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LETTER TO EDITOR

Onset and Relapse of Juvenile Dermatomyositis Following Asymptomatic SARS-CoV-2 Infection

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Dear Editor, SARS-CoV-2 infection drives a marked inflammation and has been described to precede the appearance in rare occasion of various autoimmune and inflammatory diseases including clinical, radiological, muscle biopsy, and serological features consistent with dermatomyositis [1, 2]. A working hypothesis is that juvenile dermatomyositis (JDM) is a type 1 interferon-driven inflammatory response, triggered by one or more environmental stimuli, such as infection. In order to test the hypothesis that SARS-CoV-2 could promote JDM, we studied SARS-CoV-2 infection history in the 10 JDM patients with disease onset (n = 6) or relapse (n = 4) seen in our center since the start of the pandemic. IgG and IgM directed against 5 different portions of the virus were measured in patients plasma at the time of diagnosis: whole spike protein, spike receptor-binding domain (RBD), spike S2 subunit, nucleocapsid protein (NP), and a membrane-envelope fusion glycoprotein (ME) [3]. Out of the 10 patients, we identified high titers of both IgG (Fig. 1a) and IgM (Fig. 1b) antibodies directed against SARS-CoV-2 proteins in one new onset (P1) and one relapsing patient (P2) (Fig. 1a) indicating a recent history of infection by SARS-CoV-2.

P1 is a 15-year-old girl that developed a JDM associating poor general state, fatigue, weight loss, symmetrical polyarthritis, mild proximal muscle weakness, and skin features: erythema and papule at the joint extensors, erythema and painful hyperkeratosis papules palmar and plantar, purple eyelids, and telangiectasia at the root of nails and gingival margins. Muscle biopsy's features were consistent with the diagnosis of JDM. Creatine kinase (CK) was elevated 545 U/L (< 150). She was negative for muscle-specific

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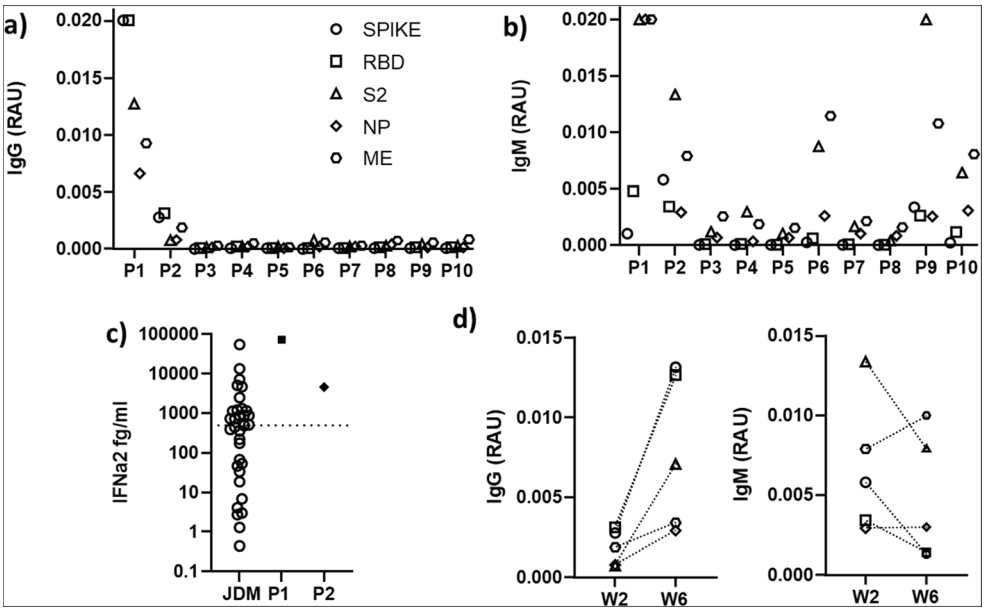

Fig. 1 (**a**) Dosage of anti-SARS-CoV-2 whole spike protein, RBD, S2, NP, and ME IgG and (**b**) IgM measured in relative antibody units (RAU) in the plasma of 10 patients with JDM onset or relapse diagnosed since the beginning of the pandemic in France. (**c**) Quantification of IFNα2 protein in the plasma of 33 active JDM patients followed in our clinical center (median: black dotted line), of P1 2 weeks post-onset and of P2 two weeks post-relapse. (**d**) Dosage of anti-SARS-CoV-2 whole spike protein, RBD, S2, NP, and ME IgG and IgM at week 2 and week 6 post-JDM relapse in P2 measured in relative antibody units (RAU)

autoantibodies (MSAs). Interferon-α protein (IFNα2) in the plasma, measured by Simoa assay (Quanterix Homebrew) [4], was markedly elevated (73476 fg/mL) (Fig. 1c). Concomitant infection by SARS-CoV-2 was demonstrated by positive nasopharyngeal antigenic test 2 weeks before JDM onset and high IgG and IgM titer against whole spike protein, RBD, and S2 2 weeks after JDM onset (Fig. 1 a and b). Treatment with intravenous immunoglobulins, corticosteroids, and tofacitinib 5 mg b.i.d led to remission of the disease.

P2 is a 12-year-old girl who developed a skin relapse of typical JDM diagnosed 8 years earlier. At diagnosis, she presented with mild muscle involvement and CK level was normal. Muscle magnetic resonance imaging showed muscle edema, and muscle biopsy's features were consistent with the diagnosis of JDM. There were no MSAs detected. Cutaneous lesions consisted of erythema and Gottron's papule at the joint extensor, erythema and painful hyperkeratosis papules palmar and plantar, heliotrope eyelids, erythema and edema of the ears, shawl sign with flagellate erythema. Treatment with corticosteroids and methotrexate led to a complete remission of 8 years including 6-year off therapy. Two weeks after being in contact with a COVID-19-positive family member, she experienced a purely skin relapse of the disease. Cutaneous involvement was similar to the lesions observed at initial diagnosis of JDM. No muscle involvement was noted and MSA remained absent. IFNα2 concentration was markedly elevated at diagnosis (4612 fg/mL) (Fig. 1c). The presence of anti-SARS-CoV-2 RBD, S2, and whole spike protein IgM in the plasma 2 weeks after onset of the symptoms, along with limited IgG, followed by increased levels of IgG and decrease of most IgM at week 6, suggests that the infection occurred at the same time as the JDM relapse (Fig. 1d). Treatment with intravenous immunoglobulins and corticosteroids led to skin lesions remission and progressive decrease of IFNα2 concentration: 1466 fg/mL 10 weeks after the relapse.

Altogether, out of the 10 patients with onset or relapse of JDM features seen in our center between April 2020 and March 2021, we identified 2 (20%) with a concomitant history of SARS-CoV-2 infection. These patients had features consistent with typical JDM, according to the ENMC 2018 dermatomyositis classification criteria [5]. Considering that skin manifestations were completely similar at relapse and at diagnosis in P2, we think that the cutaneous involvement is mostly related to JDM rather than to SARS-CoV2 *per se*. Importantly, no other documented environmental stimulus temporally associated with the manifestations of JDM has been documented in these patients. A few cases of COVID-19-related myositis have been previously reported and may be attributable to direct myocyte injury or to induction of autoimmunity [1, 2]. Although the precise role of IFNα in the pathophysiology of JDM still needs to be deciphered, it is interesting to note that P1and P2 had very high levels of circulating IFNα2 compared to the median value (491 fg/mL) in 33 patients with active JDM followed in our clinical center (150- and 9-fold increase, respectively) (Fig. 1c). Altogether, these data strongly suggest that SARS-CoV-2 infection could trigger the development of JDM, possibly through induction of IFNα. Moreover, given that both patients were asymptomatic for COVID-19 symptoms, our observation also suggests that viral induction of JDM might be more frequent than expected as it could occur in patients without any manifestation of viral infection. Systemic evaluation of recent SARS-CoV-2, and other virus infection in newly diagnosed or relapsing patients, would help to estimate the extent of this observation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-021-01119-y.

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Author Contribution **MPR, BBM**: Conceptualization, methodology, resources, validation, investigation, data curation, writing-original draft, writing-review and editing, supervision, project administration. **SP, VB, MW, DD**: Formal analysis, methodology, resources, validation, investigation, data curation, writing-review and editing. **AF**: Validation, investigation, original draft, writing-review and editing. **AWM, IM, LCVW, EM, JLC, MAA, JPH, JB**: Resources, validation, investigation, writing-review and editing. **CG**: Conceptualization, methodology, resources, investigation, validation, writing-review and editing.

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Data availability Results from all IgG and IgM dosages presented in this study are in supplementary Table 1.

Declarations

Ethics Approval This study was approved by the CPP Sud est V: N° EudraCT: 2018-A01358-47/1.

Consent to Participate Patients and parents provided consent to participate to this study.

Conflict of Interest/Competing Interests The authors declare no competing interests.

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