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Hypersensitivity reactions to COVID-19 vaccines: a case of eosinophilic pneumonia following Sinovac/CoronaVac vaccination

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Key words

COVID-19; COVID-19 vaccines; SARS-CoV-2; Sinovac/CoronaVac; eosinophiles; eosinophilic pneumonia; rash.

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Doi
10.23822/EurAnnACI.1764-1489.247

Summary

Hypersensitivity reactions have been reported with COVID-19 vaccines. Acute eosinophilic pneumonia has not been reported yet after Sinovac/CoronaVac vaccine. A 73-year-old woman presented with maculopapular rash, cough and dyspnea following Sinovac/CoronaVac injection. The complete blood count (CBC) indicated eosinophilia, and further evaluation of the eosinophilia with CT and bronchoscopy confirmed a diagnosis of acute eosinophilic pneumonia. After methylprednisolone therapy, her rash resolved with marked improvement of the dyspnea. She is still on treatment and on the follow-up period, we plan to continue steroid treatment at least 3 months.

Impact statement

Aluminum adjuvants in vaccines may cause eosinophilic inflammation in the lungs. This immunologic reaction seems to be reversible. Th2-mediated eosinophilic immune responses is decreasing with steroid treatment and do not relapse over time.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is first detected in Wuhan, China, in December 2019, and then defined as a novel coronavirus which caused coronavirus disease 2019 worldwide named as "COVID-19 pandemic". A total of 163,312,429 confirmed cases of COVID-19, including 3,386,825 virus deaths have been reported worldwide as of 18th May 2021 (1). Vaccination is the most effective strategy to control the pandemic and COVID-19 vaccines were an urgent need for this pandemic. The first mass vaccination program started in early December 2020 and Pfizer/BioNTech BNT162B2, Moderna mRNA-1273 and AstraZeneca recombinant adenoviral ChAdOx1-S became first approved COVID-19 vaccines in the United Kingdom (U.K.) on 30th December 2020 (2). Pfizer/BioNTech BNT162B2 vaccine was listed for WHO Emergency Use Listing (EUL) on 31st December 2020. The SII/Covishield and AstraZeneca recombinant adenoviral ChAdOx1-S were given EUL on 16th February. The Janssen/Ad26.COV2.S, the Moderna mRNA-1273 and Thee Sinopharm COVID-19 vaccine was listed for EUL on 12th March 2021, 30th April 2021 and 7th May 2021, respectively (1).

COVID-19 vaccines are now available in many European countries, the United States (U.S.A.), and worldwide. As of 17th May 2021, a total of 1,407,945,776 vaccine doses have been administered

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worldwide (1). Soon after global use of COVID-19 vaccines, severe allergic hypersensitivity reactions to mRNA-based vaccines were reported (2). For example, 11.1 cases of allergic reactions including anaphylaxis occurred per 1 million doses of the Pfizer/BioNTech BNT162B2 COVID-19 vaccination (3) and of 64,900 employees who received their first dose of a COVID-19 vaccine including Pfizer/BioNTech BNT162B2 and Moderna mRNA-1273 vaccines, acute allergic reactions were reported more frequently with the Moderna vaccine compared with Pfizer-BioNTech (4). For the Pfizer/BioNTech BNT162B2 COVID-19 vaccine, 71% of allergic reactions occurred within 15 min of vaccination (3). While there are no added adjuvants or preservatives in mRNA based novel COVID-19 vaccines, different stabilizers including polyethylene glycol (PEG), polysorbates, tromethamine/trometamol were found to be potential to elicit systemic allergic hypersensitivity reactions (5).

Sinovac/CoronaVac COVID-19 vaccine is a 2-dose β-propiolactone-inactivated, aluminum hydroxide-adjuvanted COVID-19 vaccine authorized by the China National Medical Products Administration on 6th February 2021 (6). Phase 3 trial in Brazil including 8,840 participants who received any dose/schedule of Sinovac product reported only mild or moderate adverse events (AE) which were most commonly pain at the injection site, headache, fatigue, and myalgia. There were few allergic reactions, and all were Grade 1 or 2 (6). 260 million doses of Sinovac/CoronaVac have been distributed to the public domestic and overseas markets for use in adults ≥ 18 years (6), and COVID-19 vaccination program has been started by Sinovac/CoronaVac and Pfizer/BioNTech BNT162B2 vaccines in Turkey on 14th January and 2nd April, respectively. As of 19th May 2021 total 26,869,851 doses COVID-19 vaccine including mostly Sinovac and fewer Pfizer/BioNTech BNT162B2 vaccines has been administered to healthcare workers and elderly population (7). In Turkey Phase 3 Sinovac/CoronaVac study including 13,000 healthy participants with the age of 18-59 years, severe adverse events have not been reported (6). However, COVID-19 vaccinations including m-RNA based vaccines and Sinovac/CoronaVac seems to be associated with acute allergic reactions. Even though anaphylaxis is rare, the other hypersensitivity reactions such as acute eosinophilic pneumonia may be associated with COVID-19 vaccinations. To the best of our knowledge acute eosinophilic pneumonia, rash and dermatitis has not been reported yet after Sinovac/CoronaVac vaccination. This paper therefore aims to provide a concise review of the diagnosis and management of vaccine related acute eosinophilic pneumonia and maculopapular rash through a case presentation.

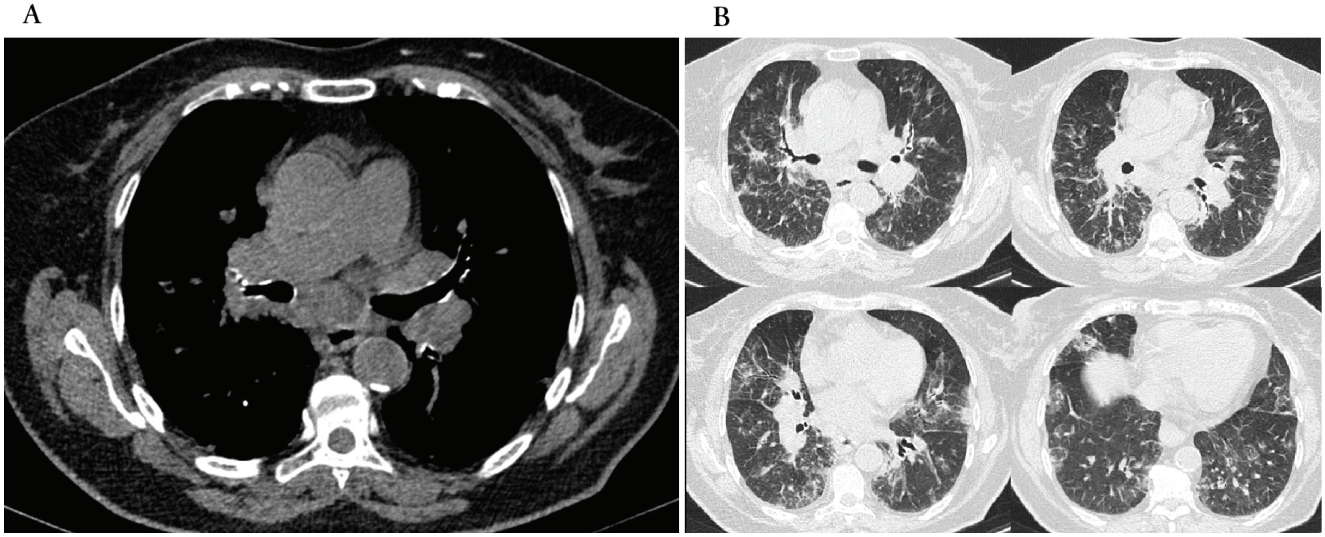
Case presentation

We report a 73-year-old woman who presented to our pulmonology and allergy clinic with maculopapular rash, cough and dyspnea after Sinovac/CoronaVac vaccination. Her cough started after first dose of the vaccine, and it was an isolated symptom and then manifested as maculopapular rash and dyspnea after 4th day of second dose of the vaccine. There was one month period between first and second dose of the vaccine. Antihistamines were not effective for her rash. The patient denied any allergy, history of allergic disease such as asthma or allergic rhinitis, newly started medication, herbal product use and smoking. She did not report any constitutional symptoms including weight loss, fever, chronic pain, fatigue, arthralgia, or night sweats. She had hypertension and diabetes history. Her vital signs were stable on presentation (**table I**). The CBC results indicated eosinophilia (eosinophile count = 600 k/μl). Further evaluation of the eosinophilia with CT scan could not exclude COVID-19 pneumonia (**figure 1**). Because she had dyspnea and there were diffuse ground glass densities, consolidation and linear densities in all segments of both lungs. While the SARS-CoV-2 PCR were negative and her anti SARS-CoV-2 anti-spike antibody level were positive at the effective level, favipiravir treatment was started. During the evaluation period, she had another negative PCR test for SARS-CoV-2. After third day of favipiravir treatment the oxygen saturation was 87% at room level and oxygen treatment were started. Blood eosinophile count has increased to 2300 k/μl. Fiberoptic bronchoscopy was performed and specimens of bronchoalveolar lavage (BAL) fluid obtained from right middle lobe. Multiple biopsies were obtained from the right lower lobe basal segments. Transbronchial needle aspiration (TBNA) was performed from 7 (right upper hilar) and 11 (left hilar) node stations by using EBUS. Skin biopsy was also obtained. The findings of BAL were as follows: macrophage 42% (normal > 90%), lymphocytes 11% (normal < 5%), neutrophils 11% (normal < 5%), and eosinophils 36% (normal < 1%). Eosinophile infiltration also detected in lung tissues (**figure 2**). There was no granuloma, malignant tumor or eosinophile infiltration in lymph nodes. Skin biopsy revealed oedema of the superficial dermis and a dense infiltrate of lymphocytes which was found to be associated with drug induced (vaccine) dermatitis. 1 mg/kg methylprednisolone therapy was started. After seven days of this treatment, her rash resolved with marked improvement of the dyspnea. Thereafter, the patient was continued on treatment with oral methylprednisolone (40 mg/day), the dose was planned gradually to be tapered after a period of 4 weeks. A follow-up chest X-ray revealed marked improvement and total Ig E decreased from 9662 IU/ml to 2000 IU/ml. Eosinophile levels was detected at the normal range. She is still on treatment and on the follow-up period we plan to continue steroid treatment at least 3 months.

Discussion

Eosinophilic pneumonia adverse reaction (AEs) after vaccination has rarely been reported. Only two cases have been reported following influenza and pneumococcal vaccination until today. To the best of our knowledge, this is the first report of acute eosinophilic pneumonia and maculopapular rash developed after Sinovac/CoronaVac vaccination. Based on 35.8 million doses distributed in Chine, 49 serious AEs reported, including anaphylaxis,

Figure 1 *- CT results.*



(A) Enlarged precarinal, subcarinal, pretracheal and paratracheal multiple lymph nodes were observed in the anterior mediastinum. The largest one was measured as 22 × 15 mm in the subcarinal area. **(B)** Diffuse ground glass densities, consolidation and linear densities in all segments of both lungs.

Table I *- Initial work-up of a case.*

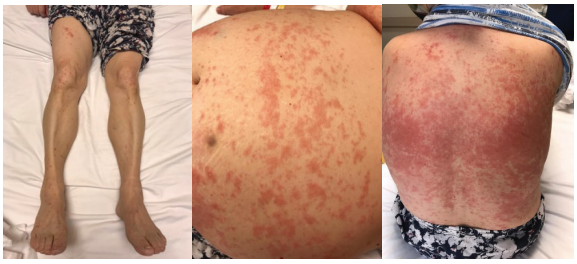
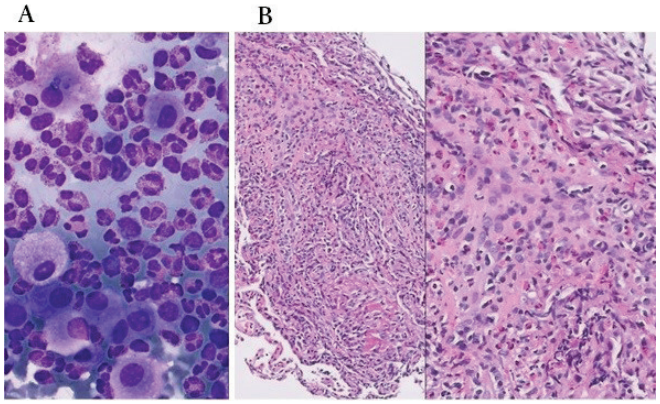
Physical examination	**Laboratory values**
Respiration: clear on auscultation bilaterally, no wheezes or crackles	CBC: Eosinophilia
Oxygen saturation: 92% at room air	WBC: 14,280 k/µl
	Lymphocyte count: 1,300 k/µl
	Eosinophile count: 600 k/µl (HIGH)
	CRP: 27.4 mg/l-D-Dimer: 3,170 µg/l
	Negative PCR test for SARS-CoV-2
	Anti SARS-CoV-2 antibody Ig G (anti-spike): positive
	IgE: 9,662 IU/ml
	LDH: 301 U/l
	Ferritin. 471 ng/ml
	IL-6: 5.3 pg/ml
Cardiovascular: clear S1 and S2, no extra sound	
No organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)	
Generalized maculopapular rash	

Figure 2 *- Eosinophilic infiltration in the lung tissues and BAL.*



(A) Eosinophiles in the BAL. **(B)** Eosinophiles in the lung tissue.

Henoch-Schonlein purpura, laryngeal oedema, demyelination, cerebral hemorrhage (6). Based on 17 million doses distributed in Brazil/Indonesia, 162 serious AEs reported, including fever, dyspnea, death, and headache (6). Based on 3.7 million doses distributed in Chile, 90 serious AEs reported including anaphylaxis with the rate of 1.7/100,000 doses (6). While there were gaps in the detection of rare adverse events especially in older adults, there were no reported acute eosinophilic pneumonia and maculopapular rash after Sinovac/CoronaVac vaccination.

Sinovac/CoronaVac COVID-19 vaccine is an aluminum hydroxide-adjuvanted COVID-19 vaccine (6). Aluminum-containing compounds, primarily aluminum hydroxide (AH), have been widely used as adjuvants in the number of other vaccines such as hepatitis A, hepatitis B, diphtheria-tetanus-containing vaccines, *Haemophilus influenzae* type b, and pneumococcal vaccines (8). Immunization with aluminum adjuvants induces a Th2 type cell mediated immune response which plays an active role in development and differentiation of eosinophiles after the release of several cytokines including interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-5 (IL-5) (8). Aluminum adjuvant-containing vaccines do not activate Treg cells to control strong Th2-mediated immune responses (8). Therefore, aluminum adjuvants can induce the production of eosinophils and eosinophilia which may cause eosinophilic pneumonia or dermatitis after vaccination.

In the literature, two cases of eosinophilic pneumonia have been reported following influenza and pneumococcal vaccination. First case is 86-year-old Thai man with severe COPD presented with eosinophilic pneumonia after seven days of inactivated influenza vaccine (Vaxigrip, Sanofi Pasteur) injection (9). Second case is A 68-year-old Japanese woman presented with eosinophilic pneumonia which developed two days after she received her second vaccination with PPV23 (Pneumovax® NP) (10). Our patient was a 73-year-old woman who presented with maculopapular rash, cough and dyspnea after 4th day of second dose of the Sinovac/CoronaVac vaccine. Seasonal influenza (except Fluad) and PPV23 are adjuvant-free vaccines suggesting that the vaccination-associated eosinophilia in previous cases were not caused by aluminum adjuvants. In these patients without any adjuvants another pathway may lead to eosinophilia. However, in our case hypersensitivity syndrome associated with eosinophilic infiltration of the lung tissue could be related with aluminum adjuvants. Older age and repeated vaccine injections may increase the risk of hypersensitivity reactions and COVID-19 vaccines may also be more prone to allergic or hypersensitivity reactions. However, in cases of drug-induced eosinophilic pneumonia reported in the literature, skin eruption is never reported which is an important part of the clinical picture of our case. Skin rash was suggestive of DRESS (The Drug Reaction with Eosinophilia and Systemic Symptom) and features of the case were a delayed onset. However, the diagnosis of DRESS is challenging because the pattern of cutaneous eruption and the types of organs involved are various. In our case, organ involvement including kidney, hearth and liver, lymphadenopathy and fever was not detected. There was a lung involvement manifested as an eosinophilic pneumonia. We did not do a patch test with diluted vaccine which could better clarify the pathogenesis of the disease. It was our limitation. We used the RegiSCAR's scoring system which was published to classify the cases with DRESS reported in the literature (9) and our case had less likely DRESS when we used this scoring system. A clinical framework is given in **table II**.

This immunologic reaction seems to be reversible and previous case results indicate that Th2-mediated immune responses is decreasing with steroid treatment and do not relapse over time. However, there may be a relation between repeated aluminum adjuvants exposure and acute eosinophilic pneumonia frequency. A proven diagnosis of hypersensitivity to a vaccine component could be difficult. However, aluminum-containing vaccines such as Prevenar 13 should be avoided in patients who had a history of hypersensitivity reactions to any aluminum-containing vaccines. Based on the experience with other case reports, patients whose symptoms fully resolve after steroid treatment should be under treatment at least 3 months and should be followed up at least one year for the relapse (10, 11). Systemic corticosteroids also have been accepted as the gold standard treatment for clinical symptoms of DRESS too. Systemic corticosteroids are recommended to be tapered over 6 and 8 weeks to prevent the relapse of various symptoms of this syndrome and to be administered for 2 and 3 months (12).

Conclusions

In conclusion, diagnosing and treating patients who had hypersensitivity reactions after COVID-19 vaccines is challenging and there are still unanswered questions about the long-term adverse effects of the COVID-19 vaccines. Adjuvants and stabilizers such as polyethylene glycol (PEG) and aluminum seems to lead to allergic and hypersensitivity reactions. Pandemic is urgent and

Table II *- A clinical framework.*

Diagnostic criteria for DRESS by the RegiSCAR (12)	**Our case**	**Scoring system for classifying DRESS cases as definite, probable, possible, or no case, from Kardaun *et al.* (9)**
Acute rash	(+)	1
Reaction suspected drug-related	(+)	
Hospitalization	(+)	
Fever (> 38 °C)	None	-1
Laboratory abnormalities (at least 1 present) a) Lymphocyte above or below normal; b) Low platelet; c) Eosinophilia	(-) a) Lymphocyte count: 1,300 k/µl; b) Platelet count: 361,000 k/µl; c) Eosinophile count: 600 k/µl *Eosinophile count less than 700 k/k/µl is accepted as negative eosinophilia	0
Involvement of > 1 internal organ	Lung involvement	1
Enlarged lymph nodes > 2 sites	None	0
The first 3 criteria are necessary for diagnosis, and the presence of 3 out of the other 4	Final Score: 1	Final score < 2: no case Final score 2-3: possible case Final score 4-5: probable case Final score > 5: definite case

we need to continue vaccination. In the upcoming years, more data will become available to assess the incidence of different and rare hypersensitivity reactions related with various types of COVID-19 vaccines and then we may have a new perspective about the risk factors link with vaccine hypersensitivity reactions.

Fundings

None.

Conflict of interests

The authors declare that they have no conflict of interests.

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