OPIS PRZYPADKU / CASE REPORT
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Cutaneous reaction reported after three Spikevax doses. Case report and literature review

Reakcje skórne po trzech dawkach szczepionki Spikevax. Opis przypadku i przegląd piśmiennictwa

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Summary

Introduction. Spikevax is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus. It is indicated for active immunization against SARS-CoV-2 in individuals aged 6 years and more. The active substance in Spikevax is the mRNA encoding the SARS-CoV-2 virus spike protein. Like all medicines, this vaccine can have adverse effects, including skin reactions. ***Material and methods.*** We present a 37 years old female patient who developed this undesirable vaccine reaction after receiving each of the three doses of Spikevax. ***Results.*** The rashes appearing on the patient's body resolved spontaneously after the first two doses, while adverse effects associated with the 3rd dose required oral administration of calcium. ***Conclusion.*** The described case confirms the risk of cutaneous undesirable reactions as an adverse reaction after Spikevax vaccine. *(Farm Współ 2022; 15: 50-55) doi: 10.53139/FW.20221505*

Keywords; Spikevax, cutaneous reaction, undesirable vaccine reaction

Streszczenie

Wstęp. Spikevax jest szczepionką stosowaną w celu zapobiegania chorobie COVID-19 powodowanej przez wirus SARS-CoV-2. Jest wskazana w celu osiągnięcia czynnej immunizacji przeciwko SARS-CoV-2 u osób w wieku 6 lat i starszych. Substancją czynną w Spikevax jest mRNA kodujące białko szczytowe wirusa SARS-CoV-2. Jak każdy lek, szczepionka ta może powodować działania niepożądane, między innymi reakcje skórne. **Materiał i metody.** Przedstawiamy 37-letnią pacjentkę u której po podaniu każdej z trzech dawek szczepionki Spikevax wystąpił ten niepożądany odczyn poszczepienny. **Wyniki.** Wysypki pojawiające się na ciele pacjentki po pierwszych dwóch dawkach ustąpiły samoistnie natomiast po trzeciej dawce po zastosowaniu doustnym wapna. **Wnioski.** Opisany przypadek potwierdza ryzyko wystąpienia reakcji skórnych jako niepożądanego odczynu po szczepionce Spikevax. *(Farm Współ 2022; 15: 50-55) doi: 10.53139/FW.20221505*

Słowa kluczowe: Spikevax, reakcja skórna, niepożądany odczyn poszczepienny

Introduction

COVID-19 is a pneumonia-like disease caused by SARS-CoV2 [1]. Since the beginning of the pandemic it affected more than 470 million people and resulted in more than 6 million deaths [2]. To effectively control the pandemic, vaccines were developed using modern methods of genetic engineering. To date, five COVID 19 vaccines has been approved by EMA: Comirnaty, Spikevax, Vaxzevria, Janssen COVID 19 vaccine and Nuvaxovid [3].

Spikevax is an example of mRNA vaccines. The mechanism of action of such preparations is quite straightforward (figure 1): cells at the administration site use the mRNA encoding a target antigen directly to produce the protein *in situ*. The presence of the antigen induces the adaptive immune response resulting in immunological memory [4]. Spikevax'es mRNA encodes SARS-CoV2 spike (S) glycoprotein as it is the major surface protein of the virus, responsible for binding the angiotensin-converting enzyme 2 (ACE2) receptor and viral entry [4]. The mRNA in the vaccine underwent some modifications including modulation

of 5' and 3' untranslated regions (UTRs), replacement of uridines by N1-methylpseudouridine (m1Ψ) and replacement of amino acids 986 and 987 with prolines. These modifications resulted in increased stability, translation efficiency and stabilization of S protein in the prefusion conformation [4,5]. Such prepared mRNA is then complexed with lipid nanoparticles which protect it from degradation *in vivo* and facilitate cellular uptake [5].

Spikevax efficacy reached 97.1% during the clinical trial with very low incidence of serious adverse effects [6]. The increasing number of vaccinated people result in regular reporting of undesirable side effects that occur after vaccination. In the article we present a case of rash that occurred after Spikevax vaccine in a 37 years old female.

Case description

A 37 years old woman received the first dose of Spikevax (Moderna) COVID-19 vaccine on 10 May 2021. About three to four hours after vaccine administration a post-vaccination reaction in the form of a non-itchy rash all over the body occurred. The rash disappeared spontaneously after 2-3 days. Other adverse reactions included pain at the injection site and very slight swelling. The second dose of the vaccine was administered on 14 June 2021 and triggered similar adverse effects: a rash all over the body (which disappeared spontaneously after 2-3 days) and raised swelling at the vaccination site. The patient also reported fatigue during the next day after vaccination. The booster dose of the vaccine was administered on 28 December 2021 and resulted in pyrexia (38,7°C) during next day's morning. The patient's arm felt painful at the injection site but no swelling occurred. Since the morning, the resting heart rate has also increased, oscillating between 80-95 beats per minute (the reference range is 60-65). As the body temperature rose, the patient felt noticeable chest tightness. The fever started to drop after 7 p.m. leading also to the gradual relief

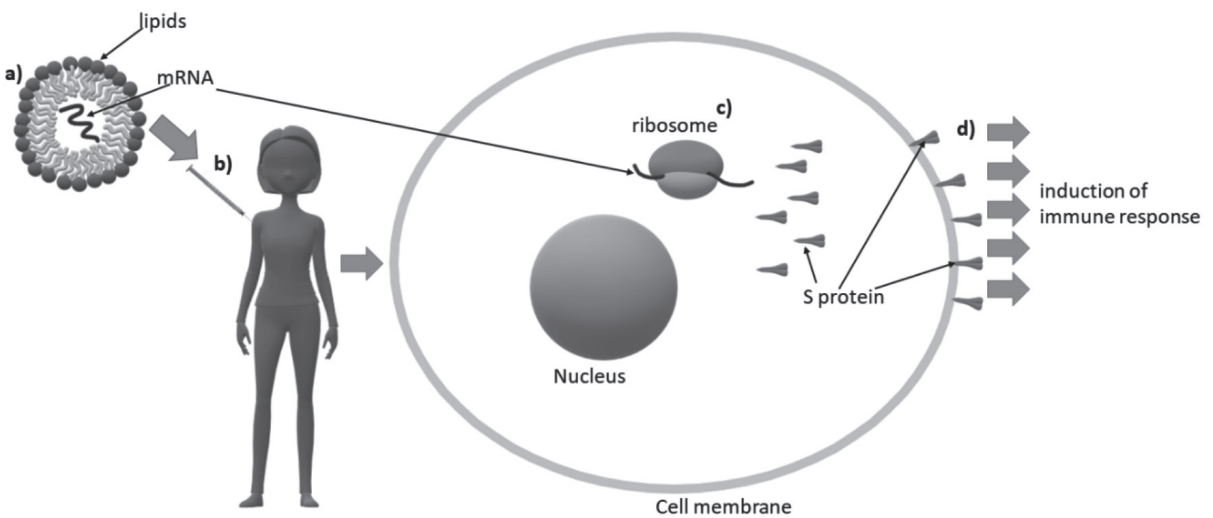

Figure 1. Mechanism of action of Spikevax mRNA vaccine. The vaccine is built from mRNA encoding SARS-CoV-2 spike protein encapsulated with lipid nanoparticles (a). After vaccination (b) the mRNA is used directly as a matrix for ribosomes to produce viral spike protein in the cells at the administration site (c). Synthesized spike protein molecules are transported to the cell membrane and induce immune response (d)

Rycina 1. Mechanizm działania szczepionki mRNA Spikevax. Szczepionka zawiera cząsteczkę mRNA kodującą białko kolca SARS-CoV-2 w nośniku nanolipidowym (a). Po podaniu szczepionki (b), mRNA jest wykorzystywane bezpośrednio przez rybosomy do biosyntezy wirusowego białka kolca w komórkach w miejscy podania (c). Wytworzone białko jest następnie transportowane na powierzchnię komórki i indukuje odpowiedź immunologiczną (d)

of chest tightness. The next morning the body temperature dropped to 37 degrees and the chest tightness completely disappeared. However, a rash all over the body appeared. The rash was getting more red by the evening and it started to itch slightly. It disappeared after taking 3 pills of Calcium. On the third day after vaccination the patient suffered from migraine. All symptoms were gone by the evening.

Discussion and conclusion

The most common adverse effects associated with Spikevax include pain, redness or swelling at the site of vaccine inject, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, muscle pain, and joint pain. In rare situations, anaphylactic shock may occur [7]. In Poland, reported adverse effects after Spikevax constituted 0.041% of all administered vaccine doses (table I) [8].

Table I. Adverse effects that occurred within 30 days after receiving the Spikevax vaccine in Poland. The report covers the period 27.12.2020 - 28.02.2022 [8]

Tabela I. Działania niepożądane jakie wystąpiły w ciągu 30 dni po otrzymaniu szczepionki Spikevax, odnotowane w Polsce. Raport za okres 27.12.2020 - 28.02.2022 [8]

Spikevax (28.02.2022)		
Number of vaccinations		3625086
Adverse effects (% vaccinations)	mild	1335 (0.037)
	serious	133 (0.004)
	severe	29 (0.001)
	total	1497 (0.041)

Table II. The incidence of rash after Spikevax vaccine. Calculations based on [9-12]

Tabela II. Częstość występowania wysypki po szczepionce Spikevax. Obliczono na podstawie [9-12]

	Europe	USA	Total
Number of doses	191551949	209886918	401438867
Number of rash cases	8308	20485	28793
Incidence	$4.34 \cdot 10^{-05}$	$9.76 \cdot 10^{-05}$	$7.17 \cdot 10^{-05}$

Table III. Rash after Spikevax vaccine in sex and age groups in the EU. Based on the data from EudraVigilance [12]

Tabela III. Wysypka po szczepionce Spikevax w grupach płci i wieku w krajach Unii Europejskiej. W oparciu o dane z bazy EudraVigilance [12]

Sex	Age	Events Reported	Percentage
Female	Not Specified	207	2.49
	12-17 years	30	0.36
	18-64 years	5220	62.83
	65-85 years	744	8.96
	85+ years	58	0.70
	Total	6259	75.34
Male	Not Specified	60	0.72
	12-17 years	21	0.25
	18-64 years	1522	18.32
	65-85 years	338	4.07
	85+ years	29	0.35
	Total	1970	23.71
Not Specified	Not Specified	17	0.20
	18-64 years	52	0.63
	65-85 years	10	0.12
	Total	79	0.95
Total		8308	100.00

Table IV. Rash after Spikevax vaccine in sex and age groups in the US. Based on the data from VAERS [11]
Tabela IV. Wysypka po szczepionce Spikevax w grupach płci i wieku w Stanach Zjednoczonych. W oparciu o dane z bazy VAERS [11]

Sex	Age	Events Reported	Percentage
Female	< 6 months	5	0.02
	1-2 years	1	0.00
	3-5 years	1	0.00
	6-17 years	4	0.02
	18-29 years	1543	7.53
	30-39 years	2581	12.60
	40-49 years	2779	13.57
	50-59 years	2741	13.38
	60-64 years	1319	6.44
	65-79 years	3589	17.52
	80+ years	653	3.19
	Not Specified	730	3.56
	Total	15946	77.84
Male	1-2 years	1	0.00
	6-17 years	1	0.00
	18-29 years	438	2.14
	30-39 years	544	2.66
	40-49 years	583	2.85
	50-59 years	649	3.17
	60-64 years	351	1.71
	65-79 years	1159	5.66
	80+ years	255	1.24
	Not Specified	221	1.08
	Total	4202	20.51
Not Specified	18-29 years	6	0.03
	30-39 years	5	0.02
	40-49 years	12	0.06
	50-59 years	11	0.05
	60-64 years	6	0.03
	65-79 years	21	0.10
	80+ years	3	0.01
	Not Specified	273	1.33
	Total	337	1.65
Total		20485	100.00

According to European and American data, the average incidence of rash after Spikevax vaccine is $7.17 \cdot 10^{-5}$ (table II) [9-12]. It is also more often reported by women (table III, IV).

In 2021, a case report was published, describing a situation very similar to our patient: priuritus and pain in the area overlying the deltoid muscle injection site, observed after each dose of Spikevax [13].

Early American reports indicated that 10 cases of anaphylaxis were observed after the administration of 4,041,396 first doses Spikevax vaccine [14]. Additional data was provided by the international registry of cutaneous manifestations of SARS-CoV-2 established by the American Academy of Dermatology and the

International League of Dermatological Societies – 414 patients reported one or more cutaneous adverse reactions after Spikevax (83%) or Comirnaty (17%) vaccine from December 24, 2020, to February 14, 2021 [15]. The most common adverse reactions included delayed large local reactions, local injection site reaction, urticarial, morbilliform and erythromelalgia.

Allergic reaction to the vaccine may result from the following mechanism [16]:

1. Reactions via the pathway of mast cell activation and degranulation as IgE/antigen through cross-linking of FcεRI on mast cells.
2. Non-IgE-mediated mast cell degranulation performed via activation of the complement system that leads to the generation of anaphylatoxins C1q, C3a C4, and C5a and Factor B, which are strong inflammatory stimulators able to induce mast cell activation and degranulation.
3. Direct activation of the Mas-related G protein-coupled receptor X2 (MRGPRX2).
4. Type IV hypersensitivity or delayed reactions derived from overstimulation of T cells and monocytes/macrophages and release of cytokines that cause inflammation, cell death, and tissue damage.

It is notable that such reactions are rarely caused by the vaccine itself but result from other inactive components (e.g. egg protein, gelatin, formaldehyde, thimerosal, or neomycin) or excipients (inert substances added to vaccine to improve stability, increase solubility, improve absorption, influence palatability, or create a distinctive appearance). As a result, they can contribute to specific IgE-mediated and immediate reactions. Such potential excipients present in Spikevax vaccine include acetic acid, lipids (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), polyethylene glycol, sodium acetate, sugar (sucrose), tromethamine and tromethamine hydrochloride [16].

Conclusion

Allergic reactions following the administration of Spikevax may be due to the mechanism of action of the vaccine, but may also be caused by the excipients it contains. Clinical manifestations of this adverse post-vaccination reaction can occur in the form of a variety of skin reactions following life-threatening systemic reactions. Some skin reactions develop soon after immunization, while others develop up to 14 days later - the time it takes for a rash to appear can therefore vary widely. Most of the reactions resolved without any medical intervention. Others have been treated with antihistamines, topical steroids, or other agents recommended by dermatologists.

Conflict of interest
None

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