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Blood Cells, Molecules and Diseases 85 (2020) 102481

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Potential 'significance' of monoclonal gammopathy of 'undetermined significance' during COVID-19 pandemic

ARTICLE INFO

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To the editor,

(See Tables 1 and 2.)

Monoclonal gammopathy of undetermined significance (MGUS) is the commonest premalignant condition [1]. In addition to its malignant transformation potential, MGUS is also associated with immunoparesis, hypercoagulability, and organ damage [2]. End-organ damage causally related to MGUS is defined as monoclonal gammopathy of clinical significance (MGCS) [3]. Here, we review the potential significance of MGUS during COVID-19 pandemic, and discuss the possible implications of COVID-19 for patients with MGCS.

MGUS is present in about 3% people > 50 years, 5% people > 70 years, and 6.6% people > 80 years of age [1]. Conceivably, MGUS represents an elderly population, and therefore, could compound the age-related medical challenges, like immunosuppression. Advancing age is associated with impaired humoral, and cellular immunity. Immunoparesis is characteristic of MGUS. Hypogammaglobulinemia is seen in about 25% MGUS cases [4]. Importantly, presence of MGUS further impairs the already senescent immune system of the elderly population.

In the epidemiological studies, people with MGUS were shown to have a 2-fold increased risk of developing bacterial, and viral infections, and an excess mortality risk due to bacterial infections as compared to the healthy controls (HC). Pathogen-specific IgG antibodies against varicella, mumps, and rubella were significantly reduced in people with MGUS as compared to HC [2,4]. Therefore, presence of MGUS could possibly increase the susceptibility, and severity of COVID-19, and might account for an increased mortality (15%) due to COVID-19 observed in the elderly population [5]. In a recent case series of seven COVID-19 positive MGUS patients, 71% were hospitalized. There were no intensive care unit (ICU) admissions or deaths. One patient had acute kidney injury (AKI) which recovered after hemodialysis [6]. Two New York (NY)-based studies [7,8], and one UK-based study evaluated the impact of COVID-19 in multiple myeloma (MM) patients [9]. Hospitalization rates of COVID-19 positive MM patients were higher as compared with the respective general COVID-19 populations (62–74% vs 25.8% in NY studies [7,8,10], and 96% vs 14.7% in the UK study) [9,11]. In the NY studies, ICU admission rates of COVID-19 positive MM patients were higher as compared to the general COVID-19 population (24–30% vs 14.2%) [7,8,10]. Mortality rates in COVID-19 positive MM patients from NY were similar to the general COVID-19 NY population (18–24% vs 21%) [7,8,10], whereas mortality rate was significantly higher in the UK study as compared to the general UK COVID-19 mortality (54.6% vs 14%) [9,11]. As compared to the general COVID-19 population, COVID-19 positive MM patients mounted a delayed antibody response (2–3 weeks vs 32 days) [8,12], and had delayed virus clearance (median 9.5 days vs median 43 days) [8,13]. Baseline hypogammaglobulinemia was significantly associated with increased mortality, and predicted for lower anti-COVID-19 antibody titers in one study [8]. Above studies are limited by small sample size, lack of comparison with age/sex-matched HC, and incomplete assessment of immunoparesis. Nevertheless, this data indicates the potential severity, and delayed clearance of SARS-CoV-2 in MM patients. Elderly population, and also people with MGUS were shown to have impaired immune response to influenza vaccination [4]. These preliminary observations could be potentially relevant in the current COVID-19 pandemic since vaccines against SARS-CoV-2 epitopes are being developed to provide active immunity against COVID-19. Age/MGUS related immune dysfunction could result in a suboptimal response to SARS-CoV-2 vaccine in people with MGUS.

Population-based studies demonstrated that people with MGUS have about 2-fold increased risk of both venous and arterial thrombosis as compared to age/sex-matched HC [2]. Hypercytokinaemia-mediated coagulopathy, and presence of lupus anticoagulant pose a high thrombotic risk to COVID-19 patients [14]. Whether MGUS adds to the hypercoagulable milieu of COVID-19 is unknown. This consideration may have potential clinical relevance regarding the anticoagulant dose. Routine heparin prophylaxis has been suggested for COVID-19 patients admitted to ICU [14]. Since antithrombin levels could be decreased in both COVID-19 and MGUS [14,15], patients with MGUS/COVID-19 may have a sub-therapeutic anticoagulant effect with heparin. Therefore, in such patients, physicians may have to consider increasing the heparin dose guided either by antithrombin levels, or coagulation indices like APTT for unfractionated heparin, and anti-Xa activity for low molecular weight heparin [16]. Alternate anticoagulants with antithrombin-independent mechanisms of action like directly acting anticoagulants (Argatroban, or possibly Dabigatran) could also be used [17].

MGCS refers to MGUS-mediated end-organ damage in the absence of either MM, Waldenstrom's macroglobulinemia, or treatment requiring B-cell lymphoproliferative disorder. MGCS includes monoclonal gammopathy of renal/neurological/dermatological significance (MGRS/MGNS/MGDS, respectively). Diagnosis of MGCS requires tissue demonstration of monoclonal immunoglobulin deposits in the setting of organ dysfunction [3]. Certain MGRS entities could have a systemic presentation. Cardio-renal involvement is most characteristic for immunoglobulin light-chain (AL) amyloidosis, and monoclonal

https://doi.org/10.1016/j.bcmd.2020.102481
Received 20 July 2020; Accepted 21 July 2020
Available online 24 July 2020

Table 1
Considerations for prophylaxis and treatment of patients with MGCS during COVID-19 pandemic.

Prophylaxis considerations*		
	Comment (s)	Suggestion (s)
Anti-COVID-19 prophylactic medications	1. Uncertain benefit of HCQ and macrolides both for primary as well as post-exposure prophylaxis [25] 2. HCQ and macrolides are potentially cardiotoxic** 3. HCQ is renally excreted [19]	1. Use of HCQ/macrolide prophylaxis for MGCS patients must follow national guidelines, but in general should be restricted. 2. Use of HCQ in patients with MGRS could be further detrimental to cardiac and renal functions, and therefore, must be avoided.
SARS-CoV-2 Vaccination	1. Use of antigen-based SARS-CoV-2 vaccines in MGCS could be safe. 2. Underlying 'MGUS', and clone-directed therapies could compromise vaccine efficacy	Apart from the routine seasonal influenza, and pneumococcal vaccines, vaccination against SARS-CoV-2 when available, must be considered for patients with MGCS***
	Bortezomib reduced the post-vaccine protective antibody titer by ~30% in patients with SLE [26]	Consider usual SARS-CoV-2 vaccination in MGCS patients on a PI***
	DARA did not affect the antibody response to seasonal influenza vaccine in patients with heavily pre-treated MM[27]	Consider usual SARS-CoV-2 vaccination for patients with MGCS on DARA.
	Rituximab causes profound B-cell depletion, and complete B-cell recovery could take 6–12 months after the last dose****[28]	Consider SARS-CoV-2 vaccination either prior to, or atleast 6-months after the last dose of Rituximab in MGCS patients
	IMiDs were shown to augment the vaccine response [29]	Consider usual SARS-CoV-2 vaccination in MGCS patients on IMiDs+
Other prophylactic medications	Acyclovir is potentially nephrotoxic	Continue acyclovir for HZ prophylaxis with PI and DARA, albeit dose-modified according to renal function for MGRS patients
Dialysis for MGRS patients	Maintain social distancing, and adequate sanitization in the nephrology dialysis units	Consider shifting patients from hemodialysis to peritoneal dialysis after nephrology consultation
	Treatment considerations for patients with MGCS during COVID-19 pandemic	
General measures	MGCS could represent an immunocompromised population, and may be at a higher risk of infection and death during COVID-19	1. Consider general hand hygiene, and social distancing 2. Consider COVID-19 by PCR-based assays before initiating any immunosuppressive treatment for new MGCS cases [24]
Modifications of clone-directed chemotherapy regimens [24,31,32]	CyBorD++ [24]	1. Consider SC bortezomib instead of IV route 2. Reduce Dexamethasone dose to 20 mg/week instead of 40 mg/week 3. Consider oral cyclophosphamide instead of IV route 4. Consider renal modification of cyclophosphamide dose 5. Consider 2-weekly bortezomib administration instead of weekly administration+++
	DARA was shown to be safe and effective in patients with certain MGRS entities [30]	1. Consider 90-min IV infusion instead of conventional 4–6 h infusion in those with an uneventful first infusion 2. Consider SC DARA formulation 3. Consider reducing the frequency of DARA administration to every 4-weeks instead of every 2-weeks after initial 2-months of treatment.
	IMiDs (lenalidomide and pomalidomide) are potentially myelosuppressive and prothrombotic	Avoid use of lenalidomide and pomalidomide, particularly in MGRS during COVID-19 pandemic
	Ixazomib: Oral administration, and its potential anti-SARS-CoV-2 properties are particularly desirable during COVID-19 pandemic#[31]	1. Ixazomib may be preferred over bortezomib for patients with newly diagnosed AL amyloidosis, or RR cases## 2. Consider Ixazomib instead of Bortezomib for maintenance###
	Purine analogues like Bendamustine, cladribine, and fludarabine cause prolonged lymphopenia	1. Avoid these drugs as chemotherapy backbone with Rituximab$ 2. Alkylators (chlorambucil, cyclophosphamide) may be used as chemotherapy backbone with Rituximab$$
	1. Rituximab can cause hypogammaglobulinemia, and prolonged B-cell depletion [28]. 2. IV Rituximab administration is prolonged, and needs hospital visits	1. Maintenance Rituximab may either be omitted, or increased in frequency from 2-monthly to 3-monthly infusions$$$ 2. Consider SC Rituximab wherever available to reduce hospital visits
	Autologous HSCT causes profound and prolonged immunosuppression [24]	Both autologous HSCT, and renal transplant must be delayed for patients with MGRS, atleast till the COVID-19 pandemic is reasonably controlled
	Treatment of MGCS in patients with COVID-19	
Immunosuppressive medications [19]	PI, IMiDs, corticosteroids, DARA, alkylators, and Rituximab are potentially immunosuppressive	1. Withhold all the immunosuppressive therapies at the first diagnosis of COVID-19 2. Resume treatment of MGCS later, once the patient recovers fully from COVID-19
General measures	Risk of worsening cardiac, and renal function with COVID-19 in MGRS	1. Treatment of MGCS must be supportive 2. Meticulous monitoring of fluid, and electrolyte balance for MGRS patients
	Treatment of COVID-19 in patients with MGCS	
Anti-COVID-19 drugs [19,33]	1. Remdesivir, Lopinavir/Ritonavir, Favipiravir, and dexamethasone have shown some efficacy 2. Cardiotoxic- Remdesivir, Lopinavir/Ritonavir 3. Nephrotoxic- Remdesivir	1. These drugs may be cautiously used to treat COVID-19 in patients with MGCS as per national and institutional guidelines 2. Remdesivir must not be used in MGRS patients with severe renal insufficiency, or on renal replacement therapy@
Tocilizumab [19]	Could cause cardiovascular complications	Use cautiously particularly for patients with MGRS

(*continued on next page*)

Table 1 (*continued*)

Prophylaxis considerations*		
Anti-coagulation	1. Patients with AL amyloidosis have vascular friability, and haemostatic abnormalities which could predispose them to bleeding [19] 2. LMWH is renally excreted [16] 3. Reduced AT levels could reduce the efficacy of heparin [17].	1. Cautious use of anti-coagulant drugs in AL amyloidosis 2. Renal modification of anticoagulant dose, and Anti-Xa activity-guided LMWH dosing for MGRS patients [16] 3. AT level-guided heparin dosing, or use of anticoagulant drugs with AT-independent mechanism of action (Argatroban, Dabigatran) [17]

COVID-19: Coronavirus disease 2019; HCQ: hydroxychloroquine; MGCS: monoclonal gammopathy of clinical significance; MGRS: monoclonal gammopathy of renal significance; MGUS: monoclonal gammopathy of undetermined significance; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MM: multiple myeloma; DARA: Daratumumab; SLE: systemic lupus erythematosus; PI: proteasome inhibitors; HZ: herpes zoster; PCR: polymerase chain reaction; CyBorD: cyclophosphamide, bortezomib, dexamethasone; SC: subcutaneous; IV: intravenous; IMiDs: immunomodulatory drugs; AL: immunoglobulin light chain amyloidosis; RR: relapsed/refractory; HSCT: hematopoietic stem cell transplant; AT: antithrombin III; LMWH: low molecular weight heparin.
*These considerations are in addition to the recent recommendations of reducing the frequency of hospital visits for people with MGUS [24]. General measures of hand hygiene and sanitisation are mandatory for all MGCS patients.
**QT prolongation.
***subsequent vaccine dose may be considered for MGCS patients based upon the SARS-CoV-2-specifc IgG titer measured after the first dose.
***** Although Rituximab does not affect the pre-existing PC, it reduces the genesis of new long-lived PC. Likewise, administration of multiple courses of Rituximab could cause hypogammaglobulinemia, and impair the vaccination response [28].
+ It would be interesting to evaluate the role of IMiDs as an adjuvant to the SARS-CoV-2 vaccine.
+ + Given the rarity of MGCS, different regimens have not been tested in randomized controlled trials (RCT). However, bortezomib-based regimens have been used most commonly, and are renal-safe.
+ + + For patients with complete organ response, or complete haematological response with stable organ function.
# No data is available for the use of Ixazomib, an oral PI in MGRS entities other than AL amyloidosis.
Although Ixazomib is not approved for the frontline use in AL amyloidosis, preliminary clinical data indicates rapid and deep haematological response (HR) rates with upfront Ixazomib and low-dose dexamethasone combination (Id) [34]. In a phase-I/II study, Ixazomib showed impressive HR (52%) and organ response (OR) (56%) rates in patients with relapsed/refractory (RR) AL amyloidosis [35].
Phase-II clinical trial evaluating Ixazomib maintenance for AL amyloidosis is currently ongoing (NCT03618537).
$ Addition of Rituximab to the chemotherapy backbone has been shown to improve overall response rates, and PFS for patients with B-cell lymphoma [36]. Therefore, patients with LPL/B-cell-associated MGCS must be treated with Rituximab combinations, albeit with some modifications of chemotherapy backbone.
$$ In one RCT, BR was shown to have PFS advantage, but no overall survival (OS) benefit over R-CVP [37].
$$$ Use of maintenance Rituximab for low-grade B-cell lymphoma was shown to improve PFS, but not OS in an RCT [38].
@ Patients with severe renal impairment (estimated glomerular filtration rate $<$ 30 ml/min/1.73m^2, on hemodialysis, or peritoneal dialysis) were excluded from the recent Remdesivir trials [33].

Table 2
Unanswered questions pertaining to MGUS and COVID-19, and their potential research strategies.

	Unanswered questions pertaining to MGUS and COVID-19	Potential research strategies
1	Do people with MGUS have an excess risk of contracting COVID-19?	Antibody-based estimation of seroprevalence of COVID-19 in the general population, * and comparison of the seroprevalence results between MGUS and non-MGUS populations. **
2	Does COVID-19 in people with MGUS have a more aggressive course?	Review of the nation-wide hospital data of COVID-19 cases to identify patients with concurrent MGUS, and comparison of disease severity, outcomes, and differences in the immunological indices between MGUS, and non-MGUS groups.
3	Do people with MGUS have a suboptimal response to COVID-19 vaccine?	1. Pre-vaccination measurement of serum immunoglobulin levels, or lymphocyte subset analysis to predict post-vaccine immune response [40]. 2. In-vitro studies based on lymphocyte-stimulation by SARS-CoV-2 antigens to assess the immune-responsiveness of people with MGUS to COVID-19 vaccines [41].
4	Does MGUS add to the hypercoagulable milieu of COVID-19?	Screening the admitted COVID-19 patients for the presence of MGUS may provide some clue to the excess thrombotic risk, and/or different pattern of coagulopathy conferred by MGUS to COVID-19 patients

MGUS: monoclonal gammopathy of undetermined significance; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory distress syndrome coronavirus 2.
* Antibody-based assays have a relatively high false-negative rate as compared to conventional polymerase chain reaction (PCR)-based assays, and are therefore, not routinely recommended for COVID-19 diagnosis during the acute stage. However, antibody-based tests may represent a reasonably acceptable, and cost-effective strategy to screen for asymptomatic COVID-19 cases for an epidemiological survey [39].
** Since people with MGUS may have an impaired anti-viral antibody response [4], a lower SARS-CoV-2-specific IgG in the MGUS population as compared to the HC in the serology-based epidemiological studies would suggest an increased susceptibility of people with MGUS to COVID-19.

immunoglobulin deposition disease (MIDD) [18]. Although, COVID-19 is predominantly a respiratory illness, involvement of cardiac, gastrointestinal, kidneys, central nervous system (CNS), skin, and hematoimmune systems have been recognised [19]. COVID-19-related myocarditis may cause elevation of biomarkers of cardiac injury like troponins, and N-terminal pro-brain natriuretic peptide (NT-Pro-BNP). AKI has been reported in about 0.5%–25% COVID-19 patients, and about 43.9% of such cases may have proteinuria [19]. Such a multisystem involvement in COVID-19 could pose several diagnostic, and therapeutic challenges for patients with MGCS. (1) Diagnosis of MGRS, particularly AL amyloidosis may be overlooked in patients with COVID-19-related myocarditis, or AKI resulting in diagnostic delays. Evaluation for an alternate cause for elevated cardiac biomarkers, or renal impairment should be pursued when either of these derangements are disproportionate to the clinical severity of COVID-19, or if they persist despite recovery from COVID-19. Due to its potential organ threatening

nature, diagnostic work-up for MGRS as recommended even during COVID-19 pandemic [18]. Organ-directed biopsy may be compromised during the COVID-19 pandemic due to limited availability of healthcare resources for performing the invasive procedures, or reluctance of the patients to seek medical attention due to the fear of COVID-19 [19]. Lesser invasive sites of tissue sampling like abdominal fat pad, or gingival biopsies may be considered for AL amyloidosis, although a negative result from these sites does not necessarily exclude the diagnosis [18]. For other MGRS entities, kidney biopsy is essential, and efforts must be made to obtain tissue diagnosis at the earliest in an appropriate clinical context. Similarly, diagnosis of MGDS, and MGNS could be overlooked in COVID-19 patients with cutaneous lesions, and peripheral neuropathy (PN), respectively. Neurotropism of SARS-CoV-2 usually manifests with CNS symptoms [20]. Occurrence of PN in patients with COVID-19 is only anecdotal [21]. Therefore, alternative causes for PN must be sought in COVID-19 patients. Given the relatively non-invasive nature of skin and nerve biopsies, diagnostic algorithm for MGDS, and MGNS should remain unaltered during the COVID-19 pandemic. (2) Elevation of cardiac biomarkers due to COVID-19 myocarditis could confound the assessment of cardiac involvement in patients with AL amyloidosis and MIDD. Endomyocardial biopsy could help distinguish monoclonal protein vs COVID-19 induced cardiac damage [22]. However, due to risk of complications in the sick patients with COVID-19, endomyocardial biopsy may be deferred until the patient recovers from COVID-19. (3) Due to renal tropism of SARS-CoV-2, and cytokine-mediated myocardial damage, patients with MGRS may experience a rapid worsening of their renal, and cardiac functions due to COVID-19. Patients with AL amyloidosis and MIDD have poor cardiac reserve, autonomic neuropathy, intravascular volume depletion due to hypoalbuminemia, and are usually on diuretics [19]. These factors predispose them to cardiac decompensation during COVID-19-cytokine storm, and must be considered carefully while treating these patients during COVID-19. (4) Moreover, worsening of cardiac, and renal functions could make haematological, and organ response evaluation in patients with MGRS (AL amyloidosis) challenging. In the setting of COVID-19-related AKI, 'renal-range' for serum free light chain assay should be used for haematological response evaluation [18]. BNP-based cardiac response assessment tools may be preferred over NT-Pro-BNP-based tools due to lesser renal-dependence of the former [23].

MGCS is treated with B-cells, or plasma cell-targeted chemo/chemo-immunotherapies [3,18]. Therefore, like patients with 'cancer', MGCS patients also have a higher risk of contracting, and dying from COVID-19. Considerations for prophylaxis, and treatment for patients with MGCS during COVID-19 pandemic are summarized in Table 1 [24–38]. In conclusion, although research during COVID-19 pandemic has focused on cancer patients, MGUS does have potential clinical significance during the current COVID-19 pandemic. Epidemiological/hospital cohort studies must be conducted to answer several unknown aspects of MGUS/COVID-19 (Table 2) [39–41].

Funding source

None.

Competing interests

None.

Author contribution

AJ wrote the draft. AJ and KR reviewed and approved the final draft.

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