Association of anti-SARS-COV-2 vaccine with increased incidence of myositis-related anti-RNA-synthetases auto-antibodies

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ABSTRACT

Introduction: SARS-CoV-2 is a RNA virus that associates with heterogeneous clinical manifestations and complications. Auto-antibodies are identified in approximately 50% of hospitalized COVID-19 patients. Objectives: To determine the global incidence of myositis-related auto-antibodies (non Jo1-RNA synthetases: anti-PL7, anti-PL12, anti-EJ, anti-OJ and RNA-sensor: anti-MDA5) in our laboratory during COVID-19 pandemics, and to describe the clinical and laboratory features of these patients. Study design: A retrospective study was performed from 2015 to 2021 in a cohort of 444 patients with suspected inflammatory myopathy. The incidence of positive results for the MSA was expressed as absolute value per year for the reference population. Immunoblot analysis, indirect immunofluorescence and HLA typing of 36 patients with positivity for MSAs were collected and analyzed. Results: We observed MSA positive in 28 patients in 2020 and 36 patients in 2021, representing a mean increase of 6-fold respect to previous years since 2015 (range, 0 to 19). In 2020, the most common antibody detected was anti-MDA5 (68%). In contrast, in 2021 the most common antibodies were anti-PL7 and/or anti-PL12 (69%). All patients in 2021 with positive anti-synthetases were fully vaccinated, 4 had previous documented infection, with median time from vaccine to MSA positivity of 5 months. Eight out of 36 patients (22%) reported clinical onset after SARS-CoV-2 vaccination and 6 out of 36 (17%) presented clinical and/or radiological worsening after SARS-CoV-2 vaccination. All patients presented with a known human leukocyte antigen (HLA)-DRB1* allele associated with ASS. The most prevalent alleles identified were DRB1*03:01, DRB1*04, DRB1*11:01, corresponding to 70% (16/23) of our cohort. Conclusions: Our preliminary data show an increased incidence of anti-synthetase antibodies during COVID-19 pandemic and SARS-CoV-2 vaccination associated to HLA DRB1* risk allele. Differential profiles of MSA specificities were observed: mainly against RNA-sensors in 2020 and against RNA-synthetases in 2021. Further studies are needed to support the association between SARS-CoV-2 infection and/or vaccination and the occurrence of this autoimmune syndrome.

1. Introduction

Idiopathic inflammatory myopathy (IIM) is an autoimmune disorder

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that affect muscles, skin, lungs and the joints, with an incidence of 11 per 1 million person years [1–3]. The autoimmune basis of IIM is supported by the presence of inflammatory infiltrates in the biopsies, complement-mediated cytotoxicity, and the expression of human leukocyte antigen (HLA), among others [4]. IIM comprises three entities: dermatomyositis; inclusion body myositis (IBM) and polymyositis, this last include immune-mediated necrotizing myopathy (IMNM) and anti-synthetase syndrome (ASS). Approximately, 70% of patients with IIM develop myositis-specific antibodies (MSAs) and/or myositis-associated antibodies (MAA) [5]. Despite of its low frequency, MAAs can coexist with MSAs, being anti-Ro52 one of the most frequent, helping to identify patients with more severe interstitial lung disease (ILD) and poorer outcome [6]. Additionally, patients with anti-Jo-1 autoantibodies have a better survival rate than those with other anti-RNA synthetase (ARS) autoantibodies, such as MDA5, PL-7 and PL-12 [7,8]. More than a third of patients with myositis have some type of ILD and a proportion of those patients experience risk of malignancy and higher mortality [9].

Some of the most significant triggering factors for IIM are virus infections, vaccines, drugs and ultraviolet light exposure [10,11]. In 1964, Bitum et al. published the first report of IIM following vaccination in a series of 13 cases with dermatomyositis. In 2012, 119 cases of IIM were reported to the Vaccine Adverse Event Reporting System (VAERS) database. During the coronavirus disease 2019 (COVID-19) pandemics, two mRNA COVID-19 vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) received emergency use authorization by the U. S. Food and Drug Administration (FDA) in December 2020, followed by viral vector vaccines ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and Ad26.COV2.S (Johnson and Johnson).

Most side effects attributed to vaccines are mild and transient. Nonetheless, rare more severe reactions, such as hypersensitivity and induction of autoimmunity may occur [12]. Cumulative evidence of new-onset autoimmune manifestations following COVID-19 vaccination have been reported (myocarditis, IgA vasculitis, Guillain-Barré syndrome, autoimmune liver diseases, etc [13]). It is postulated that mRNA vaccines exhibit a property of self-adjuvation, acting as both antigen and adjuvant. They are recognized by endosomal toll-like receptors (TLRs) and cytosolic inflammasome components driving inflammation and immunity [14]. Molecular mimicry has been also proposed as an immune mechanism in COVID-19, where viral proteins elicit immune cross-reactivity with human tissue self-antigens [13]. Few cases of IIM have been reported to date and some scientists have claimed to screen the presence of anti-MDA5 auto-antibodies in severe COVID-19 patients [15].

The main purpose of this study was to determine the global incidence of myositis-related auto-antibodies (non Jo1-RNA synthetases: anti-PL7, anti-PL12, anti-EJ, anti-OJ and RNA-sensor: anti-MDA5) in our laboratory during COVID-19 pandemics, and to describe the clinical and laboratory features of these patients.

2. Materials and methods

2.1. Study design

A single-centre retrospective observational study was conducted at the Hospital Clínico San Carlos of Madrid, Spain, which has a reference population of approximately 366,000 inhabitants. We retrieved 444 samples with 255 positive results obtained in our laboratory between January 1st, 2015 and December 31st, 2021. Patients with suspected IIM were tested for MSA against the following RNAAs: OJ (isoleucyl-tRNA synthetase), EJ (glycyl-tRNA synthetase), PL-12 (alanyl-tRNA synthetase), PL-7 (threonyl-tRNA synthetase); and MAA: antibodies anti-Ro52 (full-length Ro52) and anti-RNA sensor MDA5 (anti-melanoma differentiation-associated gene 5).

2.2. Patient clinical data

Data on demographics, clinical, and laboratory findings were recovered from the medical records of the 36 positive patients diagnosed in 2021 for clinical diagnoses of IIM, other autoimmune disorders, lung involvement and malignancy, from the time of symptoms onset until present. Written informed consent for clinical data and blood sample collection were requested.

2.3. Immunological assessment

For anti-nuclear antibodies (ANA), MSAs, and MAA antibody testing, two methods were used in parallel: indirect immunofluorescence (IIF) and immunoblot analysis, respectively.

2.3.1. Indirect immunofluorescence assay

ANA screening was performed using the IIF method on HEp-2 cells. Fluorescence patterns were evaluated in two ways: (i) by automated immunofluorescence microscopy using HELIOS Device software, automated IFA system and reader (AEEKU.GROUP GmbH, Wendelsheim, Germany), according to the manufacturer’s recommendations; and (ii) confirmed by two laboratory experienced specialists using the Nikon Eclipse E400 microscope. Sera with an antibody titer ≥1:100 were considered as positive: low titers ≥1:160, medium ≥1:320 and high titers ≥1:640. ANA patterns were based on the International Consensus on ANA Patterns (ICAP) standards.

In case of positive ANA result, samples were tested to determine the cellular specificity (anti-dsDNA and specific extractable nuclear antigens (ENAs): chromatin, centromere B, Sc1-70, RNP (RNP-A, RNP-68), Sm, RNP/Sm, Ro (SSA-52, SSA-60), SSB/La, Jo-1 and ribosomal P protein) using BioPlex® 2200 System (Bio-Rad Laboratories, Hercules [CA],

| Abbreviations | Descriptions |
|---------------|--------------|
| AI | autoimmune related disease |
| ANAs | Anti-nuclear antibodies |
| ARS | aminoaaryl-tRNA synthetase |
| ASS | antisynthetase syndrome |
| CAM | cancer-associated myositis |
| COVID-19 | coronavirus disease 2019 |
| DM | dermatomyositis |
| ENA | extractable nuclear antigens |
| FDA | the U.S. Food and Drug Administration |
| IBM | inclusion body myositis |
| ICAP | International Consensus on ANA Patterns |
| IFF | indirect immunofluorescence |
| IIM | idiopathic inflammatory myopathy |
| ILD | interstitial lung disease |
| IMNM | immune-mediated necrotizing myopathy |
| LI | lung involvement |
| MAA | myositis-associated antibodies |
| MCH | major histocompatibility complex |
| MDA5 | melanoma differentiation associated protein 5 |
| MSAs | myositis-specific antibodies |
| PE | phycoerythrin |
| SD | standard deviation |
| SLE | Systemic lupus erythematosus |
| TLRs | endosomal toll-like receptors |
| VAERS | Vaccine Adverse Event Reporting System |
US). This assay based on multiplexed technology, uses beads coated with individual antigens and murine monoclonal anti-human IgG antibody, conjugated to phycoerythrin (PE). The presence of any antibody in the patient sample is determined by the fluorescence of the dyes. Cut-off levels established were 10 IU/mL for anti-dsDNA Ab and 1 IU/mL for the remaining antibodies.

2.3.2. Immunoblot analysis

For MSAs and MMA, samples were analyzed by automated immuno-blotting using EUROBlotOne device (EUROIMMUN AG, Lübeck, Germany). Membrane strips with purified autoantigens (OJ, EJ, PL-12, PL-7, SRP, Jo-1, Ro52, PMSc100, PM-Sc175, Ku, SAE1, NXP2, MD5, TIF1γ, Mi-2α and Mi-2β) were used and incubated with previously diluted patient’s samples (1:100). Intensities of the strips were analyzed using the EUROLineScan system resulting in semi-quantitative units. Following the manufacturer’s recommendations, myositis antibody band intensity values were classified as: negative (≤7); low positive (8–34); positive (35–70); and strong positive (>70).

2.4. HLA typing

In order to analyze genomic DNA, MagNA Pure Compact Nucleic Acid Isolation Kit (Roche®, Darmstadt, Germany) was used for its extraction following the manufacturer’s procedures. To determine low resolution MHC Class I (HLA-A and -B) and Class II (HLA-DRB1, -DQA1 and -DQB1) typing, LIFECODES HLA-SSO Kit was utilized where polymerease chain reaction products were hybridized onto oligonucleotide probes attached to microspheres and labeled with streptavidin-conjugated phycocerythrin. These beads were analyzed with the Luminex® 100/200 TM System (Luminex Corp., Austin, Tex., USA) which is based on flow cytometry and uses the principles of xMAP® Technology.

2.5. Statistical analysis

Descriptive data and continuous variables are presented as mean ± standard deviation (SD) or median values (range, max - min), according to the normal or non-normal distribution of the data. Categorical variables were described as counts and percentages of subjects. Results were analyzed using Microsoft Excel (v.14.1.0) and GraphPad Prism software (version 8.1.0).

3. Results

3.1. Immunological and epidemiological characteristics of the study population

A total of 444 adult patients’ samples referred to the Immunology Department due to IIM suspicion were evaluated in the last 5 years. We identified a significant increase of anti-synthetase and RNA-sensor auto-antibodies coinciding with COVID pandemics (2020 and 2021) based on immunoblot results. An increase of MSAw incidence in 2020 and 2021 was observed, with two different patterns of antibodies specificities: patients with anti-MDA5 peaked to 68% (n = 28) in 2020; while patients with anti-PL7 and/or PL-12 autoantibodies (69%, n = 36) in 2021. Incidence of patients with MSAs from 2015 to 2021 varied from 0 to 19 (mean, 6.2) as shown in Fig. 1.

In 2021, we identified 36 adult patients with positive non-Jo-1 anti-ARS synthetase antibodies or anti-MDA5 MSA. The mean age of all patients was 64.30 ± 12.78 years (range: 27–87 years), with predominance in women (60%). The mean age of females and males were 62.90 ± 13.60 years (range: 27–87 years) and 66.75 ± 11.98 years (range: 43–85 years), respectively. All patients had received at least two-doses of vaccine against SARS-CoV-2, except for one patient who had received one dose. No further vaccination was administered in this patient due to severe adverse reaction (aseptic meningitis requiring hospitalization), and no previous SARS-CoV-2 infection was reported.

Fig. 1. Patients with positive myositis-specific auto-antibodies per year (from 2015 to 2021). The blue line shows the patients with auto-antibodies against anti-PL7 (aPL7) and/or anti-PL12 (aPL12); and the green line shows the cases of auto-antibodies against anti-MDA5 (aMDA5).

Natural immunity to prior SARS-CoV-2 infection was documented in only 5 patients (13.88%): 4 infected before vaccination and 1 patient after vaccination. The antibody patterns identified in these 36 patients were the following: anti-PL7 + PL12, anti-PL7, anti-PL12, anti-MDA5, anti-PL12 + Ro52. With respect to the type of vaccine administered, 55.56% (n = 20) received BNT162b2; 11.11% (n = 4) mRNA-1273; 8.33% (n = 3) ChAdOx1 nCoV-19; and 25% (n = 9) with a dual combination of vaccines (Pfizer, AstraZeneca, Moderna and Janssen). The median time from vaccine to MSAs positivity was 5 months.

3.2. Associated clinical expression and underlying conditions

Beyond traditional subgroups of polymyositis and dermatomyositis, patients were classified according to clinical manifestations: lung involvement (LI) (39%, n = 14); myopathy (25%, n = 9); autoimmune disease background, including: SLE, systemic sclerosis, anti-phospholipid syndrome, Raynaud phenomenon, rheumatoid arthritis and immune thrombocytopenia (17%, n = 6); LI and myositis (8%, n = 3); lung and cutaneous involvement (3%, n = 1) and underlying malignancy in cancer-associated myositis (CAM) (8%, n = 3). All but 1 of 36 patients were received anti-SARS-CoV-2 vaccine as mentioned above. Eight out of 36 patients (22%) reported onset of clinical manifestations soon after SARS-CoV-2 vaccination and 6 out of 36 (17%) presented clinical and/or radiological worsening after vaccination. According to Solomon anti-synthetase diagnosis criteria [16], a total of 14 patients meet criteria for ASS (39%), in 8 of them developed post SARS-CoV-2 vaccine. Interestingly, 2 patients with positive anti-PL7 Ab and clinical worsening of ILD and myopathy after vaccination had tested negative in 2020.

One patient developed bilateral pneumonia due to Chlamydia with onset 3–4 days after the 3rd dose of vaccine. After 3-weeks antibiotic treatment, marked ILD pattern persisted in thoracic CT. This patient had been diagnosed with bilateral hyperkeratosis dermatitis in hands two years before, which remitted a few days after the second dose of RNA vaccine. The youngest patient is a 27-year-old woman who had positive ANAs for 6 years without antigenic specificity, in the setting of a resolved febrile episode with thrombocytopenia. She developed anti-PL12 antibodies in November 2021 after the second dose of BNT162b2 (Pfizer-BioNTech).

Another patient was a 37-year-old woman with generalized arthralgia, Raynaud’s phenomenon and allergic asthma, diagnosed with fibromyalgia in May 2021. In November 2021, she went to her general practitioner due to worsening respiratory symptoms (cough, expectoration and dyspnea) after the second dose of BNT162b2 (Pfizer-BioNTech). A thoracic CT scan was normal and a myositis panel showed...
positivity for anti-PL12 and OJ antibodies.

One patient passed away due to respiratory insufficiency and another patient died associated with lung adenocarcinoma and myopathy.

### 3.3. Radiological findings

Overall, 10 patients had baseline pulmonary involvement before SARS-CoV2 pandemic. Of these, 6 (60%) experienced radiological worsening of their pulmonary pathology after the second dose of the vaccine, two patients with previous COVID19 infection. Two out of 36 patients (6%) presented onset of symptoms and radiological findings with diagnosis of nonspecific interstitial pneumonia (NSIP) and bronchiolitis obliterans organizing pneumonia (BOOP) after the first and third doses, respectively. No evidence of prior SARS-CoV-2 infection was reported in these patients. Another patient presented a pulmonary thromboembolism 3 months after ChAdOx1 nCoV-19 vaccine and an additional patient with pleural and pericardial effusion 2 months after the second dose of BNT162b2 (Pfizer-BioNTech).

### 3.4. Autoantibody testing

Screening testing resulted in the identification of one or more autoantibodies in our cohort. Whilst most of these cases had a single autoantibody specificity (63.8%), 10 patients (27.7%) had autoantibodies targeting multiple IIM autoantigens; and 8 patients associated positivity for anti-Ro52 Ab.

IIF-ANA screening was performed in 33 of patient sera showing the following patterns: homogeneous (9.09%), nucleolar (9.09%), speckled (12.12%), cytoplasmic (24.24%) including 3 clearly related to the PL12 antigen (Fig. 2) and 4 mixed patterns (12.12%). ANAs were negative in 33.33% of the patients. All of these patterns had been previously described in other laboratories associated with IIM. We also found related ENAS in 12.12% of cases.

### 3.5. Human leukocyte antigen alleles associations among idiopathic inflammatory myopathy

A total of 23 (64%) patients were studied for HLA typing. All patients presented with known HLA DRB1* allele associated with ASS: DRB1*03 (n = 6), DRB1*04 (n = 6), DRB1*11 (n = 4), DRB1*07 (n = 3), DRB1*01 (n = 2), DRB1*08 (n = 1), DRB1*13 (n = 1). DRB1*0301 allele was present in 6/23 (26%) of our patients, similar to previous studies. There were three patients with homozgyous haplotypes (13%), all of them associated myositis and lung involvement. The haplotype HLA-B*08:01, DQB1*02:01 and DRB1*0301 was identified in one patient with previous diagnosis of pulmonary fibrosis, in which clinical worsening was identified after SARS-CoV-2 vaccine associated to positive anti-MDA5 antibodies. This haplotype has been previously described associated to anti-Jo-1 autoantibodies. Interestingly, the presence of HLA-DRB1*07:01 was detected in other additional 3 patients - previously described as a protective factor against ASS-associate to ILD, rheumatoid arthritis and pericardial and pleural effusion post SARS CoV2 vaccine.

### 4. Discussion

A 6-fold increased incidence in ARS-synthetase and RNA sensors autoantibodies was observed in 2020–2021, with differential patterns. To note, autoantibodies directed to ARS have less than 5% prevalence in IIM, while are highly specific and strongly associated with complicating ILD [17]. In 2020, we observed an increase in positive cases for anti-MDA5 that could be attributed to the recognition of the coronavirus through RNA sensors inducing an antiviral response by producing type-I interferons and tumor necrosis factor (TNF). On the other hand, in 2021 there was an increase in anti-PL-7 and anti-PL-12 autoantibodies, suggesting that SARS-CoV-2 vaccination might induce a strong reactions between Spike 1 proteins and a variety of tissue antigens in genetically predisposed individuals. It has been postulated that the presence of IIM antibodies in sera from patients suffering from myositis reflects a previous specific viral infection, based on previously reported interaction between some synthetases and the RNA of certain picornaviruses [18, 19]. A study in dermatomyositis patients identified three T cell receptor epitopes specific to SARS-CoV-2 suggesting a potential for the virus to contribute to myositis development [20]. In our cohort, only 4 patients had prior SARS-CoV-2 infection before vaccination, one of them after the second dose, which would not justify the remaining positive cases. Vaccine-associated autoimmunity in other diseases is a well-known phenomenon [14] for instance, in genetically predisposed subjects who have an impaired clearance of nucleic acid [21]. Unfortunately, no clinical data of anti-MDA5 positive patients in 2020 was available. Recently, demographic and clinical features of myositis following COVID-19 vaccination have been reported [22–25]. Some authors have suggested that ARS autoantibodies are overexpressed in damaged muscle cells and their pro-inflammatory properties leads to the development of myositis [26]. Eloranta et al. suggested that immune complexes containing either anti-Jo-1 or anti-Ro in the presence of RNA may act as endogenous inducers of type 1 IFN-α. We hypothesize that the lysis of muscle cell fibers by specific anti-spike CD8+ T cells after mRNA COVID-19 vaccine injection might lead to the release of cryptogenic epitopes and RNA transferases that in turn would trigger the production of MSAs in genetically predisposed individuals (Fig. 3).

COVID-19 mRNA vaccine in individuals suffering a pre-existent immune dysregulation has not been investigated. It has been hypothesized that immunosuppressive agents mitigate or even prevent side effects related to vaccine immunogenicity. In our cohort, most of the positive cases occurred in patients with autoimmune background or underlying autoimmune disease (AD). As a unifying characteristic of ADs,
serological expression of autoantibodies associate with specific diseases and often exhibit pathogenic potential [27].

In the last years, two important concepts in autoimmunity have been described: “Overt Polyautoimmunity” implying clinical coexistence of two or more ADs fulfilling classification criteria, and “Latent Polyautoimmunity” described as the presence of autoantibodies unrelated to an index AD, without clinical criteria fulfillment [28–30].

In our cohort, most of the patients with myositis-related autoantibodies had autoimmune background or an unclassified autoimmune disease. There were 6 new-onset of AD in 7 patients, all women (crioglobulinemic vasculitis, myositis, Sjögren syndrome, rheumatic polymyalgia). Given the presence of MSAs autoantibodies, close monitoring should be necessary since prognostic and therapeutic implications may be important. Therefore, recent publications indicate that those patients with latent PolyA may develop overt PolyA in the future [29].

Recognition of differential immunological patterns on autoimmunity may allow the implementation of personalized strategies in the management of AD [28]. Despite no specific MSAs pattern was identified probably related to the limited number of patients, prospective studies are needed to relate the presence of previous autoantibodies with post classification clinical characteristics and genetic and epidemiological factors.

As published, young and female patients who are already affected or predisposed to autoimmune or autoinflammatory disorders should be carefully evaluated for the benefits and risks of COVID-19 mRNA vaccination [31].

SARS-CoV2 vaccination could have accelerated an on-going disease process. Our data revealed an increase in the incidence of ARS-synthetase antibodies within approximately 5 months after SARS-CoV2 vaccination. As we mentioned before, some vaccines may trigger autoimmunity in genetically predisposed individuals. SLE onset was reported after different vaccinations, while narcolepsy was reported as having a strong link with HLA-DQB1*0602 allele after H1N1 vaccine [32]. To date, 8.1 ancestral haplotype-associated alleles DRB1*0301 and B*0801 are the main HLA risk markers for IIM [33]. The most prevalent alleles identified were DRB1*03:01, DRB1*04, DRB1*11:01, corresponding to 70% (16/23) of our cohort. Another allele identified was DRB1*04 (26%), linked mostly to myositis and Raynaud phenomenon. Interestingly, we also found 13% of HLA homozygous, that has been described as a gene dose effect in celiac disease and associated with worse clinical course. No specific MSAs pattern was associated to HLA-DRB1 and HLA-B carrier in our cohort. Therefore, we consider of great value to determine the association between HLA risk alleles and the severity of IIM as a part of future research.

Only 63.8% of our patients were positive for ANAs, suggesting that certain MSAs (especially anti-ARS autoantibodies) can yield a negative or only weakly positive ANA test, yet a cytoplasmatic speckled staining pattern should be present but is often not reported by some laboratories...
work of our nurse Antonia Rodríguez de la Peña contributed to the immunological study of IIM. The authors would like to acknowledge the careful and excellent work of our nurse Antonia Rodríguez de la Peña at the Immunology Department of the Hospital Clínico San Carlos. We are sincerely grateful to all patients who participated in this study.

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References

5. Conclusions

Our study showed that SARS-CoV-2 vaccination could represent a precipitating factor for the diagnosis of IIM and other autoimmune diseases in genetically predisposed patients. Although anti-ARS antibodies are rarely found in patients with MII, they are considered highly specific as well as a biomarker of worse prognosis. Therefore, awareness and clinical suspicion of autoimmunity following SARS-CoV-2 vaccination is critical for early therapeutic intervention. The underlying immunological mechanism between myositis-associated autoantibodies specific patterns pre and post vaccination warranted further investigation.

Author contributions

JOG, MC and SSR contributed to the conception and design of the study. LGB, KMM and TGG contributed to the database, figure and analysis. LGB wrote the first draft of the manuscript. SSR carefully reviewed the manuscript. All authors contributed to manuscript revision, read and approved the submitted version. AR, CC and BL has contributed to the immunological study of IIM.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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