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Archives de pédiatrie 000 (2022) 1–4

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Short communication

Two pediatric cases of multisystem inflammatory-like syndrome following COVID-19 vaccination

C. Collignon[a,*], C. Frachette[b,c,k,l], D. Callot[d], Y. Pinhas[e,f], P. Bataille[f,g], B. Bader-Meunier[f,h], L. Chouchana[d], M.-L. Frémond[f,h], Z. Belhadjer[i], M. Oualha[a,f], F. Moulin[a], E. Javouhey[c,j], A. Belot[k,l,b,c], S. Renolleau[a,f]

[a] *Pediatric Intensive Care Unit, APHP University Hospital Necker-Enfants malades, Paris, France*
[b] *Pediatric Nephrology, Rheumatology, Dermatology Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, 69677 Bron, France*
[c] *Faculty of Medicine, University of Lyon, 69100 Villeurbanne, France*
[d] *Regional Center of Pharmacovigilance, Department of Pharmacology, Cochin Hospital, AP-HP. Centre – Université de Paris, Paris, France*
[e] *Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants-Malades University Hospital, APHP, Centre-Université de Paris, Paris, France*
[f] *Université de Paris, Paris, France*
[g] *Department of Dermatology, Reference Centre for Genodermatoses and Rare Skin Disease (MAGEC), Hopital Universitaire Necker-Enfants Malades, APHP, Paris, France*
[h] *Department of Pediatric Immunology and Rheumatology, AP-HP, Necker Hospital, Paris, France*
[i] *M3C-Necker Enfants Malades, AP-HP, Paris, France*
[j] *Pediatric Intensive Care Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, 69677 Bron, France*
[k] *National Referee Centre for Rheumatic and Autoimmune and Systemic Diseases in Children (RAISE), 69677 Bron, France*
[l] *Lyon Immunopathology Federation LIFE, Hospices Civils de Lyon, 69002 Lyon, France*

ARTICLE INFO

Article History:
Received 14 March 2022
Revised 23 June 2022
Accepted 25 August 2022
Available online xxx

Keywords:
Multisystem inflammatory syndrome in children
COVID-19 vaccine
Pediatric intensive care unit
Side effect
Case report

ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a novel post-infectious disease occurring in the context of SARS-CoV2 infection. COVID-19 vaccines have been authorized since December 2020, and adverse events including myocarditis have been reported following vaccination. We describe the cases of two pediatric patients presenting with clinical and laboratory features suggestive of MIS-C a few days after receiving their first dose of the Pfizer BNT162b2 vaccine. The outcome was favorable for both patients (after corticosteroid and immunoglobulin administration for one patient). These cases suggest an association between the COVID-19 vaccine and the occurrence of MIS-C.

1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a novel disease that has emerged during the COVID-19 pandemic. While the pathogenesis remains uncertain, immune activation, including the dysregulation of T-cell subsets, has been suggested [1]. Expansion of *TRBV11–2* /Vβ21.3-expressing T cells is the hallmark of the disease [1–3]. The clinical symptoms are now well described, including fever, heart failure, and systemic inflammation [4, 5].

BNT162b2 (Comirnaty ®, BioNTech/Pfizer) is a vaccine against the COVID-19 virus that has been authorized in the European Union since December 21, 2020. It relies on lipid nanoparticles containing an mRNA sequence encoding the SARS-CoV-2 spike (S) protein that encompasses the RBD domain. The vaccine was formulated using lipid particles to deliver RNA. It triggers an immune response to the S antigen with neutralizing antibodies and T-cell-specific immune responses within 2 weeks after administration [6]. Marketing authorization was extended to patients aged 12–17 years in May 2021 by the European Medicine Agency (EMA). Although these vaccines have a largely positive benefit–risk balance, an increased risk of myocarditis has been observed in adolescents and young adults, especially in males [7].

Here, we report two pediatric cases of the MIS-C-like phenotype after the BNT162b2 COVID-19 vaccine.

2. Case reports

The first patient was a 12-year-old boy with type-1 diabetes treated with an insulin pump. He received the first injection of the

* Corresponding author at: Pediatric Intensive Care Unit, Necker-Enfants malades University Hospital, 149 rue de Sèvres, 75015 Paris, France.
E-mail address: charlotte.collignon@aphp.fr (C. Collignon).

https://doi.org/10.1016/j.arcped.2022.08.018
0929-693X/

BNT162b2 vaccine on October 20, 2021 and had a medical history of SARS-CoV2 infection 7 months earlier. On October 24 he presented with fever and urticarial eruptions. The rash worsened with erythroderma; pustules in the skin folds and abdomen; cockade skin lesions on the hands, feet, and arms; and edema with papules on the face and hands (Fig. 1). Other clinical signs were conjunctival injection, pharyngitis, lethargy, and hemodynamic failure with arterial hypotension. He had no history of reactions to any vaccines and did not receive any other treatment. He was admitted to the pediatric intensive care unit (PICU) on October 26 (Fig. 1).

First-line laboratory investigations revealed elevated levels of inflammatory biomarkers (C-reactive protein [CRP]: 70 mg/L; procalcitonin [PCT]: 2.3 ng/mL; ferritin: 309 μg/L, fibrinogen: 2.9 g/L), hyponatremia (128 mmol/L), and hypoalbuminemia (23 g/L). A nasopharyngeal SARS-CoV2 polymerase chain reaction (PCR) test result was negative. His cardiac marker levels were initially normal. A diagnosis of toxic shock syndrome was considered, and he received fluid resuscitation with saline solution and subsequently norepinephrine for refractory shock, in association with and infusion of piperacillin, clindamycin, gentamicin, and acyclovir.

On PICU admission, fever and tachycardia persisted, and the skin lesions extended. Pulmonary edema with respiratory distress appeared 3 days after admission and after initial treatment, and cardiac markers increased (troponin:175 ng/L; N-terminal prohormone of brain natriuretic peptide [NT-proBNP]: 3110 pg/mL). Transthoracic ultrasound revealed diastolic alteration, but systolic function was preserved (isovolumic relaxation time 65 ms; E wave on Doppler transmural flow 120 cm/s and E' wave 24 cm/s). Coronary abnormalities were not observed. Because of the unusual cutaneous presentation, alternative diagnoses were investigated. Skin biopsy revealed keratinocyte necrosis in the superficial layers of the epidermis, with a multilocular pustule consisting of eosinophilic and neutrophilic polynuclear cells. In the superficial and middle dermis, a perivascular inflammatory infiltrate was seen consisting of lymphocytes, histiocytes, and eosinophilic polynuclear cells. This aspect was suggestive of drug eruption but could also be attributed to MIS-C. No active viral or bacterial infections were documented in repeated blood cultures and viral serology tests and PCR or in specific antimicrobial tests such as for *Mycoplasma pneumoniae*. There was no evidence of autoimmune disease. The patient had the laboratory features of macrophagic activation (ferritin: 383 μg/L). Immunophenotyping revealed T lymphopenia with activated T lymphocytes. The Vβ T-cell receptor (TCR) repertoire was normal. There were increased levels of interleukin (IL)−6 up to 102.2 pg/mL. Bone marrow aspiration showed neither atypical cells nor hemophagocytosis. Serological testing on October 27 showed a high-level IgG anti-spike-binding domain (anti-S) (13,129.04 BAU/mL,N<7.1) without anti-nucleoside (anti-N) positivity for SARS-CoV-2.

The patient was administered corticosteroids and intravenous immunoglobulins. First, corticosteroids were initiated at 2 mg/kg/day, but the dose was raised to 10 mg/kg/day 48 h later because of persistent diastolic dysfunction and pulmonary edema. This dose was maintained for 3 days and then decreased to 2 mg/kg/day. The outcome was favorable without any side effects; temperature decreased and there was regression of the edema, and cutaneous lesions without a recurrence. Hemodynamic support with norepinephrine was stopped 48 h after initiation. The patient was discharged from the PICU after complete recovery. At the 2-month follow-up, transthoracic ultrasound was normal and there were no laboratory anomalies; furthermore, the patient's immunophenotype was normal, with increased NK lymphocytes.

The second patient was a 15-year-old boy with no relevant medical history. The patient received his first BNT162b2 vaccine injection on July 28. On August 1, he presented with diarrhea, fever, and abdominal pain. The patient was hospitalized on August 6 for hemodynamic failure associated with tachycardia and arterial hypotension. He received fluid resuscitation with saline solution and norepinephrine, which was quickly stopped within 24 h. He was also treated with antibiotics based on the hypothesis of septic shock because of high levels of inflammatory biomarkers (CRP: 300 mg/L; PCT: 50 ng/mL). He subsequently presented with a conjunctival infection, a rash on the right cheek, thoracic pain, and dyspnea with foot edema. Urine samples showed significant proteinuria, and renal function was altered with preserved urine output (creatinine level: 167 μmol/L). He had transient auditive and visual hallucinations, leading to lumbar puncture and cerebral computed tomography (CT) scans, which were both normal.

The laboratory cardiac markers increased (troponin: 400 ng/L; NT-proBNP: 850 pg/mL) and thoracic ultrasound revealed pericardial effusion, suggestive of myopericarditis without systolic or diastolic dysfunction (E/A 1.3 and E/E' 4.9). Thoracic CT revealed bilateral pleural effusions. Other laboratory examinations revealed hyponatremia, eosinophilia (1 g/L), and hepatic cytolysis (ALT: 1.5 upper limit of normal). A nasopharyngeal SARS-CoV2 PCR test was negative. Serological testing showed an IgG anti-spike-binding domain (anti-S) without anti-nucleoside (anti-N) positivity for SARS-CoV-2. The Vβ TCR repertory and interferon (IFN) signatures were normal.

No other etiology was found, such as infection, immunodeficiency, auto-inflammatory disease, or macrophagic activation. No specific treatment was initiated because of spontaneous improvement, and the patient's outcome was favorable.

3. Discussion

We report the cases of two pediatric patients with MIS-C-like criteria after COVID-19 vaccination with the BNT162b2 vaccine. Despite an atypical cutaneous presentation for the first patient, the clinical examination was consistent with MIS-C according to the World Health Organization criteria: patient's age, fever, shock, rashes, abdominal signs, features of myocardial diastolic dysfunction associated with elevated markers of inflammation without obvious microbial cause [8]. The US Centers for Disease Control and Prevention (CDC) bases the case definition on positive results for anti-spike or anti-nucleocapsid antibodies [9]. Several mucocutaneous symptoms have been observed; however, pustules have not yet been described, to our knowledge [10]. Laboratory investigations were also suggestive of MIS-C: elevated levels of CRP, PCT, troponin, NT-proBNP, hyponatremia, and decreased albumin [4, 11–13] . The first patient, furthermore, had associated immunological dysregulation, which was previously described in MIS-C: T lymphocyte deficiency, with

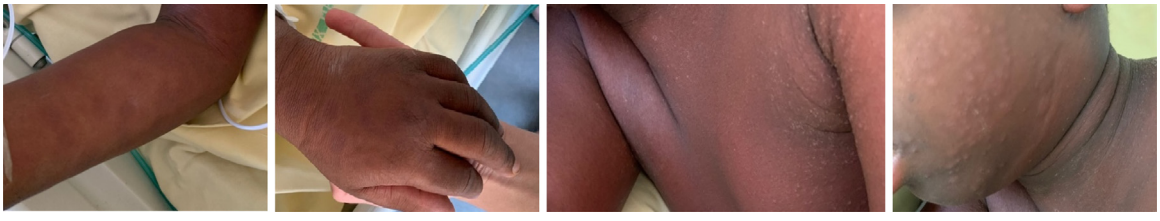

Fig. 1. Skin rash in 12-year-old boy.

the presence of activated CD8+ T cells and high levels of cytokines [1]. IgG antibodies were positive for spike antigen (anti-S) and negative for nucleoside (anti-N), which ruled out SARS-CoV-2 [14]. However, neither of the patients displayed the typical Vβ21.3 T cell expansion observed in MIS-C.

Drug reaction with eosinophilia and systemic symptoms (DRESS) might also explain the clinical presentation of acute rash, fever, decreased lymphocyte count, eosinophilia, and liver abnormalities. A skin biopsy was also consistent with this diagnosis. However, the delay after vaccination was not suggestive, and these patients had not been previously exposed to this vaccine. No other treatment was administered during the last 8 weeks of follow-up. The recovery was rapid after corticosteroid administration. The RegiSCAR score, used to establish DRESS diagnosis, was rated at 5, and both patients met three or fewer criteria established by the Japanese consensus group, which is not sufficient for a potential DRESS [15]. Eosinophilia or eosinophil infiltration has already been described after COVID-19 or VRS vaccination; however, DRESS occurrence after vaccination is very rare [16]. Moreover, cardiac involvement such as myocarditis is not common in DRESS where it may present as systolic ventricular function alteration, which was absent in both patients. The first patient also had clinical and laboratory evidence of acute generalized exanthematous pustulosis, including delay after vaccination, fever, rash, and skin biopsy results. Despite a compatible clinical presentation, this would not account for all clinical features, such as shock.

Other systemic inflammatory reports following COVID-19 vaccine administration were identified from a review of the literature. Stappers et al. reported the case of a 32-year-old woman presenting with fever, arthralgia, and vasculitis-like rash with hyperinflammation and raised anti-spike receptor-binding domain IgG antibody titers 18 days after the first dose of the ChAdOx1 nCov-19 vaccine (Vaxzevria®, AstraZeneca) [17]. Nune et al. reported the case of a 44-year-old woman with MIS-A (multisystemic inflammatory syndrome in adults) symptoms 2 days after the BNT162b2 vaccination associated with rash, cutaneous edema, gastrointestinal symptoms, fever, and elevated CRP, troponin, and creatine kinase levels [18]. Chai et al. reported the case of a 17-year-old presenting with MIS-C 5 days after the second dose of the BNT162b2 vaccine associated with fever, systolic dysfunction, myalgia, diarrhea, rash, and increased inflammatory markers [19]. Recently, in Denmark, a case of MIS-C was reported in a 17-year-old patient who had received the Comirnaty® vaccine but without a history of symptomatic COVID-19 infection [20]. Clinical presentations have also been reported in younger patients: a 12-year-old boy after the first mRNA vaccine injection, another 12-year-old boy after the second injection, and a female adolescent with sickle cell disease after complete vaccination [21–23] . All the patients had favorable outcomes. However, the EMA stated that “there is currently insufficient evidence on a possible link between COVID-19 vaccines and very rare cases of multisystem inflammatory syndrome” [24]. The delay between symptom onset and vaccination is shorter than reported between SARS-CoV2 infection and MIS-C symptoms, usually 2–6 weeks [25]. However recent surveillance investigations reported a median delay between the most recent vaccine dose and to the onset of MIS-C of 8 days (interquartile range [IQR]: 1–8; range: 1–30) for patients receiving only one dose and 5 days for patients with two doses (IQR: 4–21; range: 3–48) [26].

In our cases, the relationship between the COVID-19 vaccine and the MIS-C is probable because the symptoms, laboratory examinations, and positive anti-S IgG antibodies without anti-N IgG antibodies support this hypothesis, with a shorter delay after the vaccination than reported in previous cases. MIS-C remains a difficult diagnosis because of the absence of specific biomarkers and many potential differential diagnoses. Conversely, detection of anti-nucleocapsid antibodies is not enough to rule out other diagnoses, and the Vβ21.3 T-cell compartment was normal, challenging a diagnosis of MIS-C; however, this may be related to the massive initial apoptosis of T cells [2]. Furthermore, in periods of significant spread of COVID-19 and because of frequent asymptomatic forms, MIS-C illness caused by recent COVID-19 infection could coincidentally occur a few days after vaccination and appear to be linked to the vaccine [26].

Physicians should be aware of the possible, even exceptional, occurrence of MIS-C after COVID-19 vaccination, in order to initiate appropriate treatments. Given the good clinical outcomes of all the reported cases, health institutions should pursue efforts to encourage vaccination of eligible individuals against SARS-CoV-2 infection. A recent report suggested that COVID-19 mRNA vaccination is associated with a lower incidence of MIS-C in adolescents [27]. The latest US surveillance program reported 1.0 case per million individuals aged 12–20 years after vaccination against an incidence of 224 per million SARS-CoV2 infections in children aged 11–15 years and 164 per million in those aged 16–20 years [26].

4. Conclusion

In atypical clinical presentations of children with a compatible delay from the COVID-19 vaccination, pediatricians should be encouraged to report any cases of MIS-C that may have occurred after vaccination to pharmacovigilance systems. Further data are needed to better assess the role of the COVID-19 vaccine in the occurrence of MIS-C. These patients could probably be treated as usual for MIS-C. The description of other cases remains extremely rare and is much less frequent than MIS-C related to COVID-19 infection. These observations do not compromise the largely positive benefit–risk balance of these vaccines.

Funding

This study received no funding. The study data had no prior presentation as an abstract or a poster.

Declaration of Competing Interest

The authors report no relevant disclosures.

Acknowledgments

We thank the patients’ relatives, physicians, and nurses involved in patient care.

These cases have been reported to the French pharmacovigilance system under the numbers: FR-AFSSAPS-PV20213278 and FR-AFSSAPS-LY20219953.

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