outcomes following admission to intensive care units (ICU). Despite overall improved outcomes in haematology patients,[8] the presence of a cancer diagnosis frequently precludes admission to ICU. In a global pandemic, this disadvantage is only magnified. Comorbidity is associated with poorer outcomes in COVID-19 infection[9] and the impact of ethnicity, particularly those of black and minority ethnic subgroups, on the prognosis of COVID-19 is under review.

The national RECOVERY trial aims to identify therapies that may be beneficial for people hospitalised with confirmed COVID-19. Tocilizumab randomisation is included in the trial design for patients with progressive COVID-19 with features consistent with CRS. This arm of the trial was not available at our hospital but Roche (Basel, Switzerland), the manufacturer of tocilizumab, has a scheme to provide patients who are not eligible to clinical trials access to investigational medicines through an expanded access programme or compassionate use. Compassionate access to drugs such as tocilizumab can alter the course, prognosis and need for ICU admission in COVID-19.

Tocilizumab is an immunosuppressive therapy and serious and sometimes fatal infections have been reported following its use. CRS is indistinguishable from sepsis and the presence of superadded bacterial infections in patients with COVID-19-associated CRS should be aggressively screened for and treated. CRP is typically used to confirm the presence of significant bacterial infection but its specificity for sepsis is low. Procalcitonin (PCT), a prohormone of calcitonin, is a more specific biomarker for bacterial infection and sepsis. The low serum PCT (0·98 μg/l) in our patient, made a diagnosis of sepsis unlikely.[10]

We describe the successful treatment of COVID-19 associated CRS with tocilizumab in a patient with an uncontrolled haematological malignancy. Equality in access to investigational therapies should be actively pursued, especially in disadvantaged patient cohorts, and can be achieved outside of tertiary referral centres and the clinical trials process. Therapies such as this have the potential to change the outcome of severe COVID-19 infection and prevent ICU admission, particularly in patients believed to be unsuitable for critical care or where there is a great demand on critical care resources.

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Keywords: tocilizumab, coronavirus, chronic myeloid leukaemia

First published online 26 June 2020
doi: 10.1111/bjh.16901

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A case series of Monoclonal Gammopathy of Undetermined Significance and COVID-19

Monoclonal Gammopathy of Undetermined Significance (MGUS) is a pre-malignant clonal plasma cell disorder, with 25–30% life-long risk of progression to multiple myeloma (MM).[1] It is usually asymptomatic, but infrequently associated with several serious conditions, such as neuropathies, glomerulonephritis and acquired angioedema.[2] Moreover, a higher risk of infection and deep venous thrombosis has been reported in patients with MGUS.[3,4]

In recent studies of SARS-CoV-2 infection (COVID-19) in cancer, a higher fatality rate was found,[5] especially in haematologic malignancies.[6] While not an overt haematologic malignancy, MGUS falls within the spectrum of plasma cell dyscrasias, and has the potential to disrupt immunity and coagulation.[3,4] Therefore, MGUS could affect the course and outcome of COVID-19; however, such association remains unknown.

We describe seven patients diagnosed with MGUS who tested positive for COVID-19 from 18 March through 8 April, 2020, at Montefiore Health System, that was the epicentre of the COVID-19 pandemic in the Bronx, New York (Table I). All cases were positive by real-time reverse-transcriptase polymerase chain reaction of nasopharyngeal swabs.

Case 1: A 59-year-old Hispanic man with low- to intermediate-risk IgG-kappa MGUS, diabetes mellitus (DM) and hypertension (HTN), presented to the Emergency Department (ED) with three days of dry cough, subjective fever and myalgias. He was normotensive, afebrile, with a room-air oxygen saturation (SpO2) of 98%. He did not require hospital admission, was followed-up one month later and his symptoms had resolved.

Case 2: A 66-year-old Caucasian woman with low-risk IgG-lambda MGUS, HTN and bronchiectasis presented to the ED with one week of productive cough, subjective fever, wheezing and diarrhoea. She was normotensive, febrile to 38.9°C, with a room-air SpO2 of 98%. Her chest X-ray (CXR) showed chronic changes. She was hospitalized, started on broad-spectrum antibiotics for presumed superimposed pneumonia, and a course of hydroxychloroquine and lopinavir/ritonavir per institutional protocol. Her hospitalization was complicated by non-infectious diarrhoea, which eventually improved, and was discharged to a rehabilitation facility after a 16-day hospitalization.

Case 3: An 83-year-old African American (AA) man with high- to intermediate-risk IgA-kappa MGUS, HTN, DM and chronic kidney disease (CKD), presented with altered mental status (AMS) and lethargy noticed a few hours prior to presentation, and six days of dry cough and malaise. He was normotensive, afebrile, with a room-air SpO2 of 80%, which corrected to 96% on a nasal cannula (NC) (4 l/min). His CXR revealed multifocal bilateral infiltrates. Serum glucose was 884 mg/dl. He was started on intravenous fluids and insulin for his hyperosmolar hyperglycaemic state. D-dimers peaked at 20 μg/ml. He received broad-spectrum antibiotics for potential bacterial superinfection. His confusion gradually resolved, oxygen requirements improved and he was discharged home on hospital day eight.

Case 4: A 71-year-old man with low- to intermediate-risk IgM-lambda MGUS and HTN presented to his general practitioner's office with dry cough. He was instructed to self-isolate at home, was followed-up one month later and noted his symptoms had resolved.

Case 5: An 81-year-old AA woman with low-risk IgG-lambda MGUS, HTN, DM, CKD, congestive heart failure, and pulmonary sarcoidosis presented to the ED with 10 days of dry cough and dyspnoea. She was hypotensive (90/53), afebrile, with a room-air SpO2 of 89% which improved to 99% on a non-rebreather mask (NRB). CXR showed left lung base atelectasis. Acute kidney injury (AKI) was noted. She was hospitalized, started on intravenous fluids with resolution of hypotension, and treated with hydroxychloroquine per institutional protocol. She was transitioned to NC on hospital day 2. Her renal function and oxygenation gradually improved, and she was discharged to a rehabilitation facility after an 11-day hospitalization.

Case 6: A 76-year-old Hispanic man with low- to intermediate-risk IgA-lambda MGUS, HTN, DM and CKD presented to the ED with five days of dry cough and dyspnoea. He was hypertensive (181/78 mm Hg), febrile (38.3°C), with a room-air SpO2 of 96%. His CXR showed bibasilar infiltrates. AKI with hyperkalaemia was noted. He was hospitalized and later developed non-ST-elevation myocardial infarction, managed conservatively. His renal function deteriorated and on hospital day 6 haemodialysis was initiated. His renal function gradually improved and he was discharged home on hospital day 25.

Case 7: A 92-year-old AA man, nursing-home-resident with low- to intermediate-risk IgG-kappa MGUS, HTN, DM, CKD, epilepsy and dementia presented to the ED with AMS and lethargy noticed a few hours prior to presentation. He had a dry cough, dyspnoea and malaise for one week. He was hypertensive (158/88 mm Hg), afebrile, with a room-air SpO2 of 96%. On examination he was using accessory respiratory muscles. The patient had do-not-resuscitate and do-not-intubate orders and was therefore placed on a NRB. his CXR showed left mid-lower lobe infiltrates. He was admitted, started on broad-spectrum antibiotics and additionally treated for decompensated heart failure. D-dimers peaked at 20 μg/ml. Finally, his family opted for comfort care and he expired on hospital day 13.

COVID-19 is a heterogeneous disease that ranges from asymptomatic in some patients to fatal in others. Advanced age, male sex and comorbidities, such as HTN and DM have been identified as risk factors for adverse prognosis. Significant coagulopathy has been observed in severe cases, and elevated D-dimer levels have been shown to have prognostic significance.[7–11] In a study performed at our institution, patients with haematologic malignancies and COVID-19 had a higher mortality rate than non-cancer patients.[6]

We wanted to investigate the effects that MGUS might have on patients with COVID-19. Our patients were older adults with an age range between 59 and 92 years. They all had underlying conditions, identified as high-risk comorbidities, yet none of the patients required mechanical ventilation or ICU management, and with the exception of one fatality, they all eventually recovered (Table I). The only fatality was a patient with multiple risk factors, including male sex, advanced age, nursing home residency, multiple comorbidities and a very elevated D-dimer.

MGUS represents the earliest stage of plasma cell dyscrasia and is generally an asymptomatic phase of the disease spectrum. Still, some studies suggest MGUS patients manifest increased susceptibility to bacterial and viral infections, as well as coagulation abnormalities.[3,4] Whether these perturbations of immunity and coagulation have the potential to impact the clinical trajectory of COVID-19 remains to be

Table I. Baseline characteristics, laboratory findings and clinical course of COVID-19 patients with MGUS.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	59	66	83	71	81	76	92
Gender	Male	Female	Male	Male	Female	Male	Male
Race/Ethnicity	Hispanic	White	AA	Other	AA	Hispanic	AA
Comorbidities	DM	HTN	DM	HTN	DM	DM	DM
	HTN	CLD	HTN		HTN	HTN	HTN
			CKD		CLD	CKD	CKD
					CKD		Dementia
					CHF		
Immunoglobulin Subtype	IgG Kappa	IgG Lambda	IgA Kappa	IgM Lambda	IgG Lambda	IgA Lambda	IgG Kappa
MGUS risk stratification	Low-intermediate	Low	High-intermediate	Low-intermediate	Low	Low-intermediate	Low-intermediate
NH resident	No	No	No	No	No	No	Yes
Lab Tests							
Haemoglobin, g/l							
Prior to admission	125	127	118	135	104	125	112
Minimum	–	99	115	–	82	107	81
Platelets, $x10^9$/l							
Prior to admission	389	317	210	116	282	315	191
Minimum	–	156	89	–	185	301	141
ANC ($x10^9$/l)							
Prior to admission	6·4	6·4	2·9	1·2	4·3	2·2	1·1
Minimum	–	1·2	5·3	–	2·3	2·8	0·3
ALC ($x10^9$/l)							
Prior to admission	3·9	1·3	3·4	1·3	1·0	1·6	1·1
Minimum creatinine, mg/dl	–	0·2	1·6	–	0·6	0·4	0·4
Prior to admission	0·8	0·7	1·6	0·9	2·2	1·2	1·1
Maximum D-dimer, μg/ml	–	0·8	2·77	–	2·94	12·7	1·7
Maximum ferritin, ng/ml	–	–	20	–	1·38	2·14	20
Maximum CRP, mg/dl	–	–	1525	–	527	1575	766
Maximum	–	–	25·1	–	5·6	7	6·2
Clinical course							
Hospital admission	No	Yes	Yes	No	Yes	Yes	Yes
ICU admission	No	No	No	No	No	No	No
Intubation	No	No	No	No	No	No	No
Dialysis	No	No	No	No	No	Yes	No
LOS, days	–	16	8	–	11	25	13
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Deceased

AA: African American, ALC: Absolute Lymphocyte Count, ANC: Absolute Neutrophil Count, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, CLD: Chronic Lung Disease, DM: Diabetes Mellitus, HTN: Hypertension, LOS: Length of stay, MGUS: Monoclonal Gammopathy of Undetermined Significance, NH: Nursing Home.

[†]MGUS Risk Stratification per Mayo Clinic Criteria.

examined with large-scale data. This small case series seems to suggest that MGUS may not pose additional risks for poor outcome in COVID-19 infection.

Conflicts of interest

The authors declare no competing financial interests.

Author contributions

AV, NK and IM conceived the research; AV, VM, RK, LBR, MG, AS, RAS, KG, IB and SJ identified the cases and provided clinical information; JGL collected the data; JGL, NK, IM and AV wrote the manuscript. All the authors reviewed and approved the final version of the manuscript.

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Keywords: Monoclonal Gammopathy of Undetermined Significance (MGUS), COVID 19, coronavirus

First published online 24 June 2020
doi: 10.1111/bjh.16906

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Re The source of elevated plasma D-dimer levels in COVID-19 infection

Dear Sir,

Markedly elevated D-dimer levels are seen in severe COVID-19 infection and have been related to a poor prognosis.[1-2] D-dimers are elevated alongside other acute inflammatory plasma markers such as fibrinogen, C-reactive protein (CRP) and serum ferritin.[1] The elevation of plasma D-dimers has been taken to indicate there is a coagulopathy,[2] and the assumption has been made that the increased fibrinolysis is secondary (due to thrombin generation), indeed an indication of disseminated intravascular coagulation (DIC). However frank DIC seems unlikely as these patients do not fulfil the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC[3] and there is hardly consumption of coagulation factors and physiological anticoagulants; indeed fibrinogen levels are very elevated.[1-4]

We propose an alternative hypothesis: we suggest that the origin of D-dimers is a direct consequence of the acute lung injury seen in COVID-19 pneumonia. For one, the hallmark of acute lung injury is intra-alveolar fibrin deposition. The levels of fibrin are controlled by alveolar epithelial cells which produce urokinase and regulate extravascular proteolysis by regulating expression of urokinase-type plasminogen activator (uPA), its receptor uPAR, and plasminogen activator inhibitor-1 (PAI-1) at post-transcriptional levels. Urokinase