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LETTERS OF BIOMEDICAL AND CLINICAL RESEARCH

Clinical evolution of antisynthetase syndrome after SARS-CoV2 infection: a 6-month follow-up analysis

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Dear Editor

Although the effect of COVID-19 on patients with rheumatic disorders has been extensively assessed [1–3], the influence of SARS-CoV2 infection on the clinical course of these diseases is not fully elucidated. Diffuse lymphadenopathy and cerebritis have been reported as short-term flare-up manifestations of systemic lupus erythematosus (SLE) after COVID-19 [4, 5]. To the best of our knowledge, however, no data on longer periods are available, neither for SLE nor for other connective tissue diseases. By considering the shared expertise on antisynthetase syndrome (ASSD) [6, 7], our centres evaluated the 6-month clinical evolution of ASSD after COVID-19, looking for disease flares or the de novo occurrence of clinical findings. We have identified 12 patients, mainly females (n = 9, 75%), with a median age of 51 years (interquartile range — IQR 48–63.5) and a median ASSD disease duration of 60.5 months (IQR 21–77) at COVID-19 onset. The complete form of ASSD (arthritis, myositis and interstitial lung disease — ILD) was observed in 7 cases (58%), and 11 patients (92%) had ILD. At the time of SARS-CoV2 infection, all patients had a well-controlled ASSD for at least 6 months and did not receive the SARS-CoV2 vaccine, because it was not available at the time of their infection. As previously reported [8], immunosuppression was managed, by maintaining cyclosporine, and stopping azathioprine and methotrexate, whereas COVID-19 was treated according to the guidelines available at that time. Corticosteroids were maintained at the same or increased dosages according to COVID-19-related needs. Six patients (50%) were admitted to the hospital, mostly for COVID-19-related pneumonia (5 patients, 41.6%). Healing was achieved when patients were asymptomatic for acute COVID-19 manifestations and displayed at least one negative polymerase chain reaction (PCR) for SARS-Cov2 on a nasal swab. The median time to COVID-19 healing was 20 days (IQR 13.5–31). Two weeks after the healing, patients resumed previously stopped immunosuppressants. Among

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Table 1 "Patients' and disease's characteristics and outcomes": characteristics of enclosed patients for both disease and COVID-19 and results of pulmonary function tests before SARS-CoV2 infection (no more than 3 months) and 6 months after the healing from COVID-19

Patients' disease characteristics at COVID-19 infection									COVID-19 characteristics		
Patient	Sex	ARS	Anti-Ro52	Age (years)	Disease duration (months)	ASSD triad	Lung pattern	Ongoing treatment	COVID-19 length (days)	Hospital admission	Dyspnoea
1	m	Jo1	Negative	68	22	AMI	NSIP	Cys + MTX + PDN (5 mg/day) + O_2 (intermittent)	16	yes	yes
2	f	Jo1	Negative	26	103	AMI	UIP	Cys	24	No	No
3	f	Jo1	Negative	50	141	MI	NSIP + OP	Aza + HCQ + PDN (6.25 mg/day)	42	No	No
4	f	Jo1	Positive	38	91	AMI	NSIP	Cys	10	No	No
5	f	Jo1	Negative	49	41	AMI	NSIP	Cys + MTX + HCQ + PDN (5 mg/day)	6	Yes	Yes
6	f	PL7	Positive	51	19	MI	NSIP	Cys + PDN (7.5 mg/day) + O_2 (intermittent)	46	No	No
7	m	Jo1	Negative	44	72	AMI	OP	Cys + Aza + PDN (7.5 mg/day)	16	No	No
8	f	PL12	Negative	65	68	AM	–	MTX	28	No	No
9	m	Jo1	Negative	60	58	AMI	NSIP	MTX	50	Yes	Yes
10	f	PL7	Negative	51	12	MI	NSIP	MTX + PDN (5 mg/day) + O_2 therapy (intermittent)	14	Yes	Yes
11	f	Jo1	Negative	85	63	AMI	NSIP	Cys + PDN (7.5 mg/day) + O_2 (intermittent)	24	Yes	Yes
12	f	PL7	Positive	63	16	I	NSIP	–	9	Yes	Yes
COVID-19 characteristics					ASSD manifestations outcome						

Table 1 (continued)

Patient	Minimum SaO2	T max (°C)	Other symptoms	Covid-19 treatment	Disease flares (months after COVID-19)	New clinical findings (months after COVID-19)	Basal FVC	6 months FVC		Basal DLCO	6 months DLCO	
1	90	38.5	-	Desa + Rem + LWMH + O2	Lung (2), joints (4)	Raynaud's phenomenon (1), pulmonary hypertension (6), myocarditis (6)	87	84	p=0.128*	59	40	p=0.684*
2	97	37.5	Anosmia, diarrhea, headache	–	No	No	62	58		54	44	
3	98	36.4	Anosmia	–	No	No	106	99		57	78	
4	97	37.9	Anosmia, headache	–	No	No	80	84		76	75	
5	92	38.5	Diarrhea	Desa + LWMH	No	No	83	94		59	66	
6	97	37.7	Anosmia, ageusia	–	No	No	38	46		32	33	
7	98	36.5	Anosmia	–	No	No	78	77		45	47	
8	98	37.5	Anosmia, ageusia, headache	–	No	No	136	102		95	101	
9	93	38	Headache	–	No	No	94	85		95.6	128	
10	89	38	Diarrhea, Headache	PDN	No	No	82	82		45	42	
11	90	38	Anosmia	Desa + LWMH + O2	No	Diaphragm impairment (6)	69	42		42	35	
12	95	38	Anosmia, ageusia	–	No	no	114	100		51	45	

ASSD antisynthetase syndrome, *ARS* anti-aminoacyl tRNA synthetase antibodies, *T max (°C)* maximum body temperature in Celsius degree, *m* male, *f* female, *PL7* anti-threonyl-tRNA synthetase antibodies, *PL12* anti-alanyl-tRNA synthetase antibodies, *Jo1* anti-histidyl-tRNA synthetase antibodies, *AMI* arthritis, myositis, interstitial lung disease, *MI* myositis, interstitial lung disease, *AM* arthritis, myositis, *I* interstitial lung disease, *NSIP* non-specific interstitial pneumonia, *UIP* usual interstitial pneumonia, *OP* organizing pneumonia, *Cys* Cyclosporine, *MTX* methotrexate, *Aza* Azathioprine, *PDN* prednisone, *HCQ* hydroxychloroquine, *FVC* forced vital capacity, *DLCO* diffusing capacity for carbon monoxide, SaO_2 peripheral oxygen saturation, O_2 oxygen, *Desa* dexamethasone, *Rem* remdesivir, *LWMH* low weight molecular heparin

*Statistical analysis by paired sample *t*-test

the patients, 2 (17%) experienced significant changes in the clinical status of ASSD.

Patient 1 developed Raynaud's phenomenon after 1 month, and severe dyspnoea, which led to oxygen supplementation after 2 months. High-resolution computed tomography (HRCT) showed ILD worsening, with the appearance of ground-glass opacities (GGOs) and extension of reticulations. We transiently increased prednisone to 50 mg/day and started an anti-fibrosing drug (nintedanib) with benefit. After 4 months, the patient had an articular flare. At month 5, after prednisone tapering, dyspnoea worsened. Chest CT scans showed a reduction of GGOs and no signs of pulmonary thromboembolism. Pulmonary function tests (PFTs) were repeated, confirming a restrictive pattern with stable forced vital capacity (FVC), but showing a severe reduction of diffusing capacity for carbon monoxide (DLCO) compared to pre-COVID PFTs. At month 6, precapillary pulmonary hypertension was diagnosed at the right heart catheterization. Furthermore, magnetic resonance imaging showed signs of chronic myocarditis. The patient started sildenafil and rituximab. Patient 11 had a worsening of the dyspnoea starting from month 4 and was reassessed at month 6. Chest HRCT was stable, but a significant impairment (ultrasound assessment) and superelevation (chest X-rays) of the diaphragm were observed, leading to high doses of corticosteroid treatment. In Table 1, we report the main clinical variables collected and the results of PFTs before (no more than 3 months) and after (6 months) COVID-19. For both FVC and DLCO, no statistically significant differences were observed at the 2 established timepoints.

Our results confirm that, after healing, COVID-19 may trigger ASSD flares and induce previously lacking clinical findings. To the best of our knowledge, this is the first paper evaluating, in a prolonged period, the outcome of a rheumatic disease after SARS-CoV2 infection. A strict clinical-instrumental follow-up is necessary for ASSD patients after healing from COVID-19 because of the risk of possible worsening of the disease. In conclusion, our results support the SARS-CoV2 vaccination strategy for autoimmune diseases.

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Data availability The data that support the findings of this study are available on request from the corresponding author, VV. The data are not publicly available due to their containing information that could compromise the privacy of research participants. Data are stored in a secured pc with limited access.

Declarations

Ethics approval This study was approved by Ethics Committee Area Pavia (protocol code 20200046007, date 05/06/2020).

Disclosures None.

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