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Case Report

Neutrophilic urticaria with systemic inflammation (NUSI) following Pfizer–BioNTech COVID-19 vaccine

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ABSTRACT

The Pfizer–BioNTech mRNA vaccine has shown excellent protection against the severity of COVID-19, yet adequate research on rare adverse events is lacking. Herein, we discuss the case of a 36-year-old female who had developed an urticarial polymorphous eruption, episcleritis, and inflammatory oligo-arthritis, in keeping with neutrophilic urticaria with systemic inflammation (NUSI), following the administration of Pfizer COVID-19 vaccine. Investigations for other dermatological and rheumatological conditions were unremarkable, while multiple skin biopsies were highly suggestive of a neutrophilic drug reaction. To gain symptom control, our patient required multiple weeks off from work and was treated with several immunosuppressive, anti-inflammatory, and analgesic agents. Further research with larger numbers is needed to identify adverse events more accurately, which will aid both in early diagnosis and prompt treatment for patients.

Key words: Urticaria; Rash; Arthritis; COVID-19; Vaccination

INTRODUCTION

The Pfizer–BioNTech BNT162b2 mRNA vaccine has shown 95% protection against COVID-19 in adults in phase III clinical trials [1]. However, a systematic review of the adverse events reported revealed that they usually resolved within four days and included pain or redness on the injection site, fever, fatigue, myalgia, and arthralgia [2]. A subsequent registry-based study focusing on the cutaneous manifestations of mRNA COVID-19 vaccines further highlighted delayed cutaneous reactions, urticarial eruptions, and morbilliform eruptions, also resolving within several days and only requiring simple treatment, if any [3].

Herein, we present a case of generalized polymorphous eruption, episcleritis, and inflammatory oligo-arthritis following the administration of the second dose of Pfizer–BioNTech COVID-19 vaccine. The clinical picture presented similarly to the reported entity of NUSI, an inflammatory disorder with cutaneous involvement [4].

CASE REPORT

A 36-year-old, female art therapist presented with a generalized polymorphous eruption three days after the second dose of Pfizer–BioNTech COVID-19 vaccine. The medical history consisted of vitiligo, seasonal asthma, and hypothyroidism during pregnancy. The patient's only long-standing medication was the combined oral contraceptive pill (COCP) and inhaled salbutamol as needed. She denied any new prescribed or over-the-counter medication in the preceding three months. Although she reported no previous drug allergies, a previous reaction to morphine included nausea and pruritis.

The rash first appeared as a polymorphous eruption, consisting of erythematous, indurated plaques on the

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shoulder and upper arms (Fig. 1a) and a morbilliform eruption on the face, lower arms, legs, and torso (Fig. 1b). Interestingly, all patches of vitiligo remained unaffected by the eruption, which was fiercely pruritic and significantly affected the patient's quality of life. She also reported conjunctival injection, grittiness of the ocular mucosa, and blurring of vision. She was admitted to her local tertiary hospital, in which skin biopsies were performed and she was initiated on high-dose oral corticosteroids, oral anti-histamines, wet dressings with potent topical corticosteroids, and lubricating eye drops as per opthalmology advice. Blood tests revealed a raised white cell count (WCC) at 15.6 × 10^9/L (4.0–11.0), neutrophils at 14.0 × 10^9/L (2.0–7.5), C-reactive protein (CRP) at 25 mg/L (0.0–5.0), and an erythrocyte sedimentation rate (ESR) at 8 mm/h (1–29). Skin biopsies were most consistent with a drug eruption, showing a very mildly spongiotic epidermis with occasional apoptotic keratinocytes and underlying dermal inflammation containing some neutrophils, perivascular lymphocytes, and rarely eosinophils (Figs. 2a and 2b). After the rash and ocular symptoms subsided, corticosteroids were slowly weaned. However, her eruption and ocular symptoms returned once the dose of prednisolone reached 25 mg daily. Subsequent attempts to reduce prednisolone resulted in the same eruption, Therefore, cyclosporine was initiated at a dose of 4 mg/kg daily. During this period, the patient's eruption appeared more urticarial, yet was not evanescent. Additional skin biopsies were performed at this time, further supporting the diagnosis of a drug reaction. These revealed a similar picture, with a mild spongiotic reaction, dyskeratotic keratinocytes, and mixed dermal inflammation.

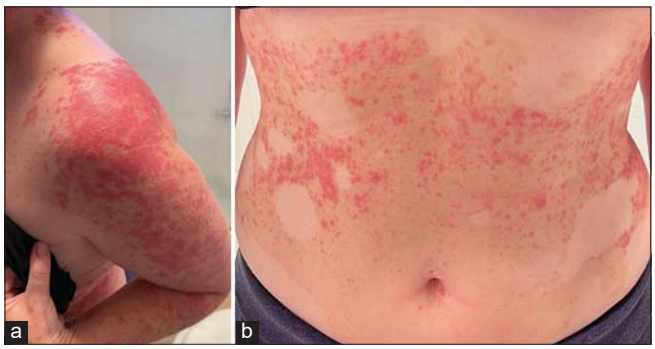

Figure 1: (a) Erythematous plaques on the shoulders. (b) Morbilliform eruption on the abdomen, notably sparing patches of vitiligo.

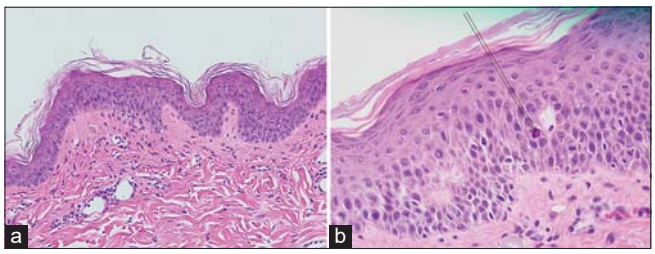

Figure 2: (a) The initial skin biopsy revealing a mildly spongiotic epidermis and mild upper dermal inflammation. (b) The initial skin biopsy revealing a mild spongiotic epidermis and a dyskeratotic cell.

Ten weeks after the initial presentation, our patient approached the emergency department with an acutely tender left elbow associated with swelling and a reduced range of motion. Further investigations revealed CRP at 10^4 mg/L and the ESR at 21 mm/h. A joint aspirate showed the WCC at 35,000 × 10^6/L (composed of 95% polymorphs, with no crystals under the microscope and no bacterial growth on culture). Anti-nuclear antibody (ANA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP), HLA-B27, anti-neutrophil cytoplasmic antibody (ANCA), double-stranded DNA (ds-DNA), extractable nuclear antigen (ENA), ferritin levels, liver enzymes, and complement levels were all unremarkable. Conditions such as adult-onset Still's disease, systemic lupus erythematosus, and Schnitzler syndrome were considered and excluded. Due to her predominant joint symptoms, cyclosporine was switched to methotrexate 10 mg weekly. She was also initiated on naproxen 750 mg twice daily and colchicine 50 mg twice daily. Nonetheless, the patient developed further joint effusions in both knees, with synovial fluid aspirates showing a similar inflammatory picture to previous. Our patient's fixed urticarial eruption with neutrophilic infiltrate and inflammatory joint symptoms were consistent with the presentation of NUSI, which is presumably mediated by interleukin-1 (IL-1). Anakinra, an IL-1 inhibitor, was subsequently administered at 100 mg daily. While this did not show the dramatic resolution of the symptoms seen in the previous case series [4], there was a notable improvement in inflammatory markers (CRP at 36 mg/L and ESR at 10 mm/h), steady improvement in the joint disease, and no flares of cutaneous involvement on the gradual weaning of corticosteroids.

DISCUSSION

Herein, we are reporting a case of widespread, polymorphous eruption and inflammatory oligo-arthritis, in keeping with NUSI, three days following the second dose of Pfizer–BioNTech COVID-19 vaccine. In this case, the patient had a history of autoimmune conditions, yet had never reported similar skin symptoms or joint disease. It was most likely

that the temporal relationship between vaccination and the disease onset was causal. Repeated biopsies were consistent with a neutrophilic drug reaction and our patient was not on any new prescription or over-the-counter medications. It is also worth noting that she was successful in gaining injury compensation from the workplace, which had mandated COVID-19 vaccinations for the employees.

The original phase III trial for the Pfizer–BioNTech vaccine acknowledged that it was "not large enough to detect less common adverse events reliably" [1]. Undoubtedly, more research is vital before we may have sufficient evidence to attribute rare adverse effects to these COVID-19 vaccines. This will not only optimize informed consent for patients, yet also aid clinicians in early recognition and treatment.

CONCLUSION

Herein, we have reported a case of NUSI with a widespread, urticarial eruption, episcleritis, and inflammatory oligo-arthritis, following the second dose of Pfizer–BioNTech COVID-19 vaccine. While it cannot be stated with certainty whether the vaccination was the cause of the patient's symptoms, multiple skin biopsies were strongly suggestive of a neutrophilic drug reaction and the patient had not been given any other new medication in the preceding three months. This highlights the need for further research on COVID-19 vaccines to identify rare adverse events. Nonetheless, the safety data for the approved COVID-19 vaccines is reassuring and the overall benefit of vaccination is clear.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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