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Incident systemic rheumatic disease following COVID-19

Although viruses can induce rheumatic diseases, the impact of SARS-CoV-2, the virus behind COVID-19, on the development of systemic rheumatic disease is unclear. COVID-19 can cause a hyperinflammatory state,[1] and multiple studies report the development of autoantibodies in patients with COVID-19.[2,3] However, progression into clinical autoimmunity in adults has only been described in case reports.

We electronically queried patients with a positive PCR result for SARS-CoV-2 at Mass General Brigham hospital in Boston, MA, USA, between Jan 30 and Nov 10, 2020 (n=15 284). For a contemporaneous comparison group, we matched each of these patients with an individual with a negative PCR test result for SARS-CoV-2 (±5 days), by age (±5 years) and sex. Of the patients who tested positive for SARS-CoV-2, we excluded 300 known to have prevalent rheumatic disease that we identified in our previous studies.[3] 141 patients had a diagnosis code for systemic rheumatic disease according to the International Classification of Diseases[3] after the date of SARS-CoV-2 PCR positivity (appendix p 2). Of the patients who were PCR-negative for SARS-CoV-2, 420 had a diagnosis code for systemic rheumatic disease after the date of SARS-CoV-2 PCR negativity. A flow diagram illustrating case identification for both groups is included in the appendix (p 4).

See Online for appendix

For patients with a diagnosis code for systemic rheumatic disease after PCR testing, we screened medical records to identify possible incident systemic rheumatic disease diagnosed after COVID-19 onset. We defined systemic rheumatic disease as incident when both symptom onset and clinical diagnosis occurred after initial COVID-19 symptoms or after a positive PCR test if asymptomatic. Two rheumatologists independently reviewed each case to verify incident systemic rheumatic disease and its onset after SARS-CoV-2 testing and extracted data about COVID-19 disease course and rheumatic disease diagnoses. Incident systemic rheumatic disease cases had to be diagnosed by a rheumatologist or other qualified clinician. In addition, two independent abstractors independently agreed with the diagnosis and its temporal relationship with SARS-CoV-2 testing or COVID-19 symptoms. Information supporting the diagnosis, including laboratory and imaging results, signs and symptoms, and classification criteria were also collected.

Among 15 284 patients with positive SARS-CoV-2 PCR results (8244 [54%] were female and the mean age was 47 years [SD 20]; appendix p 3), we identified six cases of incident systemic rheumatic disease (4 female, 2 male; appendix p 5). Among 15 284 patients with negative SARS-CoV-2 PCR results (8244 [54%] were female and the mean age was 46 years [SD 20]), we identified five cases of incident systemic rheumatic disease (4 female, 1 male; appendix p 6).

Three patients developed systemic rheumatic disease within one week of SARS-CoV-2 PCR positivity. All three patients were admitted to hospital primarily for symptoms related to the incident systemic rheumatic disease. One of these patients developed inflammatory arthritis 10 days after the onset of COVID-19 symptoms but also had known hepatitis C infection (with a stable viral load). Another patient was diagnosed with giant cell arteritis, presenting with scalp tenderness, temporal headache, elevated inflammatory markers, and complete unilateral vision loss. Unilateral temporal artery biopsy showed no obvious arteritis, but there was intimal hyperplasia and disruption of the internal elastic lamina. Magnetic resonance angiography of the neck and brain showed multiple vertebrobasilar arterial stenoses consistent with vasculitis. Therefore, this patient was diagnosed with giant cell arteritis and treated with pulse-dose intravenous glucocorticoids. He was discharged on high-dose prednisone and died from cardiac arrest 10 days after initial PCR positivity. The third patient presented with severe proximal muscle weakness, diagnosed as inflammatory myopathy due to elevated serum muscle enzymes. Deltoid muscle biopsy revealed type I interferonopathy, shown by abnormal MHC-1 and myxovirus resistance protein 1 expression, as reported previously.[5] He was treated with pulse-dose intravenous glucocorticoids and intravenous immunoglobulin. His disease is most consistent with dermatomyositis characterised by anti-Mi2 and anti-TIF1□ autoantibodies. At the time of writing, he remained on glucocorticoids and monthly intravenous immunoglobulin due to persistent muscle weakness.

The remaining three patients developed systemic rheumatic disease more than two months after PCR positivity. One patient with a history of pulmonary embolism and deep vein thrombosis (DVT) two months before COVID-19 symptom onset, in the setting of prolonged immobility due to air travel (with negative antiphospholipid antibodies and normal partial thromboplastin time at that time), was diagnosed with antiphospholipid syndrome 74 days after COVID-19 symptom onset (ie, fever, chills, and rhinorrhea). The patient developed an unprovoked DVT while on rivaroxaban for five months and had a newly positive lupus anticoagulant test, which persisted on repeat testing at three months; at the time of writing, she was being treated with warfarin. Another patient with hand arthralgias without synovitis on previous rheumatology evaluation developed seronegative inflammatory arthritis 89 days after PCR positivity. COVID-19 symptoms included fever, chills, and cough. The patient developed bilateral hand and wrist swelling and laboratory tests were negative for rheumatoid factor and anti-citrullinated protein antibodies. She was initially

treated with low-dose prednisone and hydroxychloroquine but had persistent signs and symptoms after stopping prednisone, so methotrexate and infliximab were subsequently added to hydroxychloroquine. The remaining patient was diagnosed with primary Sjögren's syndrome 104 days after PCR positivity. COVID-19 in this patient was characterised by fever, fatigue, and non-productive cough lingering for nearly two months. She was diagnosed with primary Sjögren's syndrome on the basis of new onset of sicca symptoms, bilateral parotid sialadenitis on MRI, positive anti-nuclear antibodies (1:1280, speckled pattern), high-titre anti-Ro52, anti-Ro60, and anti-ribonucleoprotein, and mildly elevated anti-Smith antibodies with no dsDNA antibodies. Clinically, she was thought to have primary Sjögren's syndrome but with some serological features of systemic lupus erythematosus or mixed connective tissue disease (no evidence of Raynaud's phenomenon) and was treated with hydroxychloroquine.

Among the matched comparators, we identified five cases of incident systemic rheumatic disease after negative PCR results for SARS-CoV-2. This number provides an estimate of the background rate of systemic rheumatic disease development in a contemporaneous population who also presented for testing for SARS-CoV-2. Interestingly, four of the five patients were diagnosed with polymyalgia rheumatica between 30 and 129 days after SARS-CoV-2 testing. The remaining patient developed seronegative rheumatoid arthritis 100 days after SARS-CoV-2 testing.

This case series and comparative study of patients with PCR-confirmed COVID-19 and incident systemic rheumatic disease shows that some patients developed systemic rheumatic diseases following COVID-19. Although COVID-19 could trigger de novo rheumatic disease by inducing type I interferonopathy, it might also accelerate the progression of pre-existing subclinical autoimmunity into clinical disease. Similarly, the COVID-19 hypercoagulable state might have increased the propensity of thrombosis in the patient with antiphospholipid syndrome. These data contribute to the evidence on the possible relationship between SARS-CoV-2 and autoimmunity, although the similar rate of incident systemic rheumatic disease among the comparators suggests that these cases of incident systemic rheumatic diseases could have been due to chance. It is also possible that individuals might have been tested for SARS-CoV-2 due to symptoms of an undiagnosed systemic rheumatic disease. We did our study at a large health-care system using a sensitive screen to maximise the ability to systematically detect all incident cases of systemic rheumatic disease after PCR testing, and we confirmed their presence and timing by medical record review. However, it is possible that some individuals might have been diagnosed with systemic rheumatic diseases outside of our health-care system and would not have generated the relevant diagnosis codes to be identified in our study. It is also possible that some patients developed incident systemic rheumatic disease but did not seek or could not access care during the pandemic, and our study would not have identified these patients. Therefore, we used a contemporary comparator group that was also navigating these health-care access difficulties. The number of incident systemic rheumatic diseases confirmed by medical record review among those that screened positive were relatively low. This result is probably because we used a sensitive screen that only required a single diagnosis code after a PCR date, and many actually had prevalent systemic rheumatic disease at the time of PCR testing. Finally, although the raw numbers of incident systemic rheumatic disease among cases and comparators were similar, nearly all of the comparators were diagnosed with polymyalgia rheumatica. It is possible that some patients with non-specific early polymyalgia rheumatica symptoms were tested for SARS-CoV-2, therefore biasing our results towards the null. The differing distributions of age, sex, and type of incident polymyalgia rheumatica in the PCR-positive group and PCR-negative group are unlikely to be explained by an imbalance of demographic factors at baseline since age and sex were matching factors. Despite these limitations, ours is the first study to our knowledge to systematically identify incident systemic rheumatic diseases within a large health-care system that included a comparator group. Further research is needed to delineate potential links between COVID-19 and autoimmunity.

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Destructive juvenile idiopathic arthritis: do not overlook rare genetic skeletal disorders

We read with interest the report by Takako Miyamae and colleagues describing severe joint damage, loss of carpal bones, and foreshortened fingers in a patient diagnosed with long-standing juvenile idiopathic arthritis.[1] We would like to bring to the reader's attention that the reported clinical and radiographic phenotype might result from rare skeletal disorders characterised by osteolysis. Juvenile idiopathic arthritis is a group of heterogenous diseases characterised by chronic arthritis leading to severe joint damage in some individuals. Diagnosis of juvenile idiopathic arthritis mainly relies on clinical, radiological, and laboratory findings and requires exclusion of similar diseases. Differential diagnosis is very broad and includes well known and common infectious, rheumatological, and neoplastic conditions but also very rare genetic diseases involving the immune system (monogenic immune-mediated disorders), metabolic pathways (storage disorders),[2] or the skeleton (skeletal dysplasias).[3] Extensive osteolysis is uncommon, even in long standing juvenile idiopathic arthritis, and should prompt the consideration of rare osteolysis syndromes in the differential diagnosis (table).[2–4] These genetic disorders cause severe osteolysis (some bones literally vanish over time) that can mimic inflammation-associated changes occurring in destructive juvenile idiopathic arthritis. Affected individuals typically present in childhood or early adulthood with multiple joints involvement (pain, contractures, or deformations) in association or not with other symptoms (table) and display poor response if usual juvenile idiopathic arthritis therapies are attempted (although few data on outcomes are available). Notably, diffuse osteoporosis frequently coexists with osteolytic lesions, and inflammatory features (such as fever) cannot alone distinguish from juvenile idiopathic arthritis.[2]

Although very rare, these conditions deserve to be considered at the initial diagnostic step in an individual with joint complaints but also in patients diagnosed with juvenile idiopathic arthritis showing an atypical evolution. Indeed, failure to recognise them leads to unnecessary immune-suppressive drugs exposure, non-specific treatment or monitoring, altered prognosis assessment, and missed opportunities for genetic counselling. We respectfully thank the authors for reporting this interesting case, which gave us the opportunity to alert the reader for the existence of these rare osteolytic disorders. We would be interested to know whether additional (genetic) tests were done to exclude these conditions in this patient, in particular the possibility of Farber disease, given the striking clinical and radiographic resemblance to the family reported by Bonafé and colleagues.[2]

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	Gene	Mode of inheritance	Pattern of osteolysis	Possible additional suggestive findings
Farber disease (type 2–3), acid ceramidase deficiency (OMIM #228000)	*ASAH1*	Autosomal recessive	Preferential involvement of carpal and tarsal bones, radius, ulna, and phalanges	Subcutaneous nodules (over pressure points); voice hoarseness; pulmonary, cardiac, and neurological defects
Multicentric carpotarsal osteolysis (OMIM #166300)	*MAFB*	Autosomal dominant	Preferential involvement of carpal and tarsal bones, relative sparing of metacarpals and phalanges	Progressive nephropathy starting in childhood; corneal clouding or opacities
Multicentric osteolysis, nodulosis and arthropathy, Torg-Winchester syndrome (OMIM #259600 and #277950)	*MMP2, MMP14*	Autosomal recessive	Preferential involvement of carpal and tarsal bones, long bones can have widened diaphyses and thin cortices	Subcutaneous nodules (palms and soles) and pigmented lesions; coarse facial features; gingival hypertrophy; cardiac defects; corneal opacities

Other genetic disorders with osteolysis (familial expansile osteolysis, progeria, Hajdu-Cheney osteolysis, mandibuloacral dysplasia, and Gorham-Stout disease) are not listed in this table because their clinical and radiographic features differ from the patient reported.

Table: **Rare osteolysis syndromes affecting the carpal and tarsal bones**