistent pyrexia and raised inflammatory markers, despite antibiotic therapy.

3. Mutli-speciality input is critical in timely diagnosis and treatment for patients presenting with multiorgan dysfunction.

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