Recrudescence of severe polyneuropathy after receiving Pfizer-BioNTech COVID-19 vaccine in a patient with a history of eosinophilic granulomatosis with polyangiitis

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SUMMARY
A middle age man with a history of diabetes mellitus type 2, hypertension, migraine and eosinophilic granulomatosis with polyangiitis (EGPA) with polyneuropathy in remission presented with paresthesia and motor weakness soon after receiving the Pfizer-BioNTech COVID-19 messenger RNA (mRNA) vaccine. The patient had polyneuropathy 10 years ago secondary to EGPA, which had resolved. EGPA was diagnosed on the basis of typical symptoms and positive sural nerve biopsy. Five days after receiving the first dose of COVID-19 vaccine, he developed heaviness and reduced dexterity of both the upper extremities, which progressed to patchy and asymmetric motor weakness of all four extremities. Given the lack of clear alternative explanation after a thorough work up, recrudescence of underlying asymptomatic polyneuropathy due to a possible reaction to COVID-19 mRNA vaccine was considered although a temporal association with vaccine dose does not prove causality. He was treated with corticosteroids with slow improvement of his symptoms.

BACKGROUND
The current COVID-19 pandemic caused by SARS-CoV-2 has upended the way of life as we know it. In the USA alone, there have been more than 80 million cases with more than 700 000 deaths to date.1 Besides the significant illness-related morbidity and mortality, there has been huge financial impact all over the world. Tremendous efforts have been made globally to develop vaccines effective against COVID-19. In the USA, this has been achieved through operation Warp speed, a partnership between various governmental/regulatory and private entities, that oversaw the accelerated development and manufacturing of COVID-19 vaccines.2 4 This led to rapid development and subsequent emergency use authorisation (EUA) of the two messenger RNA (mRNA) vaccines (Pfizer and Moderna) and one viral vector vaccine (Johnson & Johnson).3 5 Subsequently, Pfizer-BioNTech mRNA COVID-19 vaccine received full Food and Drug Administration (FDA) approval for individuals 16 years of age and older.6 The trial data for both mRNA vaccines have shown more than 90% efficacy without significant safety concerns.7 8 Our case suggests a possible need for closer monitoring of people receiving COVID 19 mRNA vaccines with underlying autoimmune conditions and/or polyneuropathy.

CASE PRESENTATION
A middle age male physician and first-line healthcare provider with a history of diabetes mellitus type 2, hypertension, migraine and eosinophilic granulomatosis with polyangiitis (EGPA) presented with paresthesia and motor weakness in all four extremities. He had been diagnosed with EGPA associated with polyneuropathy 10 years ago. At the time, he had a classic presentation of new-onset asthma, rhinosinusitis, rash and polyneuropathy. Sural nerve biopsy had findings suggestive of vasculitis. He was treated with mycophenolate mofetil for 2 years and glucocorticoids for 3 years. He had been in remission and off any treatment for vasculitis or neuropathy for past 7 years. At baseline, the patient is physically active and did not have any neuropathic symptoms except for mild sensitivity to cold in the left forearm. He was taking linagliptin/metformin XR, losartan, hydrochlorothiazide, rosuvastatin and pregabalin (for migraine prophylaxis).

The day after receiving the first dose of COVID-19 vaccine (Pfizer-BioNTech), he developed a severe influenza-like illness with temperature of 101°F and body aches. On third day, he went to emergency room, where tests for COVID-19 PCR and influenza were negative. He had mild leucocytosis at 10.24×109/L (3.98×109/L to 9.57 k/uL) and the eosinophil count slightly increased to 0.94 k/uL (0.00 k/uL to 0.50 k/uL). The Influenza-like symptoms resolved over the next day. However, on day 5 postvaccination, he noticed symmetric heaviness and tiredness of both forearms. He also had associated clumsiness of both hands with reduced dexterity. The repeat lab tests at his primary care physicians office revealed normalisation of white cell count and eosinophil count. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were normal. Antineutrophil antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were negative. Over the next week, his symptoms continued to worsen. His exertional capacity had a significant decline. On day 12 postvaccination, he noticed weakness of the left side of body. At this point, he was admitted to the hospital. His neurological examination revealed asymmetric findings. Motor strength of right side was 5-/5 for deltoid and hip muscles (adductors and abductors). Motor
strength on left side ranged from 4/5 to 5/5 in deltoid, triceps, hip muscles (flexors, adductors and abductors) and ankle muscles (dorsiflexors and planter flexors). Left pectoral and both ankle reflexes were absent. He also had reduced pin prick sensation in an asymmetric pattern (bilateral anterior thighs and left medial calf). The rest of the physical examination was unremarkable. Cerebrospinal fluid (CSF) studies were unremarkable. MRI of lumbar and thoracic spine was unremarkable. Laboratories revealed normal complete blood count, differential white blood cells and platelet count. Subsequent ANA, ANCA, anti-neutrophil cytoplasmic antibodies (ANCAs) and anti-glomerular basement membrane (GBM) antibodies remained negative. Haemoglobin A1c (HbA1c) was 7.8% (6.8% 6 months ago). MRI of lumbar and thoracic spine was unremarkable. Cerebrospinal fluid (CSF) studies revealed normal or near-normal eosinophils, ESR, CRP and negative ANCA, EGPA relapse was deemed unlikely.

**Differential Diagnosis**

EGPA relapse

At the time of initial EGPA diagnosis, patients’ neurological symptoms had some similarities with current symptoms, that is, heaviness of both arms with loss of dexterity, followed by motor weakness and pain. However, there were some notable differences such as weakness and paresthesia were symmetric with a monophasic pattern unlike the asymmetry and fluctuations noted at this presentation. Also, left foot drop is a new finding this time. Second, at the time of original diagnosis, patient had associated symptoms of rhinosinusitis over months, new-onset asthma and maculopapular rash on palms, which were not present this time. Given differences in pattern of symptoms, lack of other associated symptoms and unremarkable laboratory studies (normal or near-normal eosinophils, ESR, CRP and negative ANCA), EGPA relapse was deemed unlikely.

**Guillain-Barre syndrome**

The patient’s clinical picture that started as paresthesia and progressed to asymmetric patchy motor weakness did not fit Guillain-Barre syndrome (GBS). CSF studies and MRI of the spinal cord were unremarkable. Moreover, patient responded to steroids.

**Diabetic mononeuropathy multiplex**

Mononeuropathy multiplex has been described in the literature as a rare and atypical complication of diabetes. There are a few case reports describing this condition. It is usually seen in patients with mildly elevated HbA1c and has a subacute onset. Electrodiagnostic studies are usually abnormal and suggestive of axonal degeneration. Rapid onset of symptoms and unremarkable NCV/EMG makes diabetic mononeuropathy multiplex less likely.

**Final diagnosis**

Given the close temporal relationship after receiving the first dose of COVID-19 Pfizer-BioNTech mRNA vaccine and lack of alternative explanation it was concluded that this patient likely had a reaction to Pfizer-BioNTech mRNA vaccine leading to recrudescence of underlying asymptomatic polyneuropathy.

**TREATMENT**

Following the pulse dose steroids in hospital, patient remained in 1 mg/kg prednisone daily for 2 weeks. After follow-up with neurologist, prednisone dose was tapered every 5–7 days until a 10 mg/day dose was reached and then slowly tapered off over next 5 months.
OUTCOME AND FOLLOW-UP
The patient sought opinions from two different referral centres. He was evaluated by a neuromuscular/neuroimmunologist at a national referral centre via telemedicine and was later seen by another neuromuscular specialist at a local referral centre. A repeat NCV/EMG, done 1 week after the first one, revealed similar results without any signs of progression. It was thought that either the injury was not significant enough to show up on NCV/EMG studies or perhaps it was still too early to see the changes. A nerve biopsy was deferred as it was considered low yield and patient had already undergone sural nerve biopsy on left side which was predominantly affected this time also.

Over the next few months, he had slow improvement in his symptoms and started rehabilitation. His vision and neuropathic pain have improved. He was unable to work for first 2 months following which he returned to work with limited duties. Now 9 months since receiving the vaccine, he continues to make slow recovery with rehabilitation and is performing nearly full duties.

DISCUSSION
Vaccines are among the most effective tools in prevention of infectious diseases. On the other hand, vaccines themselves can be associated with various kinds of adverse reactions, including neurological adverse events like GBS, multiple sclerosis, neuritis and small fibre neuropathy. Various pathophysiological theories have been proposed to explain the autoimmune adverse events after receiving vaccines, including molecular mimicry, immune-mediated bystander activation, immune-mediated hypersensitivity to the solvents/adjuvants and inflammatory damage. However, the rarity of such events and variable latency period makes it extremely difficult to ascertain causality and provide an accurate pathophysiological explanation.

During this unprecedented time of the COVID-19 pandemic, the development and EUA of the vaccines has brought great hope. There were few significant safety concerns during the trials for the two mRNA vaccines. Higher rate of local reactions was noted with both the mRNA

Table 2 Additional laboratory studies

| Lab test                                      | Results prior to presentation | Results on presentation | Result on follow-up | Laboratory reference range         |
|----------------------------------------------|-------------------------------|-------------------------|---------------------|------------------------------------|
| CK                                           | 70                            | 30–200 IU/L             |                     |                                    |
| Sedimentation rate (ESR)                     | 1                             | 14                      | 2                   | 0–25 mm/hr                         |
| CRP                                          | 0.5 (1–3 mg/L)                | CRP <0.20               | ≤0.49 mg/dL         |                                    |
| Anti-neutrophil cytoplasmic Ab, IgG          | Negative                      | Negative                |                     |                                    |
| Anti-nuclear antibody                        | <1:10                         | <1:40                   | <1:80               |                                    |
| C3                                           | 165                           | 114                     | 82–193 mg/dL        |                                    |
| C4                                           | 46                            | 38                      | 15–57 mg/dL         |                                    |
| Beta-2 glycoprotein 1, IgG                   | 0                             | 0–20 SGU                |                     |                                    |
| Beta-2 glycoprotein 1, IgM                   | 1                             | 0–20 SMU                |                     |                                    |
| DNA (Ds) antibody DNA                       | Negative                      | Negative                |                     |                                    |
| SSA                                          | 1                             | <1.0                    | 0–40 AL/mL          |                                    |
| SSB                                          | 0                             | <1.0                    | 0–40 AL/mL          |                                    |
| Rheumatoid factor                           | <13.0                         | <14                     | ≤30.0 IU/mL         |                                    |
| Cryoglobulin, qualitative                    | Negative                      |                         |                     |                                    |
| Vitamin B12                                  | 268                           | 213–816 pg/mL           |                     |                                    |
| Methylmalonic acid                          | 0.24                          | 0.00–0.40 umol/L        |                     |                                    |
| HIV 1/2 Ab + HIV 1 Ag                       | Non-reactive                  |                         |                     |                                    |
| Hepatitis C antibody                         | Non-reactive                  |                         |                     |                                    |
| Hepatitis B antigen and core antibody        | Negative                      |                         |                     |                                    |
| Serum protein electrophoresis               | Normal pattern                | Normal pattern          |                     |                                    |
| Serum free light chains                      |                               |                         |                     |                                    |
| Kappa                                        | 9.82 mg/L                     | 3.30–19.40 mg/L         |                     |                                    |
| Lambda                                       | 5.02 mg/L                     | 5.71–26.30 mg/L         |                     |                                    |
| Kappa/lambda ratio                           | 1.96                          | 0.26–1.65               |                     |                                    |
| Immunofixation                               | Normal                        |                         |                     |                                    |
| Urine porphyrins random                     | Within normal limits          |                         |                     |                                    |
| Acetylcholine receptor binding Ab           | Negative                      |                         |                     |                                    |
| Acetylcholine receptor modulating Ab         | Negative                      |                         |                     |                                    |
| Striated muscle Ab screen                   | Negative                      |                         |                     |                                    |
| Lyme serology                               | Negative                      |                         |                     |                                    |
| Jo-1                                         | Negative                      |                         |                     |                                    |
| Smith                                        | Negative                      |                         |                     |                                    |
| SCL-70                                       | Negative                      |                         |                     |                                    |
| Ribosomal P                                  | Negative                      |                         |                     |                                    |
| COVID-19 IgG                                 | Negative                      |                         |                     |                                    |

CK, creatinine kinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SCL, Topoisomerase 1; SGU, standard IgG beta 2 glycoprotein unit; SMU, Standard IgM beta 2 glycoprotein unit; SSA, Anti Sjogren's syndrome A; SSB, Anti Sjogren's syndrome B.
vaccines but were not significant. Incidence of systemic reactions with fatigue, headache and fever (influenza like illness) was also higher in vaccine groups. These were mild with the first dose, but a significant number of participants had more severe systemic reaction after the second dose of both vaccines. There were no significant adverse events, including hypersensitivity reactions with either vaccine. Few cases of Bell’s were reported during the trials, which were considered to be incidental and not related to vaccines. There is lack of safety data in certain populations like pregnant women or immunocompromised patients who were not included in trials. Subgroup data for those with underlying autoimmune conditions who were included in trials are not available. While autoimmune dysregulation is thought to play a role in various complications associated with COVID-19 infection, there have been no confirmed reports of autoimmune or neurological adverse events with COVID-19 mRNA vaccines so far.

The need and importance of vaccines against COVID-19 to help control the current pandemic and reduce incidence of severe illness cannot be emphasised enough. To date, more than 255 million people have received at least one dose of COVID-19 vaccines and greater than 218 million people are fully vaccinated in USA. However, when vaccinating millions of people, emergence of new adverse events not seen during the clinical trials with its fewer patients is not entirely unexpected. Such events require further investigation to determine a relationship to the vaccine versus simply coincidental occurrences. For example, allergic reactions including anaphylaxis and inflammation of the heart (myocarditis and pericarditis) have been found to be adverse events in vaccinated individuals not seen during clinical trials with both the mRNA COVID-19 vaccines. Similarly, an increased risk of thrombosis with thrombocytopenia syndrome has been suggested with the use Johnson & Johnson Janssen viral vector vaccine in adult women younger than age 50.

Currently, CDC recommends that people with autoimmune conditions may receive an mRNA COVID-19 vaccine series along with an additional dose 28 days after completing an mRNA COVID-19 vaccine series. Additionally, a booster dose is recommended for a subset of high-risk population who have received Pfizer-BioNTech mRNA COVID-19 vaccine at least 6 months after completing the series.

Our case may represent an isolated occurrence as an individual’s personal predisposition, medical history, genetics and environmental factors play a role in their susceptibility to autoimmune reactions. While a temporal relationship with receiving the vaccine may indicate an association, it cannot determine causality without any definitive proof of diagnosis, especially when other possible conditions (eg, EGPA, diabetic neuropathy, etc) can also have similar findings. However, this case perhaps suggests a need of closer monitoring of patients with autoimmune conditions and/or neuropathies receiving COVID-19 mRNA vaccines until more data are available. Both CDC and vaccine companies have reporting systems in place for such events, where this case has been reported as well.

Acknowledgements We thank Dr Mathew Feldman for his guidance regarding vaccine related adverse events.

Contributors Conception of plan to write up the case: RG, MF. Compiling and acquisition of information regarding the case: RG, MSS, MR. Drafting the manuscript: RG. Discussion of differential diagnosis: RG, MR, MF. Revising the manuscript: RG, MF.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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