Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Short communication

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

C. Collignon,*, C. Frachette, D. Callot, Y. Pinhas, P. Bataille, B. Bader-Meunier, L. Chouchana, M.-L. Frémont, Z. Belhadjer, M. Oualha, F. Moulin, E. Javouhey, A. Belot, S. Renolleau

Pediatric Intensive Care Unit, APHP University Hospital Necker-Enfants malades, Paris, France

Pediatric Nephrology, Rheumatology, Dermatology Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, 69677 Bron, France

Faculty of Medicine, University of Lyon, 69100 Villeurbanne, France

Regional Center of Pharmacovigilance, Department of Pharmacology, Cochin Hospital, AP-HP. Centre – Université de Paris, Paris, France

Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants-Maladies University Hospital, AP-HP, Centre-Université de Paris, Paris, France

University of Paris, Paris, France

Department of Dermatology, Reference Centre for Genodermatoses and Rare Skin Disease (MAGEC), Hopital Universitaire Necker-Enfants Malades, APHP, Paris, France

Department of Dermatology, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, 69677 Bron, France

Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants-Malades University Hospital, APHP, Centre-Université de Paris, Paris, France

Department of Pediatric Immunology and Rheumatology, AP-HP, Necker Hospital, Paris, France

M3C-Necker Enfants Malades, AP-HP, Paris, France

National Referee Centre for Rheumatic and Autoimmune and Systemic Diseases in Children (RAISE), 69677 Bron, France

Lyon Immunopathology Federation LIFE, Hospices Civils de Lyon, 69002 Lyon, France

* Corresponding author at: Pediatric Intensive Care Unit, Necker-Enfants malades University Hospital, 149 rue de Sévres, 75015 Paris, France.

E-mail address: charlotte.collignon@aphp.fr (C. Collignon).

ARTICLE INFO

Article History:
Received 14 March 2022
Revised 23 June 2022
Accepted 25 August 2022
Available online 26 September 2022

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.

© 2022 Published by Elsevier Masson SAS on behalf of French Society of Pediatrics.

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
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 erythema; 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 hypertension. 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 keratinocytic necrosis in the superficial layers of the epidermis, with a multilocular pustule consisting of eosinophilic and neutrophilic polymorphonuclear cells. In the superficial and middle dermis, a perivascular inflammatory infiltrate was seen consisting of lymphocytes, histiocytes, and eosinophilic polymorphonuclear 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 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 hypertension. 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 auditory 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 systemic 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 cytolyis (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 Vδ TCR repertoire 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-spire or anti-nuclear capsid 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
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 exanthemeputulosus, 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-splice receptor-binding domain IgG antibody titer 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 (multisystem 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-AFSAPS-PV20213278 and FR-AFSAPS-LY20219953.

References

[1] Vella LA, Rowley AH. Current insights into the pathophysiology of multisystem inflammatory syndrome in children. Curr Pediatr Rep 2021;9:83–92.
[2] Moreews M, Le Gouge K, Khalidi-Plaissart S, et al. Polyclonal expansion of TCR Vβ 21.3+ CD4+ and CD8+ T cells is a hallmark of multisystem inflammatory syndrome in children. Sci Immunol 2021;6:eabj811516.
[3] Poorter RA, Paschold I, Rivas MN, et al. HLA class I–associated expanded TCRBV11-2 T cells in multisystem inflammatory syndrome in children. J Clin Invest 2021;131:e146614.
[4] Rada T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51–7.
[5] Beilhader Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children. Circulation 2020;142:429–36.
[6] Dong Y, Dai T, Wei Y, et al. A systematic review of SARS-CoV-2 vaccine candidates. Signal Transduct Target Ther 2020;5:237.
[7] Chouchana L, Blet A, Al-Khalaf M, et al. Features of inflammatory heart reactions following mRNA COVID-19 vaccination at a global level. Clin Pharmacol Ther 2022;111:605–13.
[8] World Health Organization (2020). Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, 15 May 2020. World Health Organization. https://apps.who.int/iris/handle/10665/332095. Licence: CC-BY-NC-SA 3.0 IGO.
[9] US Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (accessed Jan 14, 2022).
[10] Young TK, Shaw KS, Shah JR, et al. Mucocutaneous Manifestations of Multisystem Inflammatory Syndrome in Children During the COVID-19 Pandemic. JAMA Dermatol 2021;157:207–12.
[11] Tzoulis P. Prevalence, prognostic value, pathophysiology, and management of hyponatraemia in children and adolescents with COVID-19. Acta Biomed Atenei Parm 2021;92:e2021474.
[12] Reiff DD, Mannion ML, Samuy N, et al. Distinguishing active pediatric COVID-19 pneumonia from MIS-C. Pediatr Rheumatol Online J 2021;19:21.
[13] Nakra N, Blumberg D, Herrera-Guerra A, et al. Multi-System Inflammatory Syndrome in Children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children 2020;7:69.
[14] Anderson EM, Diorio C, Goodwin EC, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19 Update in: J Pediatric Infect Dis Soc 2020 Dec 02:: PMID:32839782; PMCID: PMC7444298. doi:10.1016/2020.08.17.2017552.
[15] Shohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. Allergol Int 2019;68:301–8.
[16] Chen WH, Strych U, Hotez PJ, et al. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep 2020;7:61–4.
[17] Stappers S, Ceuleers B, Van Brusselen D, et al. A case of multisystem inflammatory syndrome (MIS-A) in an adult woman 18 days after COVID-19 vaccination. Acta Clin Belg 2022;77:772–7.
[18] Nune A, Iyengar KP, Goddard C, et al. Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V). BMJ Case Rep 2021;14:e243888.
[19] Chai Q, Nygaard U, Schmidt RC, et al. Multisystem inflammatory syndrome in a male adolescent after his second Pfizer-BioNTech COVID-19 vaccine. Acta Paediatr 2022;111:125–7.
[20] European Medicines Agency. [Internet] Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 30 August - 2 September 2021 COVID-19 vaccines: EMA reviewing cases of multisystem inflammatory syndrome. 3 September 2021. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-30-august-2-september-2021
[21] Yalcinkaya R, Oz FN, Polat M, et al. A case of multisystem inflammatory syndrome in a 12-year-old male after COVID-19 mRNA vaccine. Pediatr Infect Dis J 2022;41: e89–9.
[22] Abdelgalil AA, Saeedi FA. Multisystem inflammatory syndrome in a 12-year-old boy after mRNA-SARS-CoV-2 vaccination. Pediatr Infect Dis J 2022;41:e93–4.
[23] Dejong J, Sainato R, Forouhar M, et al. Multisystem inflammatory syndrome in a previously vaccinated adolescent female with sickle cell disease. Pediatr Infect Dis J 2022;41:e104–5.
[24] Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 25-28 october 2021 - COVID 19 vaccines: PRAC finds insufficient evidence on a possible link with multisystem inflammatory syndrome. https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-25-28-october-2021_en.pdf
[25] Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. Children and adolescents. N Engl J Med 2020;383:334–46.
[26] Yousaf AR, Cortese MM, Taylor AW, et al. Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation. Lancet Child Adolesc Health 2022;6:303–12.
[27] Levy M, Recher M, Hubert H, et al. Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. JAMA 2022;327:281–3.