

Idiopathic inflammatory myopathies and COVID-19: an intriguing liaison?

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In this issue, Kharouf *et al.* reported an increased rate of diagnosis of idiopathic inflammatory myopathies (IIMs) during the COVID-19 pandemic compared to pre-pandemic period. Furthermore, they observed that the newly diagnosed patients displayed different demographic characteristics and more severe course of the disease than that observed before the pandemic, although the prognosis remained unchanged. They suggested that both the SARS-CoV-2 infection and SARS-CoV-2 mRNA vaccines could have been possible triggers for IIMs appearance (1).

Their observation is surely interesting and in line with the common idea of a possible link between infections and the development of autoimmunity (2), particularly, between viruses and IIMs. Since the beginning of this pandemic, we have analysed the possible immunological mechanisms involved in the development of autoimmune diseases following SARS-CoV-2 infection. Our hypothesis was mainly based on the scientific reports published up to then and our experience in other immune-mediated diseases where viruses have been recognised as triggers of disease development in genetically predisposed subjects (3-5).

Despite the different pitfalls of the paper, clearly stated by the authors, we think that the possible link between SARS-CoV-2 infection and development of IIMs deserve attention, and it may be also worthy of debate for the medical community.

How SARS-CoV-2 infection can impact the natural history of autoimmune diseases, in particular IIM have not yet been clarified, but up to now several studies have contributed to adding a piece to this complex debate. It has been postulated that an overactive innate immune response to SARS-CoV-2

might contribute to the development of autoimmune diseases. SARS-CoV-2 is capable of interfering with the correct functioning of some pathways of the adaptive immune response, leading to a hyperactivity of cellular components of the adaptive immune system with consequent production of autoantibodies. Undoubtedly, the increased rate of IIMs during the COVID-19 pandemic is an excellent starting point for discussion and ideas for further studies, in spite of some limitations of this report. First of all, this study is a retrospective analysis and a report from a single centre, probably a reference centre in the pandemic period. Furthermore, the authors did not report the laboratory tools used for detecting myositis specific and associated autoantibodies (MSA and MAA, respectively). In addition, data on these autoantibodies was not available in all cases, thus reducing the possibility of comparison between the two sub-cohorts analysed (pre- and during pandemic). Finally, the authors were not able to differentiate between patients who experienced COVID-19 before vaccination and those vaccinated without having previously contracted the infection. In fact, in the report the levels of anti-SARS-CoV-2 antibodies in both vaccinated and not vaccinated patients were not assessed. Consequently, the possible triggers for IIMs appearance in the sub-cohort of COVID-19 pandemic period could be both the SARS-CoV-2 infection and the anti-COVID-19 mRNA vaccines. As Italy was the first Country of the Western World to deal with COVID-19, and both our Hospitals were COVID-19 hub centres, we agree with the diagnostic difficulties encountered. In fact, identifying the subjects who had contracted COVID-19 was not easy at the beginning of the pandemic, due to the

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lack of nasal swabs and of laboratory able to perform the diagnostic tests (6). However, the occurrence of clinical features of SARS-CoV-2 infections, such as anosmia, ageusia, fever and pneumonitis and its time of appearance with respect to IIMs diagnosis could have been an indirect method to evaluate the occurrence and the temporal relationship between the two events. The time relationship is relevant for such cases, as recently reported in some antisynthetase syndrome patients that had a disease flare in the six months following COVID-19 healing (7). Furthermore, this observation is another evidence showing that viruses have an impact on conditions referring to myositis spectrum disorders.

We have to take in account that the testing for anti-SARS-CoV-2 antibodies before the vaccination could have been useful in order to confirm, at least in some cases, if the patients had effectively contracted the infection, adding further confirmation to authors' hypothesis. To this purpose, we agree that male gender prevalence supports the link between the infection and the disease, in line also with the established worst outcome of males with COVID-19 (8), but it is peculiar to observe that only one of the newly diagnosed IIMs had interstitial lung disease (ILD). Furthermore, lung is between the most common targets of COVID-19, and similarities between SARS-CoV-2 pneumonitis and IIMs-ILD have been reported, further strengthening the possible association between virus infection and IIMs appearance (9).

Due to the period in which the study was conducted with anti-SarsCov-2 vaccination campaign already started, the authors suggested that a potential trigger for IIMs appearance could be the SARS-CoV-2 mRNA vaccines. Up to now the data regarding a possible direct relationship between SARS-CoV-2 mRNA vaccines and IIMs development are scarce and often conflicting, as observed by the authors. However, it has been postulated that the post-transcriptional spike proteins produced by the SARS-CoV-2 mRNA vaccines may contribute to the stimulation of the adaptive immune system, result-

ing in the development of IIMs. If such hypothesis is correct, reasonably the persistence of spike proteins in COVID-19 should be a stronger trigger than that induced by the vaccination (10). In vaccinated IIMs patients, the short-term adverse events were not different with respect to other autoimmune diseases and healthy controls, except for a higher risk of rash, in particular in dermatomyositis with active disease (11). If these observations are in line with the occurrence of a link between IIMs and viruses, further confirmation may be obtained when we consider the physiological action of the antigens targeted by 3 of the most important myositis-specific and associated antibodies: the anti-melanoma differentiation antigen 5 (MDA5), the antisynthetase, and the anti-Ro52 antibodies.

The anti-MDA5 antibodies are MSA associated with the occurrence of a peculiar subset of dermatomyositis (the recently defined anti-MDA5 syndrome) at increased risk of respiratory failure (rapidly-progressive ILD), that is commonly presenting in a seasonal pattern (9, 12, 13). The target of these autoantibodies is the MDA5, a cytosolic enzyme encoded in humans by the IFIH1 gene, located on chromosome 2. MDA5 acts as a viral RNA receptor, detecting long-duplex RNAs in the genome of double stranded RNA (dsRNA) viruses or dsRNA replication intermediates of positive-strand viruses (14). MDA5 exerts an anti-viral action by activating type I interferon and NF-Kappa B pathways (15-18), the same pathways involved in anti-MDA5 syndrome (15, 19-21). Interestingly, pulmonary clinical and imaging features of severe COVID-19 pneumonia closely resemble those of anti-MDA5 positive rapidly progressive (RP)-ILD, and typical laboratory biomarkers, such as high ferritin, C-reactive protein (CRP) and lactate dehydrogenase (LDH) serum levels and lymphopenia, are recognised as negative prognostic factors in both conditions (22, 23). Moreover, anti-MDA5 autoantibodies were detected in almost 50% of patients from a Chinese cohort, with their presence being associated to a severe course and mortality (24). Finally, treatment with JAK inhibitors was

able to dramatically improve the outcome of both IIM-related RP-ILD and severe COVID-19 pneumonia (25, 26). All these evidences strongly support the idea of common pathways and even similar aetiology in the two diseases.

The antisynthetase antibodies are markers of the so-called antisynthetase syndrome, characterised by the classic triad arthritis, myositis, and ILD (27). These antibodies are addressed against different aminoacyl tRNA synthetases (ARS), cytoplasmic enzymes primarily involved in protein synthesis, and responsible for the pairing of specific aminoacid to its cognate tRNA. However, ARS have several other functions mediated by domains appended during evolution to the different enzymes (28, 29), mainly regulating different aspects of both the innate and adaptive immune systems (30, 31). ARS seem to be as an essential cellular sensor and immunoregulator upon infection, in particular for RNA virus (32). ARS can be released from the multi-ARS complexes (33), and act as active cytokines to modulate host innate immune response. Furthermore, ARS can be recruited by viruses to perform essential functions, such as virus entrance, replication, and secretion (32). It is interesting to observe that the loss of function of some ARS is associated with a systemic inflammatory syndrome characterised by lung involvement and high interferon scores (34).

The anti-Ro52 antibodies are MAA, observed in about the 50% of patients with antisynthetase syndrome (35, 36), and in about the 30% of patients with anti-MDA5 syndrome (8). These autoantibodies target the Tripartite motif-containing protein 21 (TRIM21) (37). TRIM21 is a cytosolic FC binding protein mainly involved in the intracellular antibody-mediated proteolysis pathway, crucial in the host defence against viruses (38, 39). In particular, it has been shown that the detection of the internalised antibody-virus complex by TRIM21 is responsible for activating inflammatory signalling pathways via production of inflammatory cytokines and chemokines, and it triggers an indirect antiviral antibody-dependent intracellular neutralisation (40).

It is surely interesting to observe that some of the most important MSA and MAA target antigens are strongly involved in the tight interaction between viruses and the immune system, generally acting on type I interferon and NF-Kappa B pathways, that are recognised as key players in the pathogenesis of IIMs (41, 42).

It is obvious that at present the evidence of a causative association between COVID-19 and some forms of IIMs remains largely unproven and hypothetical. Yet, we feel that the increased rate of IIMs during the pandemic is certainly sufficient to postulate an intriguing liaison between SARS-CoV-2 and autoimmunity, and stimulates more detailed prospective studies.

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