



New-onset severe eosinophilic granulomatosis with polyangiitis following the third dose of mRNA COVID-19 vaccine: A case report

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis (EGPA) is a complex multifactorial disease that results in multisystemic inflammation of the small- and medium-sized arteries. The exact pathogenesis of this syndrome is poorly understood, but it is postulated to result from a combination of eosinophilic dysfunction, genetic predisposition, and the development of autoantibodies after exposure to an unknown stimulus. We describe a case of new-onset EGPA following the third dose of the Pfizer-BioNTech mRNA vaccine in an infection-naïve middle-aged man with a background history of allergic respiratory symptoms. The patient developed acute onset of mononeuritis multiplex, pauci-immune glomerulonephritis, and leucocytoclastic vasculitis 10 days after receiving the booster dose. His laboratory markers including eosinophil count, antineutrophil cytoplasmic antibodies, and renal function tests improved markedly after the initiation of pulse steroid therapy and rituximab infusion. However, his peripheral muscle weakness and neuropathic pain did not respond to the initial therapy but improved later with intravenous cyclophosphamide and intravenous immunoglobulin. To the best of our knowledge, this is the fourth case report of post-coronavirus disease 2019 vaccination precipitation of EGPA. All reported cases including our report were in patients with previous allergic manifestations who received mRNA-based coronavirus disease 2019 vaccines, and all the patients developed mononeuritis multiplex at presentation. Despite the few reported cases of post-vaccination autoimmune phenomena, the temporal association between vaccination administration and disease onset does not indicate causality, given the mass vaccination programmes employed. However, the novel use of the mRNA platform in vaccine delivery necessitates vigilant monitoring by the scientific committee.

KEYWORDS: ANCA-associated vasculitis; COVID-19 vaccine; EGPA; mononeuritis multiplex

Introduction

The recent utilisation of mRNA platform against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) facilitated the rapid production of highly efficacious vaccines against the coronavirus disease 2019 (COVID-19) by stimulating both humoral and cellular immunity [1]. However, concerns were raised about triggering or precipitating autoimmune activities in susceptible individuals, especially since patients with autoimmune rheumatic diseases were largely excluded from the initial trials [2]. Eosinophilic granulomatosis with polyangiitis (EGPA) is classified as vasculitis of the small- and medium-sized arteries, and it is characterised clinically by allergic manifestations of the upper and lower respiratory tract as well as marked peripheral eosinophilia. Although the pulmonary tree is

the most affected system, extrapulmonary manifestations account for the majority of EGPA-related mortality and morbidity [3].

Given the complex immunological interactions between vaccines and autoimmune diseases, the scientific committee should remain vigilant in identifying possible autoimmune phenomena linked to the newly used vaccines. Herein, we present a florid case of new-onset multisystemic EGPA disease following the administration of the third dose of the Pfizer-BioNTech mRNA vaccine in a middle-aged man with a previous history of chronic obstructive pulmonary disease and allergic rhinitis. Despite the rapid improvement of the patient's skin, renal, and peripheral eosinophilia involvement with rituximab induction therapy, his neurological manifestations were more challenging to treat.



Figure 1. Multiple discrete lesions on both lower limbs typical for the palpable purpura of leucocytoclastic vasculitis.

Case presentation

A 53-year-old male patient presented to the emergency department of our hospital with a 3-day history of asymmetrical hand clumsiness associated with difficulty in walking. He also reported a history of fatigue, myalgia, and nonpruritic skin rash over the back and both lower limbs since he received the third dose of the Pfizer-BioNTech COVID-19 vaccine 10 days earlier (Figure 1). The patient had chronic neck pain that increased lately and bilateral knee pain, more on the left side. However, he denied having morning stiffness, fever, numbness, or any gastrointestinal or urinary symptoms. His background medical history included Type II diabetes mellitus and hypertension for many years, persistent allergic rhinitis symptoms for 5 years, and chronic obstructive pulmonary disease for 1 year. He had a smoking history of 25 pack-years but quit smoking 10 months ago because of worsening cough and nasal obstruction. He did not drink alcohol nor did he use over-the-counter or illicit medications. The first two doses of Pfizer-BioNTech COVID-19 vaccines were given 8 months ago, 3-week apart, and were not followed by any adverse event. He was not diagnosed to have COVID-19 disease before. His current medications included olmesartan, budesonide/formoterol inhaler, mometasone nasal spray, vildagliptin/metformin, and fluvastatin. On examination, vital signs were within normal range. The neurological assessment showed distal muscle weakness of both upper limbs (4/5) with hypotonia and sluggish reflexes and weak left-hand grip with wrist drop posture. Lower limb examination revealed a non-blanchable violaceous skin rash over both shins (Figure 1). However, there was no muscle weakness, hypotonia, or clonus. Higher cortical function, sensory, cranial nerve, and cerebellar tests were normal. There was no active joint swelling or redness, and the rest of the systematic examination was unremarkable.

The initial laboratory workup revealed marked eosinophilia with an eosinophil count of 7600/ μ l, normal

serum creatinine and transaminases, serum albumin of 29 g/l, and positive urine dipstick for protein (+2) as well as blood (+3) (Table 1). The urine protein-creatinine ratio was 225.80 mg/mmol, and 24-hour urinary protein was 1.94 g. Ultrasound examination showed normal-sized unobstructed kidneys. Chest X-ray showed mild left-sided consolidation with obliteration of the left costophrenic angle. A computed tomography of the head was reported as normal, while subsequent magnetic resonance imaging of the brain and cervical and thoracic spine was only remarkable for a few nonspecific T2-hyperintense areas in the subcortical and deep white matter of the frontoparietal region bilaterally, in addition to early degenerative changes in the spine. A computed tomography study of the chest, abdomen, and pelvis showed subtle multi-lobar patchy areas of ground-glass opacities in the lungs, small left-sided pleural effusion, and mild hepatomegaly. The autoimmune panel was positive for perinuclear Anti-neutrophil Cytoplasmic Antibodies with anti-myeloperoxidase antibody titre of >134 IU/ml, negative anti-proteinase-3 antibody, normal C3 and C4 levels, and negative anti-glomerular membrane antibody (Table 1). At this stage, the patient was started on oral prednisolone 60 mg daily and pregabalin 75 mg twice daily for neuropathic pain.

An initial nerve conduction study and electromyographic examination have been performed 2 days after the patient's presentation showed only mild peripheral sensorimotor neuropathy suggestive of distal diabetic neuropathy and mild bilateral carpal tunnel syndrome. However, 2 weeks later, a repeat study found new axonal neuropathy of both radial and anterior interosseous nerves consistent with acute mononeuritis multiplex suggesting peripheral nerve vasculitis. A skin biopsy of the leg lesions was performed and showed leucocytoclastic vasculitis, whereas the kidney biopsy confirmed the presence of pauci-immune necrotising and crescentic glomerulonephritis (Figure 2).

Table 1. Summary of laboratory investigations at presentation.

Laboratory test	Value	Normal range
Haemoglobin (g/dl)	16.7	13–17
White blood cell count ($\times 10^3/\mu\text{l}$)	17.4	4–10
Absolute neutrophil count ($\times 10^3/\mu\text{l}$)	7.0	2–7
Lymphocytes ($\times 10^3/\mu\text{l}$)	2.0	1–3
Eosinophils ($\times 10^3/\mu\text{l}$)	7.6	0–0.5
Basophils ($\times 10^3/\mu\text{l}$)	0.06	0.02–0.1
Platelet ($\times 10^3/\mu\text{l}$)	200	150–400
Urea (mmol/l)	3.1	2.5–7.8
Creatinine ($\mu\text{mol/l}$)	67	62–106
Sodium (mmol/l)	131	133–146
Potassium (mmol/l)	4.3	3.5–5.3
Bilirubin ($\mu\text{mol/l}$)	11	0–21
ALT (U/l)	41	0–41
AST (U/l)	23	0–40
CRP (mg/l)	111	0–5
ESR (mm/hour)	30	2–37
PT (seconds)	10.6	9.7–11.8
PTT (seconds)	25.6	24.6–31.2
HbA1c (%)	7.8	
Urine WBC	Negative	
Urine RBC	+3	
Urine protein	+2	
ANA (titre)	Negative	
RF (IU/ml)	30	
Anti-CCP (U/ml)	<8	
Anti-myeloperoxidase (IU/ml)	>134	
Anti-proteinase 3 (IU/ml)	Negative	
Anti-GBM (IU/ml)	Negative	
Phospholipase A2 receptor antibody	Negative	
Peripheral smear	Leucocytosis with severe eosinophilia. No immature cells were seen.	

AST: Aspartate aminotransferase; ALT: Alanine transaminase; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; PT: Prothrombin time; PTT: Partial thromboplastin time; HbA1c: Glycated haemoglobin; WBC: White blood cell count; RBC: Red blood cell count; ANA: Antinuclear antibody; RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide; GBM: Glomerular basement membrane.

Based on the systemic involvement and histopathological and autoimmune studies, we diagnosed the patient with

multisystemic EGPA. He received induction therapy of methylprednisolone 500 mg daily for 3 days followed by oral prednisolone (starting daily dose of 0.5 g/kg with gradual weekly tapering until reaching 5 mg) in addition to 1 g rituximab infusion with a repeated dose after 2 weeks. The patient received one dose of maintenance rituximab infusion 6 months later, but at Year 1 of follow-up, he was still having left wrist drop with significant wasting of the small muscles of both hands and left forearm. However, his renal function tests, urine examination, and eosinophil counts were within normal range with undetectable ANCA antibody levels. Repeated electromyographic examination and nerve conduction study showed worsening electrophysiological features of severe asymmetric and non-length-dependent sensorimotor axonal polyneuropathy consistent with severe mononeuritis multiplex. Moreover, the patient declared that he had one dose of intravenous cyclophosphamide while being abroad in India 2 months earlier. Therefore, we conducted a multidisciplinary team meeting with the primary rheumatologist, nephrologist, and neurologist, and the team decided to stop rituximab and start him on intravenous cyclophosphamide (1 g monthly for 6 months) and intravenous immunoglobulin (IVIG) (induction dose of 2 g/kg followed by 1 g/kg every 2 months for two doses) for his worsening neuropathy. On follow-up visits, the patient reported gradual improvement in his hand grip strength and neuropathic pain. The trends in eosinophil count, ANCA level, and therapeutic modalities are summarised in Figure 3.

Discussion

Considering the globally employed mass vaccination programmes against COVID-19 disease, the mere temporal association between new-onset autoimmune events and COVID-19 vaccine administration is not adequate to establish causality. Nevertheless, such events are worth monitoring and reporting to ensure safe vaccine delivery and make informed decisions about vaccination programmes for vulnerable patients.

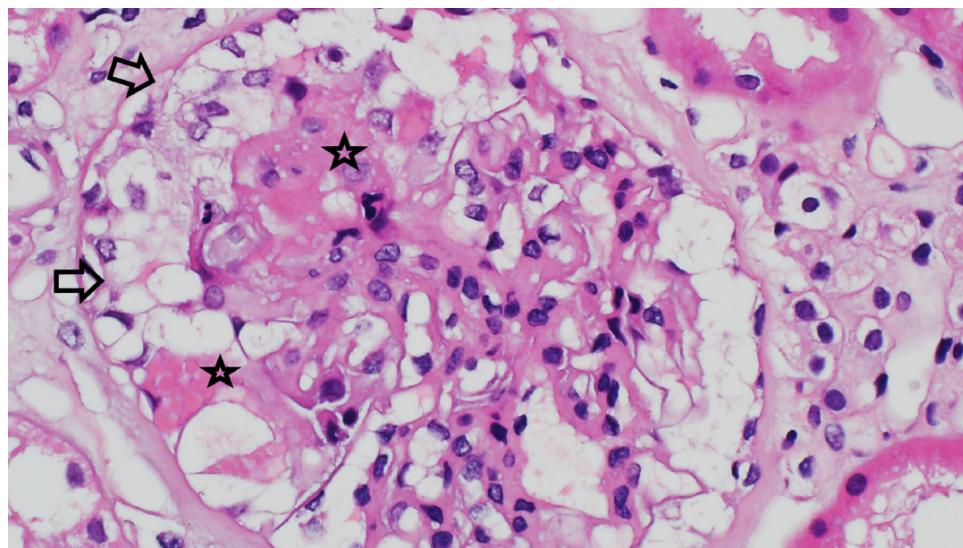


Figure 2. A representative glomerulus from the renal biopsy depicting fibrinoid necrosis (asterisk) and crescent formation (arrows). Haematoxylin and eosin stain. Original magnification 350X.

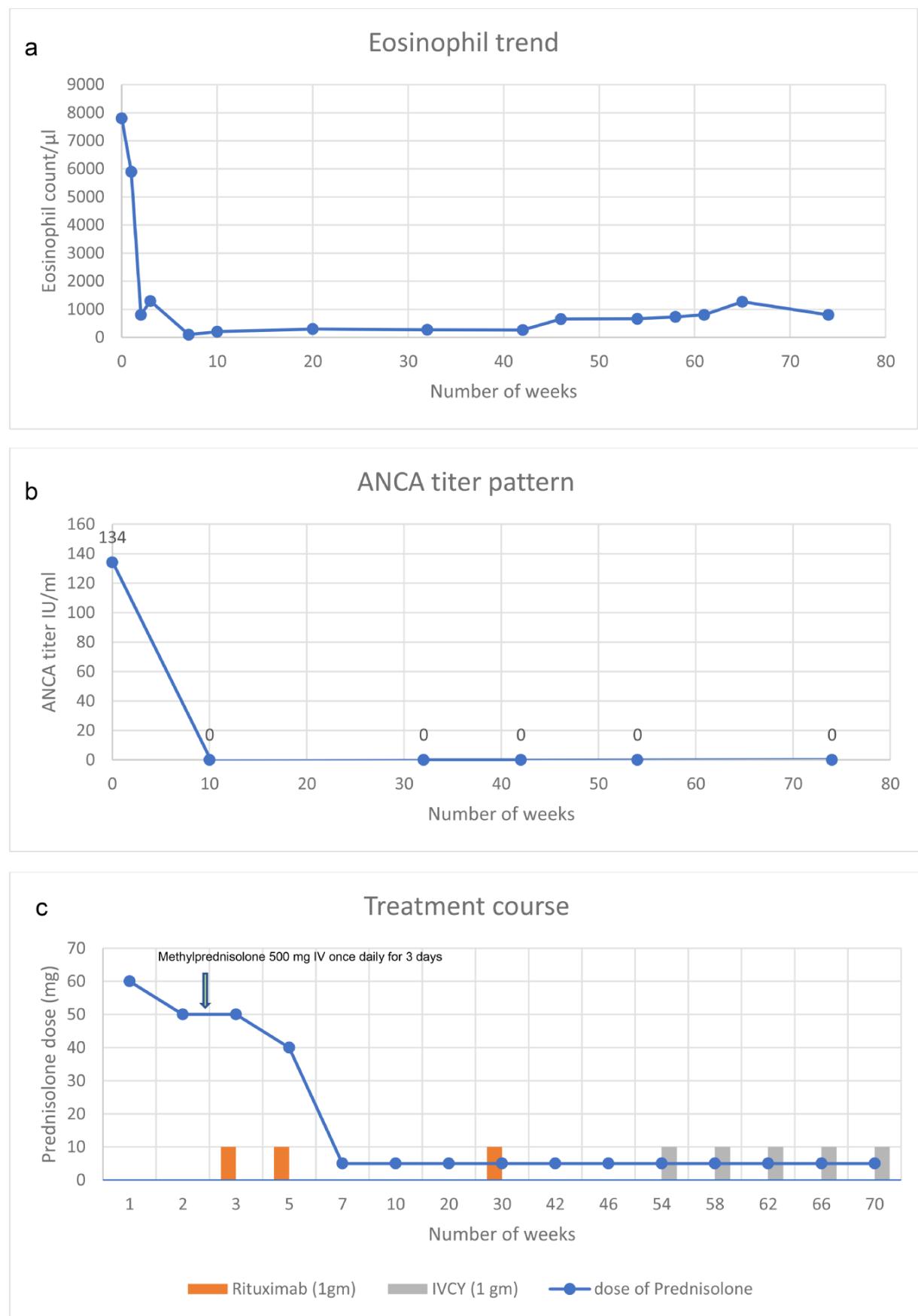


Figure 3. A demonstrative graph for the main laboratory findings and therapeutic interventions from the time of presentation until Week 70 of follow-up. (a) The trend in eosinophil count/millilitre. (b) The pattern of ANCA titre level (IU/ml). (c) The timing and dose of oral prednisolone (in mg), rituximab, and intravenous cyclophosphamide (IVCY).

The World Health Organization defined a conceptual framework for causality assessment of any adverse event following immunisation, which includes a thorough assessment of the temporal association between vaccine administration and the occurrence of the adverse event in a plausible time window, excluding other reasons that might explain the event, and the strength of this association [4]. In this case, the patient fulfilled the 2022 European Alliance of Associations for Rheumatology (EULAR) classification criteria for EGPA (total six points) 10 days post the third dose of the COVID-19 mRNA vaccine. According to a longitudinal study on the immunogenicity of the COVID-19 mRNA vaccine, the peak levels of the humoral and cellular responses were achieved 2 weeks following the second dose and then decreased gradually over the subsequent 6 months. However, the third dose of the vaccine was associated with a marked increase in SARS-CoV-2-specific T cells, Immunoglobulin G (IgG), and neutralising antibodies, especially in infection-naïve patients [5]. The onset of EGPA symptoms during the first 2 weeks post the booster dose coincides with the presumed peak of immunological response post vaccination.

We reviewed the PubMed database for previously published case reports on new-onset EGPA post-COVID-19 vaccination using the following keywords: 'Eosinophilic granulomatosis with polyangiitis' AND 'COVID-19' AND 'Vaccine' with no specified date. We identified five cases, two of which were excluded because the patients had pre-existing EGPA disease [6, 7]. The three new-onset cases of EGPA post-COVID-19 vaccination are summarised in Table 2 [8–10]. Similar to our case, all patients received mRNA-based vaccines, had a background history of allergic pulmonary disease, and had neurological manifestations of EGPA at presentation. However, they were older than the patient in our case. In comparison, an earlier cohort study of 150 patients with EGPA treated in a specialised vasculitis centre in Germany found that 35% of the cases had mononeuritis multiplex at presentation, while the 5-year cumulative percentage of mononeuritis multiplex

was 56% [17]. The observed higher rate of peripheral neurological manifestations in post-vaccination EGPA cases compared to the usual rate in EGPA requires further evaluation as it is impossible to draw conclusive conclusions based on a few case reports. Moreover, new-onset EGPA disease was temporarily associated with COVID-19 infection as well [11]. According to a recent systematic review, new-onset autoimmune rheumatological phenomena post COVID-19 vaccination occurred more frequently in individuals above the age of 50 years and with the use of mRNA-based COVID-19 vaccines. Nevertheless, the review concluded that it would be difficult to directly compare the risk of autoimmune rheumatic disease precipitation post COVID-19 infection versus vaccination [12]. Hakroush and Tampe hypothesised that the spike protein or the mRNA part of the COVID-19 vaccine might trigger a neutrophilic reaction that leads to persistent neutrophil extracellular traps and the formation of antibodies to myeloperoxidase and proteinase-3. Nevertheless, the presence of renal crescents at the time of diagnosis in many cases including our case indicates that patients might have had unrecognised underlying glomerulonephritis at the time of vaccination, which propagated the immune response in predisposed individuals [13].

The patient in our case had a particularly progressive neurological sequela of EGPA despite the complete response of his renal, dermatological, and serological markers of disease activity after rituximab therapy. Thereafter, we started cyclophosphamide therapy with IVIG with partial improvement in the patient's symptoms. An earlier double-blind, multicentre, randomised controlled trial in Japan on 23 patients with EGPA who had chronic residual peripheral neuropathy despite being in remission by laboratory indices found clinically and statistically favourable effects on the manual muscle testing and neuropathic pain scores 2-week post IVIG administration. Therefore, the authors recommended considering IVIG for EGPA patients with residual peripheral neuropathy even in patients who are in apparent remission [14].

Table 2. Summary of new-onset EGPA post-COVID-19 vaccine case reports.

Authors [Reference]	Vaccine platform	Age	Sex	Time to onset	Clinical description	Treatment	Outcome
Nappi <i>et al.</i> [8]	mRNA vaccine	63 years	Male	One day after the administration of the third dose Worsening asthma symptoms after the first two doses	Background history of asthma and allergic rhinitis presented with new-onset EGPA and marked eosinophilia involving cardiac, pulmonary, and neurological systems	High-dose steroids and cyclophosphamide	Good clinical and biochemical response
Ibrahim <i>et al.</i> [9]	mRNA vaccine	79 years	Female	Two weeks after the second dose	Background history of asthma and obstructive sleep apnoea presented with new-onset EGPA with peripheral neuropathy and marked eosinophilia	Oral prednisolone 60 mg with tapering plus azathioprine	Clinical improvement
Chan-Chung <i>et al.</i> [10]	mRNA vaccine	62 years	Female	Few days after receiving the second dose	Background history of asthma presented with new-onset EGPA and marked eosinophilia affecting the skin, neurological, and cardiac systems	Pulse steroid therapy plus rituximab	Clinical and biochemical improvement

Interestingly, Nishi *et al.* found distinct clinicopathological features of ANCA-positive EGPA neuropathy compared to ANCA-negative cases. Similar to our patient, the initial neurological involvement of myeloperoxidase (MPO)-ANCA-positive patients was more likely to affect the upper limbs with higher C reactive protein values compared to MPO-ANCA-negative patients with clinically significant *p*-values. Moreover, the study findings suggested dichotomous mechanisms for EGPA neuropathogenesis based on sural nerve biopsy where positive ANCA was more frequently associated with vasculitis type of inflammation of the epineurial vessels, whereas negative ANCA group had more frequent eosinophilic infiltration of the endoneurium and occlusion of the epineurial vessels [15]. However, the overlapping clinical features of eosinophilia and vasculitis in EGPA reflect an immunological spectrum of a systemic disease that evolves and intersects over time. Future research in precision medicine could help identify diagnostic biomarkers and develop targeted therapeutics for patients with different clinical and pathological phenotypes of EGPA and for the same patients during different stages of their disease activity [16].

Despite the few reports of post-COVID-19 vaccination precipitation of new-onset rheumatological diseases, rapidly accumulating evidence supports the safety of the newly employed COVID-19 vaccines in the general population and in patients with autoimmune rheumatic diseases [12, 17]. A detailed analysis of the EULAR coronavirus vaccine physician-reported registry on the safety of COVID-19 vaccines in people with rheumatic and musculoskeletal diseases was largely reassuring for both patients and attending rheumatologists. Although vaccine reactogenicity happened frequently in patients with rheumatic and musculoskeletal diseases, it was self-limiting. Even the few reported cases of serious adverse events were eventually resolved, and none was associated with death [17].

Conclusion

We presented a case of new-onset multisystemic EGPA following a booster dose of the Pfizer-BioNTech mRNA vaccine in a patient with a background history of allergic respiratory symptoms. Considering the complexity of EGPA pathogenesis, the temporal association between vaccine administration and disease onset is not adequate to establish a causal relationship but could work as a trigger in susceptible individuals. The novel adjuvanticity of the new COVID-19 vaccines should keep healthcare workers vigilant about new-onset autoimmune inflammatory conditions in vaccine recipients. Nevertheless, the global utilisation of different platforms of COVID-19 vaccines was the foundation for the successful management of this unprecedented pandemic, and a few reports on potential adverse events should not compromise vaccine uptake, especially for vulnerable populations.

Conflict of interest

None declared.

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Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

Ethical approval

Not applicable.

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