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Anti–glomerular basement membrane disease during the COVID-19 pandemic

To the editor: Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune small-vessel vasculitis.[1] The recent confirmation of spatial and temporal clustering of cases suggests that environmental factors, including infection, may trigger disease in susceptible individuals.[2]

Since the identification of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), we have observed an unexpected number of new cases of anti-GBM disease presenting from our local population of approximately 2 million in North West London, UK. Between December 2019 and April 2020, a total of 8 new cases were diagnosed, a fivefold increase above the background rate of 1.5 per million per year (Figure 1). These cases were typical of anti-GBM disease in their clinical features, autoimmune serology, histopathology, human leukocyte antigen associations, and outcomes (Table 1).

Prior to their presentation with anti-GBM disease, all patients reported nonspecific prodromal symptoms of 1–8 weeks duration. Five patients reported specific symptoms of respiratory tract infection and/or diarrheal illness during this period. At presentation with anti-GBM disease, 5 were tested for SARS-CoV-2 infection by viral RNA testing; none were positive. However, using serum samples stored at initial presentation, prior to immunosuppression and plasmapheresis, we detected circulating IgM and/or IgG antibodies to SARS-CoV-2 spike protein in 4 of 8 patients, suggesting recent infection and a potential role in the onset of anti-GBM disease in some cases. The detection of IgM and IgG antibodies to SARS-CoV-2, with negative testing for viral RNA, is in keeping with the hypothesis that the viral infection initiates an aberrant adaptive immune response targeting basement membrane that becomes clinically apparent days to weeks after the acute infection.

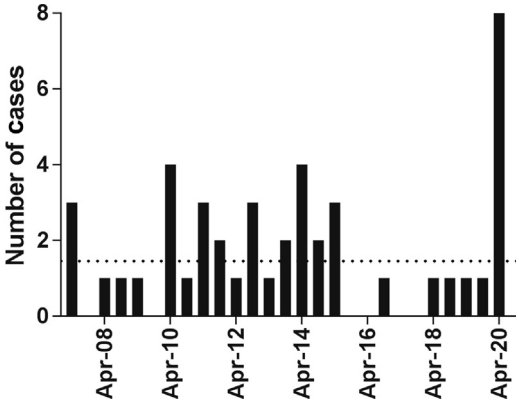

Figure 1 | Incident cases, per 6 months, of anti–glomerular basement membrane (GBM) disease in North West London 2006–2020. Between December 2019 and April (Apr) 2020, a total of 8 new cases of anti-GBM disease were diagnosed, giving an observed:expected case ratio of 5.64, based on disease incidence in the same population since November 2006. Applying a discrete Poisson temporal scan statistic over the period November 2006 to April 2020 confirmed a single significant disease cluster between December 2019 and April 2020 ($P = 0.038$). Statistical analysis was performed using SaTScan v9.6 (Martin Kulldorff and Information Management Services, Inc).

The first description of anti-GBM disease has been attributed to the American pathologist Ernest Goodpasture, who in 1919 (a century before the description of SARS-CoV-2) described a fatal pulmonary–renal syndrome that was considered secondary to an atypical influenza infection during the Spanish flu pandemic.[3] We do not know if his patient had anti-GBM disease, although there have since been descriptions of anti-GBM disease outbreaks during influenza epidemics.[4–7] The cases of anti-GBM disease reported here are the first to occur in association with SARS-CoV-2 infection, and although a causal relationship remains speculative, we highlight a novel cluster of anti-GBM disease, and the potential for viral infections to trigger secondary autoimmunity, including rapidly progressive forms of glomerulonephritis.

ACKNOWLEDGEMENTS

The authors thank Dr. Eva Santos for assistance with human leukocyte antigen–typing. We acknowledge support from the National Institute for Health Research Imperial Biomedical Research Centre.

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Kidney International (2020) **98,** 780–781; https://doi.org/10.1016/j.kint.2020.06.009

Table 1 | Cases of anti-glomerular basement membrane disease presenting since December 2019

Case	1	2	3	4	5	6	7	8
Age and gender	45F	69F	27M	63F	72F	34F	73F	37F
Ethnicity	South Asian	White British	White British	White British	Afro-Caribbean	White British	White British	South Asian
Comorbidity	Rheumatic HD	COPD	None	Bronchiectasis	SLE	None	Hypertension	Asthma
Smoking status	Nonsmoker	Ex-smoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Ex-smoker	Nonsmoker
HLA-DR	DR12, DR15 DR51, DR52	DR11, DR15, DR51, DR52	DR15, DR51	DR4, DR15, DR51, DR53	DR8, DR12, DR52	DR4, DR15, DR51, DR53	Not done	DR15, DR17, DR51, DR52
Clinical presentation								
Antecedent infection	UTI	URTI and diarrheal illness	LRTI	Diarrheal illness	None	URTI	None	LRTI
Prodrome duration	5 wk	1 wk	7 wk	3 wk	2 wk	8 wk	1 wk	2 wk
Presenting symptoms	Lethargy, anorexia, visible hematuria	Lethargy, anorexia, diarrhea, epistaxis	Nausea, vomiting, petechial rash	Lethargy, vomiting, diarrhea	Lethargy, anorexia, visible hematuria	Lethargy, visible hematuria	Lethargy, fever, dyspnea	Lethargy, dyspnea, visible hematuria
Renal status	AKI	AKI-RRT	AKI-RRT	AKI-RRT	AKI-RRT	AKI	AKI-RRT	AKI
Alveolar hemorrhage	No	No	No	No	No	No	No	No
Laboratory features								
Hemoglobin (g/l)	72	76	67	80	94	88	69	98
Platelets (x10^9/l)	232	167	121	391	282	303	96	275
Creatinine (μmol/l)	727	2849	4037	1387	1374	258	963	222
C-reactive protein (mg/l)	10	51	17	134	17	11	6	41
Anti-GBM titre (iu/ml; normal <6.9)	12	51	585	202	623	13	345	93
ANCA	Negative	MPO-ANCA	Negative	MPO-ANCA	Negative	MPO-ANCA	Negative	Negative
Renal biopsy	CGN with linear IgG	CGN with linear IgG	Not done	CGN with linear IgG	CGN with linear IgG	CGN with linear IgG	Not done	Not done
SARS-CoV-2 testing								
Viral PCR[a]	Negative	Negative	Negative	Negative	Negative	Not done	Not done	Not done
Serum IgM[b]	Positive	Negative	Negative	Negative	Positive	Negative	Positive	Positive
Serum IgG[b]	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive
Treatment and outcome								
Treatment	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	No immunotherapy	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	Plasma exchange, cyclophosphamide, rituximab, corticosteroids	Plasma exchange, cyclophosphamide, rituximab, corticosteroids
Follow-up (d)	9	13	21	37	41	61	83	128
Outcome	IP treatment ongoing	IP treatment ongoing	Receiving OP hemodialysis	Recovered kidney function, CKD V	Recovered kidney function, CKD IV	Recovered kidney function	Receiving OP hemodialysis	Recovered kidney function
Last creatinine (μmol/l)	—	—	ESKD	428	274	76	ESKD	79

AKI, acute kidney injury; AKI-RRT, acute kidney injury requiring renal replacement therapy; ANCA, anti-neutrophil cytoplasm antibody; CGN, crescentic glomerulonephritis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease; F, female; GBM, glomerular basement membrane; HD, heart disease; HLA-DR, human leukocyte antigen–DR isotope; IP, inpatient; LRTI, lower respiratory tract infection; M, male; MPO, myeloperoxidase; OP, outpatient; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; URTI, upper respiratory tract infection; UTI, urinary tract infection.
[a]Performed on Roche 6800 (Roche, Basel, Switzerland).
[b]Biomedomics lateral flow immunoassay.