New-onset dermatomyositis following SARS-CoV-2 infection and vaccination: a case-based review

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Abstract
Dermatomyositis is a rare disease with an incidence of 1 to 15 per million [1]. Apart from muscle and skin, the disease can also affect other organs, such as lungs, heart, and blood vessels with varying clinical outcomes, depending on the specific antibody [2]. Although the pathophysiology has not yet been fully elucidated, type I interferon (IFN) is now known to play a key role in the development of the disease. Induction of interferon-stimulated genes can be seen in muscle biopsies of dermatomyositis and type I IFN signature has been reported in peripheral blood samples [3, 4]. Specifically, anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody-positive dermatomyositis patients showed very high serum type I IFN signature [5].

Interestingly, MDA5 positive dermatomyositis and SARS-CoV-2 infection share clinical and laboratory features, such as inflammatory cytokine profile and interstitial lung involvement [6]. Furthermore, creatine kinase (CK) elevation has been reported in up to 27% of SARS-CoV-2-infected patients [7]. Inflammatory myopathy has been detected in infected patients as well as autoantibody production against nuclear matrix protein-2 (NXP2) and MDA5 without clinical symptoms of dermatomyositis but a correlation of worse pulmonary outcomes [8, 9].

The newly developed messenger ribonucleic acid (mRNA) vaccine is known to induce an IFN signaling, partly also via MDA5 [10]. After SARS-CoV-2 vaccination, elevated IFN levels can be detected in healthy individuals [11]. So far, the development of autoimmune diseases like systemic lupus erythematosus (SLE) [12] and autoimmune
myositis [13] after SARS-CoV-2 vaccination have been reported in a few case reports.

Both, SARS-CoV-2 infection and vaccination, may lead to new-onset dermatomyositis via autoimmunity due to interferon signaling, hyperinflammation and autoantibody induction.

Case presentation

We report four cases with the occurrence of MDA5 and/or NXP2 positive dermatomyositis directly linked to SARS-CoV-2 infection or vaccination. Our sample comprises three female and one male patient ranging from 19 to 57 years of age. Three patients experienced the onset of dermatomyositis shortly after SARS-CoV-2 mRNA vaccination with BNT162b2 (Comirnaty) (1–7 days) and one patient 2 weeks after SARS-CoV-2 infection. Intriguingly, patient 1 developed dermatomyositis after his first vaccination, whereas dermatomyositis in patients 3 and 4 evolved after the second vaccination. All patients showed typical skin manifestations and reported proximal myalgia (Fig. 1). Two patients initially presented with arthritis. One patient had severe dyspnea, and another had excessive dysphagia. Only two patients had elevated CK levels. MDA5 antibodies could be detected in three patients and NXP2 antibodies were found in two patients (patient 3 was positive for both antibodies). In three patients, muscle magnetic resonance imaging was performed, showing bilateral proximal myositis. Patient 1, furthermore, developed rapid-progressive interstitial lung disease (RP-ILD). Skin and muscle biopsies showed pathologies consistent with dermatomyositis.

All patients required immunosuppression and were treated with glucocorticoid pulse therapy. Whilst patients 3 and 4 showed mild symptoms that were successfully treated with hydroxychloroquine and azathioprine; patients 1 and 2 had a long hospitalization with multiple intensive care treatments due to life-threatening major organ involvements. Both patients required extensive immunosuppression including ciclosporin A, mycophenolate mofetil and rituximab. Table 1 displays patients’ characteristics and therapeutic concepts.

Moreover, we have noted an increase of dermatomyositis diagnoses in our center since the beginning of the SARS-CoV-2 pandemic with almost a doubling of new-onset dermatomyositis in overall inpatient cases from 0.06 to 0.15% (2017–2020) up to 0.26% in the year 2021 (Table 2).

![Patients' images](image-url)

**Fig. 1** Patients’ images: a Patient 2: facial swelling, heliotrope erythema. b Patient 1: Gottron papules c Patient 2: magnetic resonance imaging scan (T2) showing bilateral active myositis in the adductors and extensors of the thighs.
### Table 1 Patients' characteristics

| Age (years) | Sex       | Symptom onset                      | Skin manifestation                                                                 | Organ involvement                           | Muscle MRI findings                                      | Antinuclear antibody | Myositis specific antibodies | CK (U/l) (normal <190) | LDH (U/l) (normal 120–250) | CRP (mg/l) (normal <5) | Biopsies                                                                 | Treatment                                                                                           |
|-------------|-----------|-----------------------------------|------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------|--------------------|-------------------------------|-------------------------|--------------------------|---------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 19          | Male      | 5 days after 1st vaccination with  | Gottron papules and Gottron signs over extensor sides of elbows and knees, Hiker's | Proximal myalgia, arthritis, RP-ILD         | Bilateral myositis of muscles inserting trochanter minor | <1:80              | MDA5, RO-52                   | 1074                    | 839                      | <5                  | Muscle: mild myopathy and increased MHC I expression                    | Glucocorticoids, IVIG, Tofacitinib, MMF, Rituximab, Ciclosporin A, Anakinra, Nintedanib, Daratumumab |
| 20          | Female    | 2 weeks after infection           | Heliotrope erythema, Gottron papules, scalp exanthem, V and Shawl sign, facial      | Proximal myalgia (including extensive        | Bilateral myositis of muscles of the pelvic hip girdle   | 1:640              | NXP2                         | 19,647                  | 1903                     | <5                  | Muscle: necrosis, expression of MAC and MHC I                            | Glucocorticoids, IVIG, MMF, Ciclosporin A, Tofacitinib, Rituximab                             |
| 57          | Female    | 1 week after 2nd vaccination with | Gottron signs at the elbows, erythematos macular rash on forehead, Shawl sign,     | Proximal myalgia                            | Bilateral myositis of muscles of the shoulders and    | 1:2560             | MDA5, NXP2                    | 146                     | 215                      | <5                  | Skin: perivascular neutrophilic infiltrates                              | Glucocorticoids, Hydroxychloroquine, Azathioprine                                      |
| 51          | Female    | 1 day after 2nd vaccination with  | Reddened painful fingertips (Chillblain lesions) and periungual erythematos         | Proximal myalgia                            | Thighs                                                  | 1:51 20            | MDA5                         | 66                      | 125                      | <5                  | Skin: perivascular lymphocytic infiltrates consistent with DM            | Glucocorticoids, MTX s.c., Hydroxychloroquine, Azathioprine                                |

**RP-ILD** Rapidly progressive interstitial lung disease, **MRI** magnetic resonance imaging, **MDA5** Melanoma differentiation-associated protein 5, **NXP2** Nuclear matrix protein 2, **CK** Creatine kinase, **LDH** Lactate dehydrogenase, **AST** Aspartate aminotransferase, **CRP** C-reactive protein, **MHC I** Major histocompatibility complex, **MAC** Membrane attack complex, **DM** Dermatomyositis, **IVIG** Intravenous immunoglobulin, **MMF** Mycophenolate Mofetil, **MTX** Methotrexate
Methods

To identify previously reported cases of SARS-CoV-2 associated dermatomyositis, a systematic review of the literature according to PRISMA guidelines was performed. MEDLINE and Embase were systematically searched until the 25th of May 2022. The search strategy included the following terms to identify dermatomyositis cases: ‘myositis’, ‘dermatomyositis’, ‘polymyositis’, ‘rhabdomyolysis’, ‘antisynthetase syndrome’ and ‘inflammatory myopathy’. SARS-CoV-2 association was established with ‘SARS-CoV-2’, ‘COVID-19’ and ‘coronavirus’. All terms were used to search titles and abstracts of publications. The search was conducted as (‘myositis’ OR ‘dermatomyositis’ OR ‘polymyositis’ OR ‘rhabdomyolysis’ OR ‘antisynthetase syndrome’) AND (‘SARS-CoV-2’ OR ‘COVID-19’ OR ‘coronavirus’). The database search in MEDLINE identified 311 publications, the database search in Embase 422, which were independently reviewed by two authors (MTH, NR). A third independent reviewer (MK) decided in case of discrepancy. Based on the EULAR/ACR criteria for (juvenile) dermatomyositis [14], new-onset cases of dermatomyositis with a temporal relation to SARS-CoV-2 infection or vaccination were included in this review. Non-English articles, reviews without description of detailed case information and congress abstracts were excluded. Finally, 16 studies reporting 17 cases were included. The methodology flowchart is shown in Fig. 2.

Results

The clinical, laboratory, radiographic and histopathologic features of SARS-CoV-2 infection-/vaccination-associated dermatomyositis of the identified 17 cases of the systematic review are summarized in Tables 3 and 4 [13, 15–29]. Interestingly, 70.6% of the patients were female, mean age was 52.4 years. Ten cases occurred after infection and seven after vaccination. All reported vaccinations were mRNA vaccination. Six of these seven cases were after BNT162b2 (Comirnaty) and one after mRNA-1273 (Spikevax) vaccination. All identified cases had pathognomonic skin manifestations. Myocardial involvement was assumed in two cases (one after infection and one after Comirnaty vaccination). Lung involvement was reported in seven patients. Five of these lung involvements were reported after SARS-CoV-2 infection. One patient with MDA5, and two patients with NXP2-antibodies were reported. Furthermore, four Mi-2 positive patients, two RNP/TIF1γ, respectively, and one Jo-1 positive patient were identified. All patients received glucocorticoids and nine patients IVIG. One patient had a lethal disease course.

Discussion

The reported cases vary in autoimmune serology, clinical course, and prognosis. Nevertheless, the common feature was the new-onset dermatomyositis shortly after SARS-CoV-2 infection or vaccination.

Interestingly, lung involvement was the most frequent manifestation (despite skin and muscle). We would like to highlight, that after SARS-CoV-2 infection, radiographically changes of the lung might sometimes be hard to differentiate between infection- or autoimmune-disease related.

In general, viral infections are a well-known trigger of dermatomyositis [30]. Furthermore, seasonal clustering of MDA5-positive dermatomyositis with lower incidence in European summer months is known [31].

In the systematic database search, we identified ten cases of new-onset dermatomyositis after SARS-CoV-2 infection and one patient in our cohort.

In some of these cases apart from classical clinical and laboratory findings of dermatomyositis an IFN signature as well as autoinflammatory clinical aspects have been reported [15, 17, 26].

Consistent with the results of our center, Gokhale et al. also reported an increase of new-onset dermatomyositis in a center in Mumbai with five new cases of dermatomyositis in 6 months from April 2020 (usually one to two new cases per year) [20]. Furthermore, Movahedi et al. described an increase of new-onset juvenile dermatomyositis in Iran. Regularly, two to four new cases were admitted each year from the years 2014 to 2019, whereas from February 2020 to February 2021 eight new-onset juvenile dermatomyositis cases were registered [32].

MDA5- and NXP2-antibodies were reported in each of the four 21 identified cases (16.7%, respectively). Both
antibodies are associated with viral interaction in general: MDA5 is an intracellular sensor for viral RNA, triggering proinflammatory immune response especially involving type I IFN [32]. NXP2 shows RNA binding activity and upregulation of its expression has been detected in influenza infection [33]. Furthermore, the two antibodies have been associated with SARS-CoV-2 infections: In a small study of 35 SARS-CoV-2 patients, de Santis et al. reported the occurrence of NXP2 \( (n = 3) \) and MDA5 antibodies \( (n = 1) \). Both antibodies were associated with a severe disease course [9]. In SARS-CoV-2 infection, MDA5 was shown to guide an innate immune response via IFN signaling [34]. It has been hypothesized, that viral RNA may trigger MDA5 expression and cell damage may lead to MDA5 release followed by autoantibody production [35]. In addition, Wang et al. demonstrated correlative evidence between high titer of anti-MDA5 antibodies and lethal outcome of SARS-CoV-2 infection. Of the 274 patients analyzed, 48.2% were anti-MDA5 positive and high antibody titer \( (> 10 \text{ U/ml}) \) was more frequent in non-survivors [36].

In addition, muscle involvement seems to be an important feature of SARS-CoV-2 infection. Elevated CK was detected in 27% of the SARS-CoV-2 patients [7]. Furthermore, inflammatory myopathy was seen in SARS-CoV-2 patients without significant signs of viral infection of myocytes suggesting autoimmune features [8]. In addition, Manzano et al. discovered the presence of myxovirus resistance protein A (MxA), a type I IFN induced protein, in the muscle biopsy of an SARS-CoV-2 patient with proximal myopathy, suggesting parts of the inflammatory
myopathy caused by interferonopathy [38]. Another study also showed immune-mediated and inflammatory myopathy in 16 of 35 autopsies of deceased SARS-CoV-2 patients with high expression of major histocompatibility complex (MHC) I and MxA expression in some cases, which was not seen in controls [39], underlining a possible IFN and cytokine triggered mechanism. These MHC I and IFN patterns found in muscles of SARS-CoV-2 patients

### Table 3
Clinical, laboratory, radiologic and histopathologic features of SARS-CoV-2 infection/vaccination associated dermatomyositis cases found in systematic search [13, 15–29]a

| Author, year | Patient’s age in years, sex | Infection/ 1st, 2nd vaccination (with) | Myositis-specific antibodies | Creatine kinase | Muscle biopsy | MRI | Extramuscular involvement | Treatment | Outcome |
|--------------|-----------------------------|---------------------------------------|-----------------------------|----------------|-------------|-----|----------------------------|-----------|---------|
| Borges et al., 2021 | 36, Female | Infection | Mi-2 | 3518 U/l | Not performed | Not performed | Skin | GC | Improvement |
| Camargo Coronel et al. 2022 | 76, Female | 2nd vaccination (BNT162b2, Comirnaty) | Mi-2 | 3368 U/l | Consistent with DM | Not performed | Skin, dysphagia | GC, MTX | Improvement |
| Derbel et al. 2021 | 61, Female | Infection | Jo-1 | 1052 U/l | Not performed | Not performed | Skin, possibly lung, joints | GC | Improvement |
| Gokhale et al. 2020 | 64, Male | Infection | Negative | 990 U/l | Not performed | Positive | Skin, possibly lung, dysphagia | GC, IVIG, MMF | Improvement |
| Gokhale et al. 2020 | 50, Male | Infection | Mi-2 | 1169 U/l | Not performed | Positive | Skin, possibly lung | GC, IVIG, MTX | Improvement |
| Gouda et al. 2022 | 43, Female | 2nd Vaccination (BNT162b2, Comirnaty) | RNP | 3358 µg/l | Not performed | Positive | Skin, lung, joints | GC, MMF, HCQ | Improvement |
| Ho et al. 2021 | 58, Male | Infection | Negative | 9684 U/l | Consistent with DM | Not performed | Skin, possibly lung | GC, MTX | Improvement |
| Keshtkarjahromie et al. 2021 | 65, Female | Infection | MDA5 | 1222 U/l | Not performed | Positive | Skin, possibly lung, joints | GC, IVIG | Death |
| Kreuter et al. 2022 | 68, Female | 2nd Vaccination (BNT162b2, Comirnaty) | TIF1γ | Not stated | Not performed | Not performed | Skin | GC | Improvement |
| Lee et al. 2022 | 53, Male | 2nd vaccination (BNT162b2, Comirnaty) | NXP2 | 14,659 U/l | Consistent with DM | Positive | Skin, dysphagia | GC, IVIG, RTX | Improvement |
| Liquidano-Perez et al. 2021 | 4, Female | Infection | RNP | 403 mg/dl | Not performed | Positive | Skin, possibly lung, dysphagia | GC, IVIG, MTX, CsA | Improvement |
| Okada et al. 2021 | 64, Female | Infection | NXP2 | 1495 U/l | Consistent with DM | Positive | Skin | GC, AZA | Improvement |
| Rodero et al. 2022 | 15, Female | Infection | Negative | 545 U/l | Consistent with DM | Not performed | Skin | GC, IVIG, Tofacitinib | Improvement |
| Shahidi Dadras et al. 2021 | 58, Female | Infection | Negative | 2611 U/l | Not performed | Not performed | Skin, myocardial involvement | GC, MTX, HCQ | Improvement |
| Venkateswaran et al. 2022 | 43, Male | 1st Vaccination (mRNA-1273, Spikevax) | Negative | Not stated | Not performed | Not performed | Skin | GC, IVIG | Improvement |
| Vutipongssaront et al. 2022 | 55, Female | 1st Vaccination (BNT162b2, Comirnaty) | Mi-2 | 11,330 U/l | Not performed | Positive | Skin, myocardial involvement | GC, IVIG, CYC | Improvement |
| Wu et al. 2022 | 77, Female | 1st Vaccination (BNT162b2, Comirnaty) | TIF1γ | 4476 U/l | Consistent with DM | Not performed | Skin | GC, IVIG | Improvement |

*MRI* Magnetic resonance imaging, *DM* Dermatomyositis, *GC* Glucocorticoids, *MTX* Methotrexate, *IVIG* Intravenous immunoglobulin, *MMF* Mycophenolate Mofetil, *RNP* Ribonucleoprotein, *TIF1γ* Transcription intermediary factor 1γ, *MDA5* Melanoma differentiation-associated protein 5, *NXP2* Nuclear matrix protein 2, *RTX* Rituximab, *CsA* Ciclosporin A, *AZA* Azathioprine, *HCQ* Hydroxychloroquine, *CYC* Cyclophosphamide

*a alphabetically ordered
Table 4  Analysis of clinical, laboratory, radiologic and histopathologic features of SARS-CoV-2 infection/vaccination associated dermatomyositis cases found in the systematic review [13, 15–29]

| Characteristics                      | Total | Percentage |
|--------------------------------------|-------|------------|
| Sex                                  |       |            |
| Male                                 | 5     | 29.4%      |
| Female                               | 12    | 70.6%      |
| Age (years)                          |       |            |
| Mean                                 | 52.4  | –          |
| Median                               | 58.0  | –          |
| Infection                            |       |            |
| Negative                             | 7     | 41.2%      |
| Positive                             | 10    | 58.8%      |
| Vaccination                          |       |            |
| Negative                             | 10    | 58.8%      |
| Positive                             | 7     | 41.2%      |
| Vaccine                              |       |            |
| BNT162b2 (Comirnaty)                 | 6     | 85.7%      |
| mRNA-1273 (Spikevax)                 | 1     | 14.3%      |
| First vaccine                        | 3     | 42.9%      |
| Second vaccine                       | 4     | 57.1%      |
| MSA                                  |       |            |
| MDA5                                 | 1     | 5.9%       |
| NXP2                                 | 2     | 11.8%      |
| Mi-2                                  | 4     | 23.5%      |
| RNP                                  | 2     | 11.8%      |
| TIF1γ                                | 2     | 11.8%      |
| Jo-1                                  | 1     | 5.9%       |
| Negative                             | 5     | 29.4%      |
| Creatine kinase (U/l)                |       |            |
| Mean                                 | 3230  | –          |
| Median                               | 2053  | –          |
| Muscle biopsy                        |       |            |
| Not performed                        | 11    | 64.7%      |
| Performed                            | 6     | 35.3%      |
| Consistent with myositis             | 5     | 29.4%      |
| MRI                                  |       |            |
| Not performed                        | 9     | 52.9%      |
| Performed                            | 8     | 47.1%      |
| Consistent with myositis             | 8     | 47.1%      |
| Skin                                 |       |            |
| Negative                             | 0     | 0.0%       |
| Positive                             | 17    | 100.0%     |
| Not reported                         | 0     | 0.0%       |
| Lung                                 |       |            |
| Negative                             | 6     | 35.3%      |
| Positive                             | 7     | 41.2%      |
| Possible SARS-CoV-2 manifestation    | 5     | 29.4%      |
| Not reported                         | 4     | 23.5%      |
| Myocardial involvement               |       |            |
| Negative                             | 1     | 5.9%       |
| Positive                             | 2     | 11.8%      |
| Not reported                         | 14    | 82.4%      |
| Dysphagia                            |       |            |
| Negative                             | 0     | 0.0%       |
| Positive                             | 4     | 23.5%      |
| Not reported                         | 13    | 76.5%      |
| Arthritis                            |       |            |
| Negative                             | 0     | 0.0%       |
| Positive                             | 3     | 17.6%      |
| Not reported                         | 14    | 82.4%      |
| Glucocorticoids                      |       |            |
| Negative                             | 0     | 0.0%       |
| Positive                             | 17    | 100.0%     |
| Not reported                         | 0     | 0.0%       |
| IVIG                                 |       |            |
| Negative                             | 0     | 0.0%       |
| Positive                             | 9     | 52.9%      |
| Not reported                         | 8     | 47.1%      |
closely resemble the pattern found in muscle biopsies in dermatomyositis [2].

Furthermore, the development of autoimmune diseases after vaccination by molecular mimicry and bystander activation in genetically susceptible individuals has frequently been discussed [40, 41]. There have been also a few case reports of vaccinations as a potential trigger of dermatomyositis but no significant association has been established in previous vaccination studies [42].

Rare, but possible side effects after SARS-CoV-2 vaccination, such as the development of autoimmune diseases such as systemic lupus erythematosus (SLE), myocarditis, vasculitis, and thrombotic thrombocytopenia have been reported [12, 43–46]. In the last few months, since the beginning of the global vaccination campaign, apart from the mentioned autoimmune diseases after vaccination, myositis following SARS-CoV-2 vaccination has been reported. In the reviewed literature and our cohort, we detected ten patients with new-onset dermatomyositis after SARS-CoV-2 vaccination. All patients received a mRNA vaccination. Interestingly, six patients developed the disease after the second vaccination. Whilst mRNA vaccination seems to be more prevalent for dermatomyositis-association, other autoimmune diseases like thrombotic thrombocytopenia or SLE seem more likely to occur after adenovirus vector vaccine like ChAdOx1-S. Autoantibody production and activation is discussed as possible mechanism [12]. Furthermore, there are reports of myositis in temporal association to ChAdOx1-S vaccination [37].

In SARS-CoV-2 mRNA vaccines, the mRNA enters human cells via angiotensin-converting enzyme 2 and induces an immune response to develop spike antibodies against SARS-CoV-2 infection and memory T and B cells [47]. During the development of mRNA vaccine, a strong type I IFN response with MDA5 as one of the possible RNA sensing and IFN inducing mechanisms was seen [10]. Thus, the nowadays used mRNA vaccines are containing nucleoside-modified mRNA, which reduces the IFN pathway activation [10, 48]. Nevertheless, increased type I IFN levels were detected after mRNA vaccination against SARS-CoV-2, but they were comparable to IFN levels after influenza vaccination [11]. As dermatomyositis is known to be an IFN driven disease, there might be a tipping point inducing autoimmunity due to the vaccination response in some patients.

Most recently, Yin et al. were able to prove the importance of the NLRP3 inflammasome in the pathophysiology of dermatomyositis [49]. NLRP3 inflammasome activation has also been detected in myocarditis after mRNA vaccination. It is assumed, that similarly to SARS-CoV-2 infection, spike protein might trigger NLRP3 inflammasome activity, or that the lipid nanoparticles used, might stimulate the NLRP3 inflammasome [50, 51]. This might present another additional pathomechanism in the development of autoimmune diseases like dermatomyositis following mRNA vaccination.

In summary, this case series and the reviewed literature suggest an association between SARS-CoV-2 infection/
vaccination and the development of dermatomyositis, since all reported cases occurred within a very short timeframe after vaccination or infection. Possible pathophysiological mechanisms may include type I IFN pathways, the NLRP3 inflammasome and the induction of autoantibody production (especially of those antibodies, which are closely related to viral defense or viral RNA interaction like MDA5 and NXP2).

Due to the limited number of identified cases, we would like to emphasize that the association between SARS-CoV-2 infection/vaccination and the development of dermatomyositis does not necessarily prove causality, and further research is needed.

We would like to underline that the benefit of SARS-CoV-2 vaccinations highly outweighs possible very rare autoimmune phenomena. Nevertheless, rheumatologists should be aware of possible associations between dermatomyositis and SARS-CoV-2 infection/vaccination to maintain optimal medical management.

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Declarations

Conflict of interests The authors declare that they have no competing interests.

Ethical Standard This manuscript does not contain human or animal studies. All patients gave written consent to anonymously publishing their cases, including pictures, in which the patients can’t be identified.

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