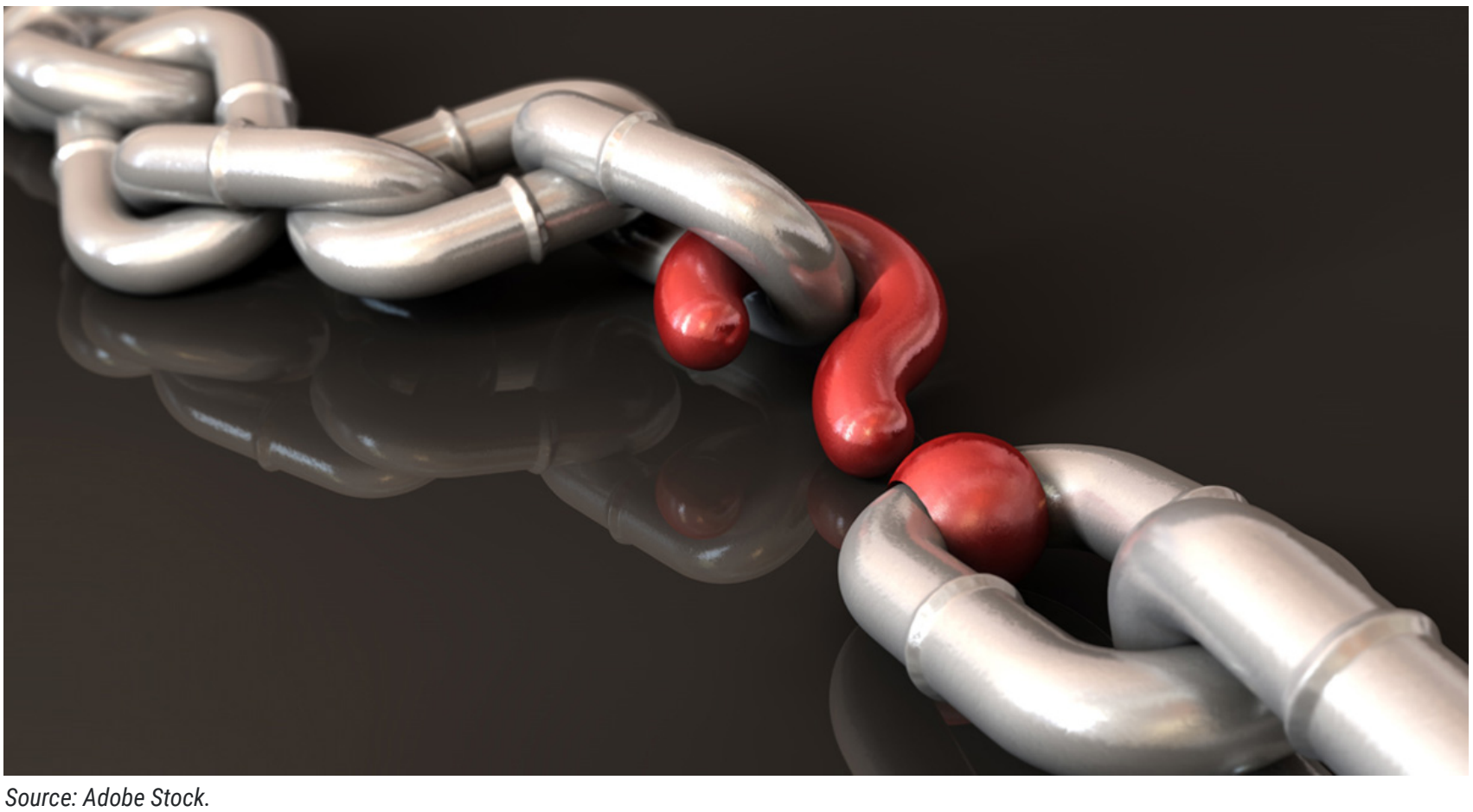
May 20, 2021 13 min read

Missing link: Lingering questions at the intersection of COVID-19 and autoimmunity

While there are few certainties when it comes to COVID-19, an indisputable body of data shows that individuals who acquire the virus produce a significant number of autoantibodies.

However, at the moment, why those autoantibodies are produced, and when, and what they mean for patients with immune-mediated inflammatory diseases, is anyone's guess.



Source: Adobe Stock.

"I think there is potential for autoimmunity living inside all of us," **Jason S. Knight, MD, PhD,** Marvin and Betty Danto Research Professor of Connective Tissue Research and associate director of the Lupus Program at the University of Michigan, told *Healio Rheumatology.* Severe COVID-19 "likely creates an emergency all-hands-on-deck immune response" that disrupts the checks and balances that regulate autoimmunity, according to Knight.

"The body perceives — and maybe not incorrectly — that it is dying and throws everything it can against the wall," he said. "In some cases, though, this does more harm than good."

The key phrase in that statement is "in some cases." Experts, including **Leonard H. Calabrese, DO,** director of the RJ Fasenmyer Center for Clinical Immunology at the Cleveland Clinic, still have a lot of questions about this autoantibody response.

"The first question is: what do autoantibodies do?" Calabrese said. "Some say it is just an epidemiological phenomenon, and that they do not do anything. Others say they have a role in COVID-19 pathogenesis."

The next question is whether acquiring COVID-19 will trigger an autoimmune disease in any, some or all patients who acquire the virus. "It is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells," **Anca D. Askanase, MD, MPH,** director of

the Columbia University Lupus Center, said in an interview. "Type 1 interferons play a critical role in the antiviral responses to SARS-CoV-2."

The next question, for Calabrese, is whether the autoantibody production has association with post-COVID-19 syndromes in the so-called 'long haulers'. "This is the forefront of research right now, and there is definitely an interesting case to be made," he said.

An additional area of research worth investigating is what happens when people with autoimmune diseases acquire COVID-19. "It is still unclear whether they make new or different autoantibodies," Calabrese said, and added one more question for consideration. "What will happen to their autoimmune disease as they age, post-COVID-19?"

"I look at this pandemic as a tremendous opportunity to uncover how autoimmunity happens in the first place and why some people develop autoimmune diseases," **Paul J. Utz, MD,** told *Healio Rheumatology.*

Source: Stanford University.

None of the answers to these questions will come easily. COVID-19 has proven as unpredictable and challenging as the autoimmune conditions it occasionally resembles.

But if there is good news, it is that the associations are evident and the will to investigate them is high. Whether the investigation will unlock the secrets of autoimmunity in both COVID-19 and the rheumatologic diseases may be the biggest unanswered question of them all.

Laying Out the Questions

In an editorial published in the *Annals of the Rheumatic Diseases,* Calabrese and **Kevin L. Winthrop, MD, MPH,** of the School of Public Health at Oregon Health & Science University, described the relationship between COVID-19 and autoimmunity as "complex and bidirectional."

Kevin L. Winthrop

It is perhaps for this reason that Askanase suggested that these associations, at the moment, "are not well understood."

In individuals with preexisting clinical or subclinical autoimmune/autoinflammatory diseases, the disease and/or its treatments may impact the clinical course of COVID-19 infection, according to Calabrese and Winthrop. Moreover, COVID-19 may influence their disease or recovery.

"For those without apparent autoimmune/autoinflammatory diseases, there is the potential for new-onset immune-mediated diseases which have been anecdotally reported and await more critical appraisal," Calabrese and Winthrop wrote.

Paul J. Utz, MD, professor of medicine in the division of immunology and rheumatology at Stanford University and an expert on autoimmunity, speculated on this potential. "Are the autoantibodies already there and the virus is selecting for people who might have preexisting or preclinical autoimmune disease?" he said. There is no answer to this question as yet.

Utz noted that in diseases ranging from diabetes to rheumatoid arthritis and lupus, autoantibodies can be present in the blood months or years before onset. "Then a trigger could come along," he said.

COVID-19 may be one of those triggers. "Data from other groups strongly support the notion that COVID-19 may also be selecting out patients who are ultimately going to have a worse case of the virus," Utz said.

The final question surrounding the presence of autoantibodies is whether they were, in fact, present prior to infection at all, or whether they formed after the onset of COVID-19. Amid the floodwaters of information on the virus, data are emerging in response to this question, as well.

Swift Response

In a paper published in *Nature Immunology,* Sanz and colleagues characterized B-cell responses using high-dimensional flow cytometry in a cohort of individuals with COVID-19. They found considerable heterogeneity in both effector and immature populations. The most critically ill patients demonstrated extrafollicular B-cell activation and shared B-cell repertoire features that have previously been described in autoimmune settings.

"Extrafollicular activation correlated strongly with large antibody-secreting cell expansion and early production of high concentrations of SARS-CoV-2-specific neutralizing antibodies," they wrote. "Overall, these findings strongly suggest a pathogenic role for immune activation in subsets of patients with COVID-19."

They added that targeted immunomodulatory therapy may benefit certain COVID-19 populations.


Jason S. Knight

"Important early work from Sanz's group at Emory University showed that B cells in COVID-19 have similar derangements to B cells in lupus," Knight said. "And so that likely explains the source of the autoantibodies."

While Calabrese remains uncertain that this is the source of autoantibodies for all COVID patients, he did describe these findings as a "really interesting" early signal that the rheumatology community should heed. It is not the only signal.

In a study published in *Annals of the Rheumatic Diseases,* Vlachoyiannopoulos and colleagues showed that 34.5% of 29 patients with COVID-19 were positive for antinuclear antibodies. Looking closer, 3.5% were positive for anti-cyclic citrullinated peptide (CCP) antibodies, 6.9% each were positive for p-anti-neutrophilic cytoplasmic autoantibodies (ANCA) and c-ANCA antibodies, 24.1% were positive for a-anticardiolipin (CL) antibodies and 34.5% were positive for anti-Beta-2 glycoprotein 1 (2GPI) antibodies.

Further findings from the Vlachoyiannopoulos data set showed that 68.7% of the cohort was positive for any kind of systemic autoantibody. "Despite this and the lack of preinfection serological data, the presence of several systemic autoimmune reactivities in almost 70% of the patients suggests a post-SARS-CoV-2 or para-SARS-CoV-2 infectious autoimmune activation," the researchers concluded. "This is not surprising, as cytokines present in the cytokine storm, for example, interleukin-6, can drive autoinflammatory reactions and autoimmunity, probably via preexisting natural B-cell clones or molecular mimicry."

"These findings, from the group in Greece, from more than a year ago, really feel like a good starting point for further research," Utz said. "But the real question in my mind is: what do they mean?"

Utz noted that data from his group show that some, but not all, patients have autoantibodies prior to infection. A pre-COVID blood sample from every COVID-19 patient would help to answer this question, but that is not standard of care.

Another confounding factor is that antinuclear antibodies are developing in "multiple patterns," according to Utz. "They tend to be in a relatively low titer," he added. Except for when they aren't, because some patients develop antibodies at an extremely high titer.

When asked how to interpret this wide array of antibody patterns, Utz had no clear answer. "My interpretation is that this virus is a particularly nasty virus," he said. "There is so much inflammation and activation of the immune system. It is possible that, for those who have a predilection toward autoimmunity, the virus is able to trigger new autoantibodies."

It is unclear whether that trigger and those autoantibodies will lead to actual autoimmune disease, but investigators are looking into it.

APS and Other Associations

Calabrese and Winthrop highlighted the fact that that antinuclear and antiphospholipid antibodies have been well documented in the COVID-19 setting. "The biological importance of these observations remains unclear, but recently, a series of intriguing studies have suggested that these autoantibodies may represent more than mere epiphenomenon but rather may be functioning as drivers of immunopathogenesis," they wrote.

In two of those studies, published in *medRxiv* and *Science Translational Medicine,* Knight and **Yu Zuo, MD,** of the University of Michigan, measured eight types of antiphospholipid antibodies in sera from 172 patients who had been hospitalized with COVID-19. Results showed that 24% had antiphosphatidylserine/prothrombin antibodies (aPS/PT) IgG, 23% demonstrated anticardiolipin IgM, while 18% had aPS/PT IgM. More than half (52%) demonstrated any antiphospholipid antibody.

Anca D. Askanase

"While patients with autoimmune diseases do not seem to be at higher risk for SARS infections or severe COVID-19 disease, it is possible that COVID-19 leads to increased autoantibodies and autoimmune disease activity," Askanase said.

In addition, IgG fractions in COVID-19 patients looked similar to those found in some patients with long-standing antiphospholipid syndrome, according to Knight and Zuo. "Furthermore, injection of these COVID-19 IgG fractions into mice accelerated venous thrombosis," they wrote. "Taken together, these studies suggest that a significant percentage of patients with COVID-19 become at least transiently positive for antiphospholipid and that these antiphospholipids are potentially pathogenic."

Askanase noted that "these antibodies had *in vitro* pathogenic consequences. Their data suggest that antiphospholipid antibodies may have pathogenic roles in the pro-coagulant events in COVID-19 patients."

Calabrese described the fact that half of patients make these antibodies as "compelling data." Perhaps more compelling are the associations between production of these antibodies and clotting.

Out for Blood

Leonard H. Calabrese

"Since clotting is a big part of COVID-19, it should not be surprising that there is increasing and compelling evidence that autoantibodies may be doing something," Calabrese said.

He noted that the new syndrome of vaccine-induced thrombotic thrombocytopenia (VITT) associated with adenovirus-based vaccines — predominantly found in young women — also appears to have an autoimmune basis with autoantibodies directed against the platelet-derived chemokine PD4.

"I think this is merely the beginning of our understanding of autoimmunity as a sequelae of COVID-19 infection, as well as the result of a new class of vaccines," Calabrese said. He expressed concerns that, with a vaccine now planned for billions of people around the world, "we should expect to see more rare and unusual complications of possible autoimmune origin."

Further data from Knight and Zuo demonstrated that higher levels of the antibodies they observed were associated with a number of alarming outcomes, including neutrophil hyperactivity, higher platelet count, more severe respiratory disease and lower glomerular filtration rate, according to the findings.

"Thrombotic events and antiphospholipid antibodies have been a major part of the COVID-19 spectrum of complications," Askanase said. "Additionally, reports of a disseminated intravascular coagulation-like syndrome in patients with COVID-19 have accumulated. SARS-CoV-2 and complement components were found in regions of thrombotic microangiopathic lesions suggesting a role for a complement-induced coagulopathy in COVID-19."

Knight noted that the activation of neutrophils, platelets and endothelial cells, along with the inhibition of interferons and other cytokines, are certainly contributing factors to clotting events. "These surely conspire to contribute to COVID-19 blood clotting," he said. "This may happen when events occur in large blood vessels, such as DVT and stroke, but also in the microscopic vessels of the lungs where they ruin oxygen exchange."

Utz noted that clots were reported in the Greek cohort, and that some animal models indicate the presence of clotting associated with COVID-19. "There is still work that needs to be done to understand just how prevalent this is," he said.

The good news is that the research that has been conducted thus far has yielded benefits in the clinic. "Anticoagulation, steroids and antiviral agents are now standard treatments for disseminated intravascular coagulation associated with COVID-19," Askanase said.

The fact that treatment paradigms are improving is good news, for one important reason: Many patients are experiencing long-term complications after COVID-19 infection. The more clinicians understand about all facets of the virus, the better they will be able to manage these complications.

In for the Long Haul

As Calabrese noted, the question that is likely to fuel research for the foreseeable future pertains to the association between autoantibodies and long-term downstream complications of the virus. Early data are showing what those complications might look like.

Talotta and Robertson published a paper in *World Journal of Clinical Cases* showing that in addition to antiphospholipid syndrome, cutaneous rashes and vasculitis, autoimmune cytopenia, central or peripheral neuropathy, myositis and myocarditis all have been described in patients with SARS-CoV-2.

"Patients with COVID-19 were reported to develop autoimmune diseases, such as Guillain-Barré syndrome or systemic lupus erythematosus," Askanase added, noting a case report from Zamani and colleagues in the *Journal of Medical Case Reports* demonstrating this effect. "More data are needed to support these reports."

In her clinic, Askanase saw several patients who presented with autoantibodies, ANA positivity, anticardiolipin antibodies and clinical symptoms suggestive of a post-viral syndrome or early autoimmune disease. She reported that while the findings are not yet published, it is important to note that the patient normalized within 1 to 2 months of follow-up.

These anecdotal data notwithstanding, experts like Knight agree that it may be too early to predict the role of autoantibodies in long haulers. "Most data that are out there are still cross-sectional," he said. "It is also important to consider that, for the most part, these data were gathered early in the pandemic. Most patients hospitalized with COVID-19 nowadays are getting treated with a hefty dose of corticosteroids in the form of dexamethasone. This is a time-tested approach to treating autoimmune conditions and we may eventually find that it turns down a lot of this autoimmune response."

If there is a component question regarding the long haulers, it pertains to the possibility of downstream onset of an actual autoimmune disease.

"This is also a very important question that we do not have an answer to yet," Knight said. "The NIH is rightfully planning to inject a lot of money into studying post-COVID-19 complications and this should give us a much better handle on the situation."

Knight believes that it is conceivable that, for the majority of patients, autoantibodies detected in the context of severe COVID-19 will go away once the immune system is no longer on fire. "But there is likely a subset of individuals who had a yet-to-be-unlocked genetic risk for autoimmunity where the process does not get shut down," he said. "They may go on to have a more chronic picture."

A lot of money and a clear plan will be necessary to really elucidate any and all long-term complications, according to Utz. "We will need to deploy a billion dollars, collect patients with complete clinical data and study them with all the technology we have available," he said.

Huge cohorts will be necessary. The fact that there will be millions of survivors of the virus to study offers both a silver lining and a grim consolation.

Seeing an Opportunity

Utz believes that the quality of information emerging as those millions of patients are studied is only likely to improve. "Most of the studies we have seen thus far have been conducted during a pandemic, when doctors and researchers have so many more pressing challenges to manage," he said. "When a patient is on a ventilator, you are not attuned to anything but trying to keep them alive."

As treatment paradigms improve, that flood of patients, hopefully, will slow to a trickle. At that point, clinicians will be better able to tie autoantibody results to patient phenotypes, according to Utz.

Another benefit of this evolving body of information may be a clear answer to the question of whether COVID-19 can induce autoimmune disease.

In another data set from *medRxiv,* Chang and colleagues also drew associations between COVID-19 and autoantibody production that is frequently seen in myositis, systemic sclerosis and CTD overlap syndromes. Importantly, they noted that a subset of patients developed these autoantibodies and anticentromere antibodies (ACA) "de novo" after COVID-19 infection, while other patients developed "transient" antibodies.

While Calabrese and Winthrop acknowledged that many viral infections have been shown to induce autoantibodies and IMIDs — and that emerging evidence implicates SARS-CoV-2 in these events, as well — questions about the pathogenesis of these events remain unanswered. The primary questions are, "whether autoantibodies produced during infection with SARS-CoV-2 are epiphenomena or drivers of clinical disease, and what are the underlying mechanisms responsible for their production," they wrote.

Askanase was clear about how these questions will be answered. "Long-term data is the only way to shed light on these phenomena," she said.

Data from the Rheumatology Global Alliance database will be crucial sources of such information, according to Calabrese. "We have learned a lot about COVID-19 in patients with autoimmunity from this database thus far," he said. "But now we will start to figure out what happens when COVID-19 resolves in these patients, and in the vast majority of people. That is going to be the question in the next several years in our center."

The same is true for Utz. "My lab has pivoted mostly to COVID-19-based research," he said, adding that they will also be looking into the extent to which autoantibodies are "clinically meaningful" in one way or another. "We will follow patients over time to see how COVID-19 behaves differently from lupus, RA or diabetes in terms of autoantibodies."

It is for this reason that Utz remains undaunted, if not optimistic, about the eventual fallout of COVID-19. "I look at this pandemic as a tremendous opportunity to uncover how autoimmunity happens in the first place and why some people develop autoimmune diseases in the first place," he said.

References:

Askanase AD, et al. *Lupus Sci Med.* 2020;doi:10.1136/lupus-2020-000396.

Calabrese L, Winthrop K. *Ann Rheum Dis.* 2021;doi:10.1136/annrheumdis-2021-219957.

Chang SE, et al. *medRxiv.* 2020;doi:10.1101/2021.01.27.21250559.

Sanz I, Woodruff MC, et al. *Nature Immunol.* 2020;doi:10.1038/s41590-020-00814-z.

Talotta R, Robertson E. *World J Clin Cases.* 2020; doi:10.12998/wjcc.v8.i17.3621.

Vlachoyiannopoulos PG, et al. *Ann Rheum Dis.* 2020;doi:10.1136/ annrheumdis-2020-218009.

Winchester N, et al. *Pathogens & Immunity.* 2021:doi:10.20411/pai.v6i1.417.

Zamani B, et al. *Journal of Medical Case Reports.* 2021;doi:10.1186/s13256-020-02582-8.

Zuo Y, Knight J. *medRxiv.* 2021;doi:10.1101/2020.06.15.20131607.

Zuo Y, et al. *Sci Transl Med.* 2020;12(570).

Read next

Rheumatology through the lens of COVID-19

In for the long haul: Clinicians wrestle with post-acute COVID-19 syndromes

For more information:

Anca D. Askanase, MD, MPH, can be reached at 630 West 168th St., P&S 10-508, New York, NY 10032; email: ada20@cumc.columbia.edu.

Leonard H. Calabrese, DO, can be reached at 9500 Euclid Ave. Cleveland, Ohio 44195; email: calabrl@ccf.org.

Jason S. Knight, MD, PhD, can be reached at 1150 West Medical Center Dr., Ann Arbor, MI 48109-5678; website: http://michmed.org/knight-lab.

Paul J. Utz, MD, can be reached at CCSR Room 2215A, 269 Campus Dr., Stanford, CA 94305; email: pjutz@stanford.edu.

Read more about

covid-19 covid-19 vaccine pandemic rheumatology

May 20, 2021 2 min read

COVID-19, the new vaccines and rheumatology: Facing the unknown unknowns

Before I say my piece on this, let me be clear that I am a strong vaccine advocate for all, including my