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A definite case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) induced by administration of the Pfizer/BioNTech BNT162b2 vaccine for SARS-CoV2



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Highlights:

- COVID 19 vaccines currently approved or authorized are effective in preventing serious outcomes of COVID 19, including severe disease, hospitalization, and death.
- The safety of COVID 19 vaccines is continuously monitored and evaluated.
- SCARs including DRESS are possible adverse reactions to COVID 19 vaccines.
- It's essential that physicians continue to be trained to recognize and appropriately treat these types of reactions.

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COVID-19: Important updates and developments

Edited by Franco Rongioletti, MD, and Leonard J. Hoenig, MD

Title: A definite case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) induced by administration of the Pfizer/BioNTech BNT162b2 vaccine for SARS-CoV2.

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ABSTRACT

At the end of December 2020, the anti-SARS-CoV2 vaccination campaign began in Italy. As the number of vaccinated subjects in the general population has increased, several adverse reactions have been observed and reported. Severe cutaneous adverse reactions (SCARs) induced by drugs or vaccines are rare but distinguished by high mortality and include DRESS syndrome or drug induced hypersensitivity syndrome (DiHS), a condition characterized by skin rash, eosinophilia, fever, lymphadenopathy, and involvement of one or more internal organs. Here we present a definite case of DRESS that occurred following the administration of Pfizer/BioNTech COVID 19 vaccine. He required hospitalization and was managed with supportive care, antihistamines, and intravenous steroid.

INTRODUCTION

At the end of December 2020, the anti-SARS-CoV2 vaccination campaign began in Italy [1]. As the number of vaccinated subjects in the general population has increased, several adverse reactions have been observed and reported, some more frequent, such as hyperpyrexia, lymphadenopathy, headache, or muscular-articular pain, and others rarer [2]. In this regard, the Italian pharmacovigilance agency (AIFA) plays a key role in monitoring adverse reactions to these vaccines [2]. Among the interregional pharmacovigilance projects promoted by AIFA, GRESIF (multiregional pharmacovigilance project "Severe systemic drug hypersensitivity reactions") has the task of detecting and analyzing severe cutaneous adverse reactions (SCARs) induced by drugs or vaccines [3]. These delayed drug reactions are rare but distinguished by high mortality and include DRESS syndrome or drug induced hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP). In particular, DRESS is a condition characterized by skin rash, eosinophilia, fever, lymphadenopathy, and involvement of

one or more internal organs [4]. Resolution of the reaction generally occurs with high-dose steroid therapy. The symptoms usually begin between 3 and 8 weeks of therapy with the culprit drug, but rare cases of this reaction with a much shorter latency following vaccination have been described [5], including a recent case of possible DRESS/AGEP overlap induced by Janssen vaccine [6] and another case of DRESS induced by AstraZeneca vaccine [7].

Here we present a case of DRESS that occurred following the administration of Pfizer/BioNTech COVID 19 vaccine.

CASE REPORT

A 47-year-old man of Asian ethnicity, suffering from ulcerative rectocolitis and allergic asthma, presented to the Emergency Department of the ASST Grande Ospedale Metropolitano Niguarda, in Milan, for high fever ($> 38.5^{\circ}\text{C}$), persistent cough, headache and a diffuse erythematous itchy rash since about a week. The symptoms had occurred after the second dose of Pfizer/BioNTech COVID 19 vaccine that has been given 3 weeks after the first one. The patient reported, after vaccination, the onset of myalgia, abdominal and chest pain associated with a productive cough followed after 5 days by fever, persistent cough and skin rash. The only known drug allergy was angioedema after acetylsalicylic acid with a negative history of allergic reactions to previous vaccinations. The patient denied taking other medications concurrently with the vaccine and in the preceding period except for home therapy consisting of inhalation therapy for asthma and mesalazine.

Physical examination revealed an erythematous, itchy, maculo-papular skin rash involving the abdomen, chest and upper limbs associated with facial edema and a generalized lymphadenopathy. Laboratory tests performed at the emergency room showed leukocytosis with severe eosinophilia (eosinophils $13,450/\mu\text{l}$), elevation of alanine aminotransferase

(230 U/L) and total bilirubin 1.87 mg/dL, elevation of creatinine 1.37 mg/dL and slight rise in C-reactive protein (CRP) to 2.2 mg/dL. Peripheral blood smear confirmed the leukocyte formula with 70% of cells represented by eosinophils. Skin biopsy could not be performed. The patient was then admitted initially to Emergency Medicine and then to the Department of Allergology and Immunology. At this time, his skin rash exhibited an erythematous and urticarial appearance (Fig. 1 and 2). Abdominal ultrasonography and echocardiogram were negative, while abdominal MRI showed inflammation of the intrahepatic biliary tract, which the hepatologist interpreted as organ involvement related to eosinophilia. The autoimmunity panel (including hepatic autoimmunity), blood cultures, parasitology and viral serologies for HHV-6, HHV-8, Parvovirus B19, Coxsackievirus, CMV, EBV and HIV were also negative. The patient was treated with antihistamine and intravenous steroid (methylprednisone) at a dosage of 1 mg/kg/day with a slow but progressive improvement of the rash associated also with a normalization of both hepato-renal function and eosinophilia. The patient was discharged in good general condition after 2 weeks of hospitalization. At a follow-up of 2 months from the discharge, the patient was doing well both from a clinical and laboratory point of view.

On the basis of the clinical presentation and the results of the investigations performed, the reaction was interpreted as a vaccine-induced SCAR and, in particular, a DRESS syndrome. This diagnosis was confirmed not only by the clinical-laboratory context but also by the application of the RegiSCAR score (see Table 1), which confirmed a definite case.

DISCUSSION

SCARs are rare conditions but associated with high mortality and morbidity. These include DRESS, a delayed drug reaction that usually occurs 3-8 weeks after initiating therapy with

the responsible drug. The diagnosis is clinical and is based on diagnostic criteria such as those of the RegiSCAR score [8]. The most widely used criteria to confirm or exclude the diagnosis of DRESS are those included in the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, based on the main clinical manifestations of DRESS [4]: fever $>101.3^{\circ}\text{F}$ or $>38.5^{\circ}\text{C}$ (core) or $>100.4^{\circ}\text{F}$ or $>38^{\circ}\text{C}$ (axillar), enlarged lymph nodes in at least two different body areas, eosinophilia, atypical lymphocytes, skin involvement (extent, rash suggestive of DRESS, biopsy), organ involvement (eg, at least twofold elevation of liver enzymes on at least two different days), and resolution >15 days. A value between -1 and 2 is assigned to each feature (Table 1). The cumulative score ranges from -4 to 9 and defines four levels of certainty regarding the diagnosis of DRESS: excluded, possible, probable, and definite. As some of the variables included in the RegiSCAR DRESS score may not be available when the patient is first evaluated, the score is most useful as a retrospective validation of suspected cases.

Potentially all drugs can cause this syndrome, but the most frequent are aromatic anticonvulsants and allopurinol [9], a fact that has also emerged from one of our recent studies [10]. However, the literature also describes rare cases associated with vaccinations, which have a shorter onset latency than other drugs [5]. Our patient represents a definite case of DRESS in close temporal association with Pfizer/BioNtech COVID 19 vaccine. Among the COVID-19 vaccine reactions reported, Lospinoso K. et al. described a case of overlapping AGEP-DRESS from Janssen vaccine [6] and, more recently, O'Connor T. and colleagues presented a case of DRESS following administration of AstraZeneca vaccine [7]. To our knowledge, our case represents the first definite case of DRESS induced by Pfizer/BioNtech COVID 19 vaccine.

As for pathogenesis, it has been suggested that an inefficient detoxification of the drug leads to accumulation of reactive metabolites, which cause an autoimmune reaction in skin and some internal organs in vulnerable patients who have genetic predisposition.

CONCLUSIONS

We want to draw attention to the possible occurrence of this type of reactions after vaccination against SARS-CoV2 which, although rare, have significant implications on the health of patients at a time when vaccination for COVID 19 is of primary importance. On the other hand, we want to emphasize the importance of a continuous updating by physicians in recognizing this type of reactions so that they can diagnose SCARs early and treat patients in the most appropriate and efficient way.

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Fig. 1, 2. Pomphoid lesions and diffuse skin edema on admission to our Allergy and Immunology Unit, during steroid therapy.



Figure 2

Table 1. RegiSCAR score system. Table modified from Kardaun et al. (8).

Score	-1	0	1	2	Min	Max
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes			-1	0
Lymphadenopathy		No/U	Yes		0	1
Eosinophilia					0	2
Eosinophils			700-1499/ μl	$\geq 1500/\mu\text{l}$		
Eosinophils, if leukocytes < 4000			10-19.9%	$\geq 20\%$		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Rash extent (> 50% BSA)		No/U	Yes			
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*		No/U	Yes		0	2
Liver, Kidney, Lung, Muscle/heart, pancreas, other organ(s)						
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes			Yes		0	1
ANA, blood culture, serology for HVA/HBV/HCV, C./M. pneumoniae, other serology/PCR if none positive and ≥ 3 of						

above negative

TOTAL SCORE

-4

9

U = unknown/unclassifiable; BSA = body surface area; PCR = polymerase chain reaction;
C./M. = Chlamydia/Mycoplasma. *after exclusion of other explanations: 1 = 1 organ; 2 = \geq
2 organs. Final score: < 2 = no case; 2-3 = possible case; 4-5 = probable case; > 5 =
definite case.

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