Evidence of autoimmunity triggered by SARS-CoV-2 in acute and Post-acute COVID-19: a systematic literature review

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Abstract

Accumulating evidence suggest that autoimmune phenomena are frequent during Coronavirus Disease 2019 (COVID-19) and may lead to clinically overt disease. The breakdown of immune tolerance and/or impaired immune reconstitution after the initial phase may be involved in the pathogenesis [1]. The ensuing autoimmunity may also be involved in Post-Acute COVID syndrome (PACS) [2]. Herein, we evaluate the current scenario based on anecdotal patient reports of new-onset autoimmune disease/diagnosis as a sequalae of COVID-19.

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To the Editor,

Accumulating evidence suggest that autoimmune phenomena are frequent during Coronavirus Disease 2019 (COVID-19) and may lead to clinically overt disease. The breakdown of immune tolerance and/or impaired immune reconstitution after the initial phase may be involved in the pathogenesis [1]. The ensuing autoimmunity may also be involved in Post-Acute COVID syndrome (PACS) [2]. Herein, we evaluate the current scenario based on anecdotal patient reports of new-onset autoimmune disease/diagnosis as a sequalae of COVID-19.

A literature review was performed on PubMed from March 1, 2020, to September 15, 2021. Medical Subject Heading (MeSH) terms included "SARS-CoV-2" OR "COVID-19" AND "autoimmunity". Extracted data included sex, age, COVID-19 severity, detected autoantibodies, the precise autoimmune diagnosis, time from COVID-19 to the autoimmune disease diagnosis as well as the outcome. We screened 910 articles by title and abstract; 44 were deemed eligible for further analysis (**see online methods**). There were two systematic reviews reporting on 33 and 94 patients respectively who developed autoimmune diseases shortly after the onset of COVID-19 (mean time 9.8 days) [3, 4]. The cases included in these studies are not reported here.

Thirty-two patients (15 females, mean age 48.7±19.6 years) developed an organ-specific or systemic autoimmune disease during the acute phase of COVID-19 (**Table 1**). All but one (31/32) were hospitalized; 5/32 required mechanical ventilation. Three patients succumbed for a mortality rate of 9.38% (Table 1).

Eighteen patients (11 females, mean age 50.9±20.9 years) developed an autoimmune disease shortly after recovery from COVID-19 (**Table 2**) Eight patients were hospitalized (none required mechanical ventilation) and ten recovered at home; all survived (Table 2). The mean time from COVID-19 diagnosis to the diagnosis of the autoimmune disease was 40±25 days.

In this systematic review, we identified 50 patients who developed an organ-specific or systemic autoimmune disease during the acute phase or shortly after COVID-19. Another 127 patients had been identified in the reviews of Saad *et al* . [3] and Taherifard *et al* . [4]. Interestingly, there was no significant predominance of females in post-COVID-19 autoimmune diseases. The age of the patients was ranging from 15 to 85 years.

During the acute phase of COVID-19, autoimmunity mainly manifests with cytopenias. Immune thrombocytopenic purpura was the most common manifestation (59/159 early cases), followed by autoimmune hemolytic anemia (31/159) and thrombotic immune-mediated disorders (19/159) (pooled analysis). Autoimmune neurologic diseases were the second most common during the acute phase of COVID-19. From the pooled analysis of the present study and that of Saad et al. [3] (n=83 in total), 17 patients developed Guillain-Barre Syndrome (all of them in the first 2-3 weeks after diagnosis) whereas 6 were diagnosed with myasthenia gravis and another 13 with various other syndromes (mainly encephalitis). The ACE-2 receptor expression on the surface of neuronal cells may underlie the pathogenesis of neurologic diseases during COVID-19 [5].

Systemic autoimmune diseases were diagnosed in 14 patients (5 SLE, 7 ANCA-associated vasculitis, one polymyositis and one systemic sclerosis). While infections are related to acute exacerbations of systemic autoimmune diseases, their association with *de novo*development of overt autoimmunity is less well known. Given that the formation of disease-specific autoantibodies often precedes the diagnosis of systemic autoimmune diseases, it is still questionable if SARS-CoV-2 is the sole cause of these entities. That said, recent report suggest autoantibodies targeting common autoantigens or cytokines develop *de novo* during severe COVID-19 acute phase [6]. This may underlie these reported diagnoses (Table1/2) and future PACS symptoms.

In conclusion, multiple organ-specific and systemic autoimmune diseases have been diagnosed in the acute phase and as a sequela of COVID-19. During the acute phase, autoimmune cytopenias and immune-mediated

neurologic disorders are the most common manifestations of clinical autoimmunity whereas systemic autoimmune diseases seem to develop after recovery. The significance of post-COVID-19 autoimmunity is expected to grow in the near future and detailed investigations are warranted to delineate the pathogenic characteristics of this association and/or confirm causation.

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Author contributions: MM conceived the idea and takes overall guarantee of the paper. KT wrote the first draft and RJ assisted with the review/search and development of manuscript.

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Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 First-author	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 PMID**	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 Age/Sex**	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 Severity**	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 Outcome**	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 Autoantibodies detected**	**Table 1. Patients developing autoimmune diseases during the acute phase of COVID-19 Autoimmune disease**

Mantovani-Cardoso et al.	**32720260**	18 / F	Mechanical Ventilation	Fatal	ANA, anti-dsDNA, anticardi-olipin antibodies, lupus anticoagulant	Systemic Lupus Erythematosus
Slimani et al.	**32926434**	23 / F	Mechanical Ventilation	Fatal	ANA, anti-dsDNA, anticardi-olipin antibodies (IgM, IgG), lupus antico-agulant, anti-b2-glycoprotein I (IgG, IgA)	Systemic Lupus Erythematosus
Bonometti et al.	**33015814**	85 / F	Hospitalized	Survived	ANA, anti-Ku antibodies, atypical ANCA	Systemic Lupus Erythematosus
Gracia-Ramos & Saavedra-Salinas.	**33543338**	45 / M	Hospitalized	Survived	ANA	Systemic Lupus Erythematosus
Hussein et al.	**32923243**	37 /F	Mechanical Ventilation	Fatal	ANCA	Granulomatosis with polyangiitis
Uppal et al.	**32839744**	64 / M	Hospitalized	Survived	Anti-MPO ANCA	Glomerulonephrit
Uppal et al.	**32839744**	46 / M	Hospitalized	Survived	Anti-PR3 ANCA	Glomerulonephrit
Moeinzadeh et al.	**32361703**	25 / M	Hospitalized	Survived	ANCA	Glomerulonephrit
Delamarre et al.	**32651243**	51 /M	Hospitalized	Survived	IgG autoantibodies	Acute necrotizing encephalopathy
Gutiérrez-Ortiz et al.	**32303650**	50 /M	Hospitalized	Survived	Anti-GD1b IgG antibodies	Miller Fisher Syndrome
Gutiérrez-Ortiz et al.	**32303650**	39 / M	Hospitalized	Survived	Anti-GD1b IgG antibodies	Polyneuritis cranialis
Pinto et al.	**32522768**	44 / F	Hospitalized	Survived	Anti-MOG IgG antibodies	Anti-MOG disease
Zhou et al.	**32604245**	26 / M	Hospitalized	Survived	Anti-MOG IgG antibodies	Anti-MOG disease

Sriwastava et al.	**33047223**	65 / F	Hospitalized	Survived	Acetylcholine receptor binding antibody Striational antibody Acetylcholine receptor modulating Antibody	Ocular Myasthenia gravis
Restivo et al.	**32776781**	64 / M	Hospitalized	Survived	Acetylcholine receptor antibodies	Myasthenia Gravis
Restivo et al.	**32776781**	68 / M	Hospitalized	Survived	Acetylcholine receptor antibodies	Myasthenia Gravis
Restivo et al.	**32776781**	71 / F	Mechanical Ventilation	Survived	Acetylcholine receptor antibodies	Myasthenia Gravis
Harris & Mushref	**33521256**	21 / F	Recovered at home	Survived	Thyroid stimulating immunoglobulin antibodies Thyrotropin receptor antibodies	Grave's Disease
Vadlamudi et al.	**32850163**	23 / F	Hospitalized	Survived	Anti-immunoglobulin G and anti-complement antibodies	Evans Syndrome
Hossri et al.	**32512349**	29 / F	Mechanical Ventilation	Survived	Anticardiolipin antibodies (IgM, IgG)	Antiphospholipid syndrome
Hossri et al.	**32512349**	58 / M	Hospitalized	Survived	Anticardiolipin antibodies (IgM, IgG)	Antiphospholipid syndrome
Gruden et al.	**33995989**	83 / F	Hospitalized	Survived	Antiplatelet antibodies	Severe immune thrombocytopenia (ITP) and hemolytic anemia
Liput et al.	**33927918**	33 / F	Hospitalized	Survived	Anti-IgG and anti-C3 antibodies	Warm Autoimmune Hemolytic Anemia
Gaughan et al.	**33397771**	16 / F	Hospitalized	Survived	Anti-Ro and anti-GAD antibodies	Encephalopathy

Jumah et al.	**33607505**	61 / M	Hospitalized	Survived	IgG anti-MOG antibodies	Myelitis
Allahyari et al.	**33904138**	18 / F	Hospitalized	Survived	Anti-NMDAR antibodies	Anti-NMDAR Encephalitis
Duran et al.	**34100115**	26 / M	Hospitalized	Survived	Anti-myeloperoxidase and anti-proteinase 3 antibodies	ANCA-associated vasculitis (AAV)
Duran et al.	**34100115**	36 / F	Hospitalized	Survived	Anti-proteinase 3 antibodies	ANCA-associated vasculitis (AAV)
Reiff et al.	**34353302**	17 / M	Hospitalized	Survived	c-ANCA and anti-proteinase 3 antibodies	ANCA-associated vasculitis (AAV)
Alfishawy et al.	**34368517**	17 / M	Hospitalized	Survived	Anti-GAD and islet cell antibodies	Pancreatitis and type 1 diabetes
Maritati et al.	**34373831**	64 / M	Hospitalized	Survived	Anti-proteinase 3 antibodies	Pauci-immune glomerulonephriti
Bahramnezhad et al.	**34321077**	56 / M	Hospitalized	Survived	Anti-phospholipid antibodies	Anti-phospholipid syndrome

ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein	ANA: antinuclear antibodies, ANCA: antineutrophil cytoplasmic antibodies, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, MPO: myeloperoxidase, PR3: proteinase 3, MOG: myelin oligodendrocyte glycoprotein

Table 2. Patients developing autoimmune diseases after the acute phase of COVID-19

First-author
Zamani et al.
Corrêa et al.
de Ruijter et al.
Gigli et al.
Assini et al.
Brancatella et al.
Mateu-Salat et al.
Marchand et al.
Sacchi et al.
Bhandarwar et al.
Ayuso et al.
Masuccio et al.
Fineschi et al.
Knack et al.
Mausoleo et al.
Qureshi & Bansal
Lanzolla et al.
Emekli et al.
ANA: antinuclear antibodies, CCP: cyclic citrullinated peptides, ANCA: antineutrophil cytoplasmic antibodies, MPO: myel