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Case Study

Pityriasis Rosea Induced by Fifth Dose of COVID-19 Vaccine: Case Report

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ABSTRACT

COVID-19 vaccines and severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) infection have been associated with a variety of dermatological presentations, including pityriasis rosea (PR) and pityriasis rosea-like eruption (PR-LE) (1). Initial Phase III trials reported only localised injection-site dermatological reactions, but a number of case reports and series have since described generalised PR and PR-LE (7). Currently, all reported cases of PR following the COVID-19 vaccine have occurred after the first or second dose (1). We present a case of a 29-year-old female, who developed PR one day after receiving the COVID-19 Comirnaty® Vaccine (Pfizer/BioNTech, BNT162b2, mRNA Vaccine). This was her fifth dose of the COVID-19 vaccine and she had had no cutaneous symptoms to the previous 3 doses or following the SARS-CoV-2 infection 8 months prior. To our knowledge, this is the first case of PR occurring only after the fifth dose of the COVID-19 vaccine, with no reactions to the preceding four vaccines or SARS-CoV-2 infection. With the increasing use of the COVID-19 vaccines, it is important for patients and clinicians to be aware of the potential cutaneous complications that may arise. To our knowledge, this is the first case report of this presentation.

INTRODUCTION

Both the COVID-19 vaccines and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have been associated with a variety of dermatological presentations, including pityriasis rosea (PR) and pityriasis rosea-like eruption (PR-LE) (1). Pityriasis rosea, meaning "rose-coloured scale" is a benign skin condition (2). It is also known as pityriasis circinate, roseola annulate and herpes tonsurans maculosis and it is an acute self-limiting, exanthematous skin condition (2). It usually presents with a primary solitary lesion called a Herald patch, which is followed by diffuse, pink, scaly, oval secondary papulosquamous lesions within 1 to 2 weeks of onset (2). These lesions can be severely pruritic (in

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about 25% of cases) and frequently accompanied by a prodrome of viral symptoms, such as a sore throat, fever and lethargy (2). It most commonly affects the trunk, chest and proximal extremities along Langer's lines or in a Christmas tree distribution (2). The lesions blanch with pressure and can contain fine, collarette scaling (2). The secondary condition is self-resolving by 6-8 weeks in 80% of patients (2), but medications can be used for symptomatic control and faster resolution of the rash (11, 12). The prevalence of PR in adults is estimated to be between 0.5% to 2% (3). It is most common in young adults between the ages of 15 and 30, but can also be seen in children and older adults (3). The exact pathogenesis of PR remains unknown and the way in which the COVID-19 vaccine causes PR is also unclear (3, 4). However, various theories have been postulated and it is likely that several mechanisms are involved simultaneously (5). Here we present a case of a 29-year-old female, who developed PR one day after receiving the COVID-19 Comirnaty® Vaccine (Pfizer/BioNTech, BNT162b2, mRNA Vaccine). This was her fifth dose of the COVID-19 vaccine and she had had no cutaneous symptoms to the previous 4 doses or following the SARS-CoV-2 infection 8 months prior. To our knowledge, this is the first case of PR occurring only after the fifth dose of the COVID-19 vaccine, having had no reactions to the preceding four vaccinations or SARS-CoV-2 infection. With the increasing use of the COVID-19 vaccines, it is important for patients and clinicians to be aware of the potential complications, side effects and risks that may arise, including cutaneous presentations. To our knowledge, this is the first case report of this presentation.

CASE DESCRIPTION

A 29-year-old female of Chinese ethnicity presented to the GP practice with numerous pruritic, scattered, salmon-coloured, macular rash. One day prior to this, she had noticed a single, salmon-coloured, scaly herald patch on her lower abdomen. This was around 3cm by 2cm. She explained that the secondary rash had started on her abdomen and spread to her chest, back, groin and proximal extremities. She complained of no other symptoms at presentation and denied having any recent contact with similarly affected individuals. The herald patch had appeared 1 day after the patient had received her fifth dose of the COVID-19 Comirnaty® vaccination (Pfizer/BioNTech, BNT162b2, mRNA Vaccine). 5 hours after receiving the vaccine, the patient experienced abdominal pain, nausea, malaise and diarrhoea, which resolved without treatment after 24 hours. She denied having a fever, sore throat or any recent viral infections. She denied any reactions or complications from the previous 4 doses of the COVID-19 vaccinations, or to the SARS-CoV-2 infection 8 months prior. The infection had resolved without complications. Physical examination revealed a scaly, blanching, salmon-coloured, macular rash over the trunk, chest and proximal extremities. In the right lower abdomen, a single, larger, pink, oval plaque was noted, consistent with a herald patch. The patient was afebrile and otherwise well. Her temperature was 36.9°C, heart rate 96/min, respiratory rate 18/min, blood pressure 118/80 and oxygen saturations were 98% on room air. She was alert and comfortable at rest. The patient had a history of polycystic ovarian syndrome, for which she was taking ethinylestradiol/desogestrel 20/150mcg with good effect. She had been taking Quetiapine 500mg and Vortioxetine 20mg for depression for over 3 years with no complications. The findings were consistent with typical PR, likely secondary to the Pfizer Comirnaty® Vaccine (Pfizer/BioNTech, BNT162b2, mRNA Vaccine). The diagnosis was made clinically and no further invasive investigations or laboratory workup were deemed necessary. The patient was advised to apply Hydrocortisone 1% over the affected areas

twice a day and she was prescribed Promethazine 50mg before bed to help manage the pruritus, which she complained was worst at night. The rash responded well to the treatment and resolved without complications over the course of 4 weeks.

DISCUSSION

The World Health Organisation (WHO) has reported that as of 8/10/2023, a total of 13,516,282,548 COVID-19 vaccine doses have been administered globally (14). Initial Phase III trials reported only localised injection-site reactions following the COVID-19 vaccinations, but a number of case reports and series have since described generalised PR and PR-LE occurring in some patients following the vaccine (7). The most recent review (by Wong et al., May 2023) reported 102 cases of PR following COVID-19 vaccination (1). The majority were associated with the Pfizer BNT162b2 vaccine (42 or 41.2%), 22 were following Moderna mRNA-1273 (21.6%) and 29 (28.4%) were post Covishield™, CoronaVac, or Oxford/AstraZeneca and the remaining 9 (8.8%) were not reported (1). The mRNA vaccines have been most frequently associated with PR, although the pathophysiology of this remains uncertain. Whilst the greatest number of PR have been reported in patients who received the Pfizer/BioNTech vaccine, followed by the Moderna vaccine, it is important to recognise that the Pfizer/BioNTech BNT162b2 vaccine is currently the leading vaccination used globally, followed by Moderna (8,15). This may therefore result in a disproportionately high number of cases (8, 15). As of 18/10/2023, in the European Union, 654.77million doses of Pfizer/BioNTech BNT162b2 have been administered, 155.10 million doses of Moderna, 67.16 million doses of Oxford/AstraZeneca and 18.70million doses of Johnson&Johnson vaccine (15). 46 cases of PR (45.1%) were post-first dose and 38 (37.3%) were post-second dose (1). The remaining 18 (17.6%) were not reported. None have been reported following the third dose and to our knowledge, this is the first reported case where the PR reaction only occurred after the fifth dose of the vaccination, with no adverse symptoms reported following the four prior doses or following the SARS-CoV-2 infection 8 months prior (1). In the 102 cases of PR, the rash appeared between 0 to 30 days following the administration of the vaccine, with an average onset of 10.2 days (1). Recurrence with subsequent doses was rare, with only 3 (1.9%) patients experiencing a recurrence (1). In our patient, the initial herald patch appeared 1 day following the vaccination and the secondary eruption appeared 5 days later. It has been suggested that a greater number of COVID-19 vaccine doses is associated with a shorter time interval between the administration of the vaccination and the onset of the rash (9, 10). This would explain the occurrence of the rash in our patient appearing just 1 day following the vaccination. Johnston et al. suggested that a delayed localised hypersensitivity reactions to the COVID-19 vaccination may play a role in the pathogenesis (10) Ogata et al. have detected viral spike protein antigens as soon as 1 day following vaccination, whilst peak levels appear on average 5 days following the vaccination (9). This could explain why the symptoms can appear so soon after vaccination in some patients. PR is an acute self-limiting, exanthematous skin condition (2). It usually presents with a primary solitary lesion called a Herald patch, which is followed by diffuse, pink, scaly, oval secondary papulosquamous lesions within 1 to 2 weeks of onset (2). These lesions can be severely pruritic (in approximately 25% of cases) and is frequently accompanied by a prodrome of viral symptoms, such as a sore throat, fever and lethargy (2). It most commonly affects the trunk, chest and proximal extremities and appears along Langer's lines or in a Christmas tree distribution (2). The lesions blanch with pressure and can contain fine,

collarette scaling (2). The secondary condition is self-resolving by 6-8 weeks in 80% of patients (2), but medications can be used for symptomatic management and promote faster resolution of the rash (11, 12). PR is usually diagnosed based on history and clinical examination, without the need for invasive investigation such as biopsy (2, 11). However, if a skin biopsy is performed, the most common findings are non-specific, similar to those found in chronic dermatitis (2). If there is further uncertainty about diagnosis, dermatoscopy can be helpful (2). PR is generally self-limiting with an excellent prognosis, although it can recur in 2-3% of patients (2). Although PR is not associated with long-term scarring, hyperpigmentation is a common complication (2,4). Currently, the NICE CKS guidelines advise emollients, oral antihistamines and topical steroids (11), although other treatments, such as acyclovir, erythromycin and Narrowband ultraviolet B phototherapy have also been used with success (2, 4, 12). In most cases, reassurance and supportive management is usually sufficient, although patient symptoms and clinical judgment should guide this decision. A review by Wong et al. (May 2023) demonstrated that the vast majority of cases will resolve with only symptomatic supportive treatment or spontaneously without treatment, supporting that the presence of PR should not interfere with global vaccination efforts (1). It should, however, be noted that PR in pregnancy must be managed promptly, since infection within the first 15 weeks of gestation can lead to adverse pregnancy outcomes, including premature delivery and foetal death (2, 4, 11). The exact pathogenesis of PR is unknown, and the way in which the COVID-19 vaccine causes PR is also unclear (3, 4). However, various theories have been postulated and it is likely that several mechanisms are involved simultaneously (5). PR remains a condition of undetermined etiology, but proposed theories include infectious causes, atopy and autoimmunity (2). PR and PR-LE have been reported following various vaccinations, including Bacillus Calmette-Guerin (BCG), influenza, H1N1, diphtheria, smallpox, hepatitis B, and Pneumococcus, and most recently, COVID-19 (1, 2). PR is thought to be predominantly mediated by CD4+ T-cells and Langerhans cells, which support an underlying viral antigen processing and presentation process (2). Biopsies from PR lesions have also confirmed a lack of natural killer (NK) cells and B cells, further supporting significant T-cell activity (2). Anti-immunoglobulin M (IgM) has been found on PR keratinocytes, which may also point towards a viral cause (2). A number of theories have been proposed to explain the association between PR and COVID-19 vaccinations. Currently, the strongest evidence supports the involvement of human herpesviruses 6 and 7 (HHV6 and 7) (4, 6). Both HHV6 and 7 DNA have been isolated in PR patients, specifically in the skin lesions, saliva, serum and peripheral blood mononuclear cells (4, 6). This indicates an immune-induced reactivation of latent viruses (4, 6). Neutralising antibodies against HHV6 and 7 have also been detected, giving further weight to this theory (6). The general consensus is that systemic reactivation of the latent virus leads to PR and the virus itself does not directly infect the skin cells (4). However, the exact pathophysiology by which the vaccine leads to latent viral reactivation remains unclear. Papakostas et al. have proposed that vaccine-induced immune stimulation causes reactivation of latent HHV6 and 7 (5, 6). Alternatively, molecular mimicry involving a viral epitope may trigger a T-cell-mediated immune response, leading to viral reactivation (5). Another theory is that diversion of cell-mediated control from the latent HHV6 and 7 infections to the S proteins or SARS-CoV-2/COVID-19 proteins may lead to a level of immunosuppression, subsequently establishing an environment that facilitates the reactivation of the latent HHV6 and 7 (1, 6). There is some evidence

for the involvement of Streptococcus in the development of PR, but the evidence for this is conflicted (3, 4). It has been suggested that the presence of prodromal upper respiratory tract symptoms and raised ASLO titres, as well as responsiveness to erythromycin would support the Streptococcus theory (4). However, subsequent studies have demonstrated a negative C-reactive protein (CRP) and absence of Streptococcus haemolyticus in most patients, refuting the role of Streptococcus in the etiopathogenesis of PR (4). Other proposed theories have included a delayed hypersensitivity (type IV) reaction (8).

CONCLUSION

Recognising and managing COVID-19 vaccine-related complications and side-effects are of utmost importance. A growing number of cases describing an association between the COVID-19 vaccines and PR have been reported, most of them following the mRNA vaccinations, particularly the Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) (1, 8, 15). Whether this is a genuine correlation or an epiphenomenon due to increased interest and awareness of this association or due to these being the leading vaccinations used globally, remains unclear. Given the increasing COVID-19 vaccination efforts globally, it is important for doctors and patients to be vigilant of possible adverse events, such as PR. A review by Wong et al. (May 2023) demonstrated that the vast majority of cases of PR will resolve with only symptomatic supportive treatment or spontaneously without treatment, which suggests that the development of PR should not be a contraindication to the vaccine or interfere with the global vaccination efforts (1). Currently, there are no reported cases of severe complications following vaccine-related PR. Clinicians should be aware of the benign nature of vaccine-associated PR and be able to appropriately counsel their patients on this. In most cases, the protective benefits of the COVID-19 vaccination will outweigh the potential complication of developing PR or PR-LE. We recommend further research to clarify the relationship between the COVID-19 vaccinations and PR, and how the vaccination may cause PR, or whether the association could be an epiphenomenon. We also recommend further studies to establish the exact role of HHV6 and 7 in the etiopathogenesis of PR. Further research is warranted to examine the disproportionately high incidence of PR from Pfizer vaccines compared to the other vaccines. It could be possible that this is due to the different vaccines generating distinct immunological effects, therefore leading to the body responding in different ways to the different vaccines. Studies have shown an association between the COVID-19 vaccinations and reactivation of other latent viruses, such as EBV (Epstein-Barr Virus), VZV (Varicella Zoster Virus) and HSV (Herpes Simplex Virus) (13). Further studies are required to definitively confirm or contest this. We also recommend further research to elucidate why in this case, the reaction only occurred after the fifth vaccination and why the four previous vaccinations had not triggered a reaction. Finally, given the association between COVID-19 and reactivation of latent viruses, additional data would be helpful to determine whether this could pose a risk for certain cohorts, such as those who are immunocompromised.

DECLARATIONS

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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Not applicable.

ETHICAL APPROVAL STATEMENT

The patient consented to participation in this case report. Written informed consent was obtained from the patient for publication of this case report. Ethics approval not applicable.

AUTHORS' CONTRIBUTIONS

The data, information and interviews were conducted and collated by the lead and

corresponding author, Minna Chang. Full written consent was obtained from the patient.

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