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LETTER

Analysis of smoldering multiple myeloma according to the target of the monoclonal immunoglobulin of patients

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Antigenic stimulation initiates subsets of plasma cell dyscrasias, including monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM).[1] MGUS and MM are characterized by genetically altered clonal plasma cells that produce large quantities of a single immunoglobulin (Ig), termed "monoclonal Ig (mcIg)," or M-protein. Smoldering multiple myeloma (SMM) is the intermediate stage between asymptomatic MGUS and MM.[2–4] In clonal gammopathies, the initial antigenic stimulation can be identified by studying the specificity of recognition of the patient's mcIg. In MGUS and MM, targets of mcIgs (potential initiating events) include infectious pathogens (Epstein-Barr virus [EBV], cytomegalovirus [CMV], Enteroviruses, *Helicobacter pylori* [*H. pylori*], hepatitis C virus [HCV], hepatitis B virus [HBV]), and self-antigens (glucosylsphingosine [GlcSph]).[1,5–9] Importantly, MGUS or MM linked to CMV infection or anti-GlcSph autoimmunity seem to be benign cases,[1,5–7] and suppression of the antigen target can be envisioned as a potential therapy. Studies of MGUS during Gaucher disease (GD) showed that GlcSph, the immunogenic lipid accumulated in GD, is a frequent target of GD mcIgs.[5,6] Confirming the link between GlcSph and MGUS in GD patients, GlcSph-reducing eliglustat therapy successfully suppressed the plasma clone and mcIg production.[10] Viral target antigen reduction also improved response to chemotherapy, as observed with antiviral treatments for MM patients who presented with an HCV- or HBV-specific mcIg, thus likely had HCV- or HBV-initiated disease.[11,12]

Previous studies have shown that ~15% of sporadic MGUS and MM have a mcIg specific for GlcSph, consistent with chronic autoimmunity, and ~60% MGUS and ~30% MM patients have a mcIg specific for a pathogen, implying that infection initiated the gammopathy.[1,7–9,13] However, antigen targets of mcIg in SMM remain unknown. Here we analyzed the targets of mcIg of an SMM cohort from the Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) consortium[14,15]; patient characteristics according to the target of the mcIg; and the effect of target reduction therapy for SMM patients with *H. pylori*-specific mcIg.

We examined 182 individuals (109 males, 73 females) diagnosed with SMM in the iStopMM study during the 2016–2022 period. Serum samples were collected at diagnosis or follow-up visits (every 4–6 months), aliquoted, and frozen (−80°C). McIgs were IgG ($n = 105$), IgA ($n = 45$), IgM ($n = 1$), and light chains (LC) ($n = 26$). Five patients (P41, P107, P153, P166, P168) were bi-clonal (had two mcIgs). The male ratio was 60%, and at diagnosis, the median age of patients was 67.5 years, and the median M-protein amount was 5.1 g/L (Supporting Information S1: Table 1). According to the Mayo Clinic 2/20/20 risk stratification model,[16] 116 (63.7%) participants had low-risk, 48 (26.4%) intermediate risk, and 18 (9.9%) high-risk SMM.

Purification of mcIgs and analysis of their targets are described in the Supplement and prior publications.[1,7–9,13] The assays used to determine the targets of mcIgs included a GlcSph immunoblot assay,[1,5–7] the multiplex infectious antigen microarray (MIAA), which tests for 10 pathogens (see Supporting Information Methods), and dot and western blot assays, to confirm that infectious proteins were recognized by mcIgs.[1,7–9,13] Blood serum (i.e., polyclonal and mcIg) and purified mcIg were analyzed in parallel. IgM and LC could not be purified, so 27 individuals were excluded. The mcIg preparations of 119/155 (76.8%) SMM individuals (96 IgG, 23 IgA) were purified well enough to proceed to the analysis of antigen recognition (Supporting Information S1: Table 1 and Supporting Information S1: Figure 1). Compared with patients for whom analysis of mcIg specificity was not

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TABLE 1 Reactivity of serum Igs and specificity of recognition of purified monoclonal Igs from SMM patients, compared to MGUS and MM patients.

	SMM with non-clonal GlcSph-reactive Ig (*n* = 111)	SMM without GlcSph-reactive Ig (*n* = 68)	All SMM (*n* = 179)	MGUS[a] (*n* = 155)	MM[a] (*n* = 147)	All patients[a] (*n* = 421)	*p*
Presence of GlcSph-reactive Igs	111	0	111 (62.0%)				
Purified mcIg	67 (68.6%)	56 (82.3%)	119 (66.5%)				
Determined target of purified mcIg	46 (64.2%)	30 (53.6%)	76 (63.9%)[b,c]	120 (77.4%)[d]	69 (46.9%)	265 (62.9%)	[b]$p = 0.013727$, [c]$p = 0.005841$, [d]$p < 0.00001$
GlcSph	7 (10.4%)	0 (0%)	7 (5.9%)[b,c]	25 (16.1%)[d]	20 (13.6%)	52 (12.3%)	[b]$p = 0.008853$, [c]$p = 0.038091$, [d]NS
Infectious target	39 (58.2%)	30 (53.6%)	69 (58.0%)[b,c]	95 (61.3%)[d]	49 (33.3%)	213 (50.6%)	[b]NS, [c]$p = 0.000057$, [d]$p < 0.00001$
EBV	17 (25.4%)	15 (26.8%)	32 (26.9%)	53 (34.2%)	38 (25.8%)	123 (29.2%)	[b,c,d]NS
CMV	11 (16.4%)	6 (10.7%)	17 (14.3%)[b,c]	4 (2.6%)	0	21 (5.0%)	[b]$p = 0.000306$, [c]$p < 0.00001$, [d]NS
Enterovirus VP1	4 (6.0%)	4 (7.1%)	8 (6.7%)	13 (8.4%)[d]	3 (2.0%)	24 (5.7%)	[b]NS, [c]NS, [d]$p = 0.013857$
H. pylori	4 (6.0%)	2 (3.6%)	6 (5.0%)	3 (1.9%)	2 (1.4%)	11 (2.6%)	[b,c,d]NS
HSV-1	2 (3.0%)	2 (3.6%)	4 (3.4%)	15 (9.7%)[d]	2 (1.4%)	21 (5.0%)	[b]NS, [c]NS, [d]$p = 0.001723$
HBV	1 (1.5%)	1 (1.8%)	2 (1.7%)	nd	nd	2 (0.5%)	[b,c,d]NS
HCV	0	0	0	2 (1.3%)	1 (0.6%)	3 (0.7%)	[b,c,d]NS
VZV	0	0	0	5 (3.2%)	3 (2.0%)	8 (1.9%)	[b,c,d]NS
Undetermined target	21 (31.3%)	26 (46.4%)	43 (36.1%)[b,c]	35 (22.6%)[d]	78 (53.1%)	35 (22.6%)	[b]$p = 0.013727$, [c]$p = 0.005841$, [d]$p < 0.00001$

Note: The Chi-2 test was used to compare the % of patients in the MGUS, SMM, and MM groups. $p < 0.05$ was considered significant.

Abbreviations: GlcSph, glucosylsphingosine; Ig, immunoglobulin; mcIg, monoclonal Ig; NS, not significant.

[a]Published previous studies.[1,7–9,13]

[b]SMM versus MGUS.

[c]SMM versus MM.

[d]MGUS versus MM.

possible, the 119 patients were more likely to have IgG versus non-IgG isotype ($p < 0.001$), and a higher M-protein quantity (7.0 g/L vs. 5.1 g/L, $p < 0.001$). Eighty individuals (67.2%) had low-risk, 26 (21.9%) had intermediate risk, and 13 (10.9%) had high-risk SMM, a repartition similar to the complete SMM cohort.

Polyclonal GlcSph-reactive Ig in serum was observed for 111/179 (62.0%) individuals (Table 1 and Supporting Information S1: Figure 2), yet only 7/119 (5.9%) SMM mcIg recognized GlcSph (Table 1 and Figure 1A). Of note, all seven patients with a GlcSph-reactive monoclonal Ig had low-risk SMM.

The reactivity of other mcIgs from the SMM cohort is detailed in Table 1 and shown in Figure 1 and Supporting Information S1: Figure 3. McIg from 69/119 (58.0%) SMM individuals targeted infectious pathogens. Frequent targets were EBV (EBV nuclear antigen-1, EBNA-1), recognized by 32/119 (26.9%) SMM mcIg (Figure 1B); CMV (17/119 or 14.3%) (Figure 1C and Supporting Information S1: Figure 3, Figure 4), then *H. pylori* (6/119 or 5.0%), HSV-1 (4 cases, 3.4%), and HBV (2 cases, 1.7%) (Supporting Information S1: Figure 5A). In addition, 8 SMM mcIg (6.7%) is specifically bound to the Enterovirus VP-1 protein (Supporting Information S1: Figure 5B). We were not able to identify the target of 43/119 (36.1%) SMM mcIg (22 IgG, 21 IgA). The percentages of mcIg that bound to an infectious protein were similar in MGUS and SMM, and lowest in MM, which may reflect the level of mcIg sialylation (correlated to Ig affinity for antigen), lowest in MM.[17]

Characteristics of SMM patients were analyzed according to the target of their mcIg (Supporting Information S1: Table 2). The 76 SMM patients who had an identified mcIg target were more likely to have IgG versus non-IgG isotype (94% vs. 77%, $p < 0.001$) than those with an unknown target. At the time of SMM diagnosis, they had slightly lower platelet and leukocyte counts than other patients. Using the 2/20/20 risk stratification, 52 (68.4%) patients with an identified target for their mcIg had low-risk, 16 (21.1%) intermediate risk, and 8 (10.5%) high-risk SMM, a repartition similar to patients with a mcIg of undetermined specificity (65.1% low-risk, 23.3% intermediate risk, 11.6% high-risk SMM).

Thirty-two individuals presented with a mcIg that targeted EBV (Supporting Information S1: Table 2): 22 (68.7%) had low-risk, 7 intermediate-risk (21.9%), and 3 (9%) high-risk SMM. Compared to other SMM cases with a purified mcIg, most had IgG isotype (97% vs. 77% $p = 0.004$) and a slightly higher mean hemoglobin level. Age, sex distribution, M-protein level, leukocyte and platelet counts, and SMM risk category were similar.

Seventeen SMM patients had a CMV-reactive mcIg (Supporting Information S1: Table 2). All had IgG isotype, and lower leukocyte and platelet counts. Age, sex, and M-protein quantity were not

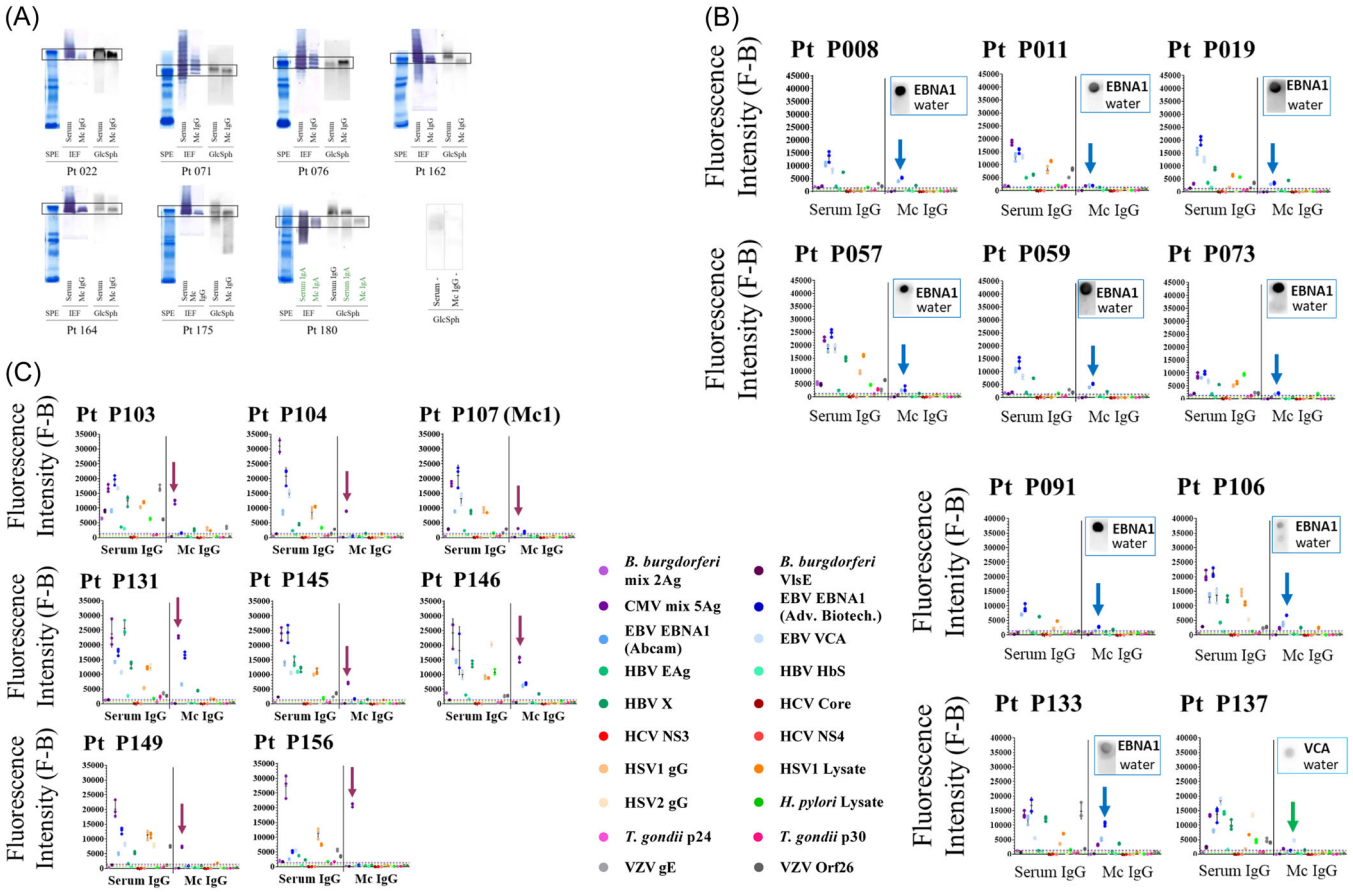

FIGURE 1 **Identified targets of purified monoclonal Ig from smoldering multiple myeloma (SMM) patients. (A)** GlcSph immunoblot assays of SMM patients with a GlcSph-reactive mcIg. For each patient, results were obtained in parallel with the unseparated serum IgG or IgA (in green) and the patient's purified mcIgG or mcIgA (in green). Measurement of Ig concentration, separation of the mcIg from other Igs by serum protein electrophoresis (SPE), and verification of the purity of the mcIg preparation by isoelectric focusing (IEF) were performed as described in the Supporting Information and published.[5,6,8] Polyvinylidene difluoride (PVDF) membranes were incubated in 100 µg/mL of GlcSph in 0.1 M sodium bicarbonate, rinsed three times, and then blocked for 2 h with 5% bovine serum albumin in phosphate-buffered saline (PBS) and 0.1% Tween 20. Samples of purified mcIg were submitted to agarose gel electrophoresis, then the gels were blotted onto the GlcSph-saturated membranes by diffusion blotting for 12 min.[5,6,8] After blocking for 1 h with 2.5% BSA in PBS and 0.1% Tween 20, membranes were incubated with peroxidase-conjugated AffiniPure donkey antihuman IgG (H+L) antibody (Jackson ImmunoResearch) or horseradish peroxidase (HRP)-conjugated goat anti-human IgA α chain antibody (Bethyl Laboratories) for 1 h, then washed and revealed with Super Signal West Pico chemiluminescent substrate (Thermo Scientific). Signals corresponding to the patient's mcIg are encircled. The negative control is a patient with no reactivity for GlcSph. **(B)** Typical MIAA and dot blot assays of SMM patients with a monoclonal Ig that targets EBV. For each patient, results were obtained in parallel with the unseparated serum IgG or IgA (Serum, left) and the patient's purified mcIg (right) using the MIAA assay; results are shown as fluorescent intensity (FI). The FI values shown for each pathogen, Ag, protein, or lysate, were obtained after subtraction of the fluorescent background (B) of each pathogen protein or lysate. The thresholds of specific positivity, shown in dotted lines, were defined for each pathogen or protein: 1400 for EBV, CMV, VZV, HBV and *B.burgdorferi*, blue threshold; 1000 for HSV-1 and HSV-2, orange dotted line; 500 for HCV, *H. pylori* and *T. gondii*, green threshold. Dots may be superimposed; horizontal bars represent the means of results obtained for a pathogen (Ag, lysate). Experiments were performed in triplicate, and repeated at least once. Inserts show the results of EBV dot blot assays with recombinant EBV EBNA-1 or VCA proteins; water was used as a negative control. Dot blot assays confirmed that the purified mcIg recognized EBV EBNA-1 or VCA, as identified with the MIAA assay. Dot blot experiments were performed at least twice. **(C)** Typical MIAA assays of SMM patients with a monoclonal Ig that targets CMV. For each patient, results were obtained in parallel with the unseparated serum IgG or IgA (serum, left) and the patient's purified mcIg (right) using the MIAA assay; results are shown as FI. The FI values shown for each pathogen, Ag, protein, or lysate, were obtained after subtraction of the fluorescent background (B) of each pathogen protein or lysate. The thresholds of specific positivity (dotted lines) were defined for each pathogen or protein (1400 for CMV, blue threshold). Dots may be superimposed; horizontal bars represent the means of results obtained for a pathogen (Ag, lysate). Experiments were performed in triplicate and repeated at least once. Parts B and C show typical results of SMM patients; the results of all patients are shown in Supporting Information S1: Figure 3.

different between groups. Of note, 13/17 (76.5%) individuals with CMV-associated SMM had low-risk SMM, and none had high-risk SMM. Twenty-seven SMM patients presented with a mcIg specific for other targets. Eighteen (66.7%) had low-risk, five (18.5%) intermediate risk, and four (14.8%) high-risk SMM.

When the three groups (EBV, CMV, and other infectious targets) were compared to patients with a mcIg of unknown target, there was no statistically significant difference in hemoglobin, leukocytes, platelets, M-protein, or SMM risk category. However, patients with a mcIg specific for CMV or GlcSph were more likely to present with low-risk SMM (83.3% vs. 60.8% respectively, $p = 0.032$, Chi-square test).

Seven patients presented with *H. pylori*-reactive mcIg. Four (P15, P41, P93, P97) agreed to undergo upper endoscopy for confirmation of *H. pylori* infection. All had positive urea breath tests and gastric

biopsies revealed positive cultures, signs of chronic inflammation, and the presence of *H. pylori*. They received eradication therapy: amoxicillin (2 × 1 g/day), clarithromycin (2 × 500 mg/day), and omeprazole for 7 days. All urea breath tests became negative. Two months later, lower M-protein levels were noted for two patients and the reactivity of mcIgs to *H. pylori* decreased, in contrast with the strong reactivity of nonclonal Igs (Supporting Information S1: Figure 6A,B). However, after 20 to 32 months of follow-up, none of the patients showed a reduction of M-protein quantity or the plasmacytic clone (Supporting Information S1: Figure 6C,D). It is possible that infection does not have an effect on the progression of SMM disease or that anti-*H. pylori* therapy occurred too late in the gammopathy evolution. Indeed, although antiviral therapy benefited patients with HCV- or HBV-initiated MM, improving their overall survival after chemotherapy,[11,12] one expects anti-infection treatments to be more efficient on the plasmacytic clone when prescribed at the MGUS stage before the accumulation of genetic defects renders clone expansion antigen-independent. Large studies of individuals identified as having *H. pylori*-associated MGUS or SMM should confirm or infirm this hypothesis.

We also analyzed the characteristics of SMM patients according to the presence or absence of auto-immune response against GlcSph (Supporting Information S1: Table 3): those with GlcSph-reactive Ig had a lower mean M-protein level (4.7 vs. 6.7 g/L, $p < 0.001$). More individuals with GlcSph-reactive Ig had low-risk SMM (77/111 or 69.4%) than other patients (38/68 or 55.9%) but the difference was not significant ($p = 0.067$). GlcSph is a proinflammatory glucolipid, and lipid-mediated inflammation can facilitate the development of malignancies.[18] Nonclonal GlcSph-reactive Igs are found in chronic inflammatory diseases, autoimmune diseases, and solid and blood cancers (e.g., myeloproliferative neoplasms, where GlcSph levels were found mildly elevated).[19] We investigated whether SMM patients with a GlcSph-reactive mcIg may have undiagnosed GD.[5,6] DNA was available for genetic studies for four patients: no β-glucocerebrosidase mutation was detected.

In conclusion, identifying the target of mcIgs was possible for 76 SMM patients, mostly with IgG SMM. As reported for MGUS, the target of SMM mcIgG was an infectious pathogen in ~60% of the cases, essentially EBV (27%) and CMV (14%). Thus, EBV and CMV infection were frequent initial triggers of clonal gammopathy in this SMM cohort. Importantly, our study indicates that SMM linked to CMV or GlcSph appears to be low risk. Consequently, identification of the target of mcIgs may provide new prognostic markers, and novel targets for MGUS, SMM, or MM therapy.[20] Indeed, knowing the initial antigenic trigger (mcIg target) of clonal gammopathies in large cohorts, coupled with the analysis of patient characteristics, should allow us to determine the impact on prognosis (low- or high-risk gammopathy) and therapy (usefulness of antigen suppression?) depending on the initial trigger. Part of these studies can be done retrospectively if serum samples of patients are available. Presently, the MIAA assay remains a research assay and works best for IgG. The panel of infectious pathogens tested may be expanded: for instance, depending on geographic localization, it may be useful to add endemic pathogens potentially associated with monoclonal gammopathies.

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AUTHOR CONTRIBUTIONS

Sylvie Hermouet, Edith Bigot-Corbel, and Sigurdur Y. Kristinsson designed the research, analyzed data, and wrote the initial manuscript draft. Nicolas Mennesson, Sophie Allain-Maillet, and Edith Bigot-Corbel performed experiments and edited the manuscript. Andri Olafsson, Brynjar Viðarsson, Páll T. Önundarson, Bjarni A. Agnarsson, Margrét Sigurðardóttir, Ingunn Þorsteinsdóttir, Ísleifur Ólafsson, Elías Eyþórsson, Ásbjörn Jónsson, Thorvardur J. Love, Saemundur Rognvaldsson, Einar S. Björnsson, Sigrún Thorsteinsdóttir, and Sigurdur Y. Kristinsson contributed patient samples and clinical data. Sigrún Thorsteinsdóttir analyzed data, performed statistical analysis, and helped write the manuscript. All authors gave final approval of the initial and revised versions submitted to publication and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

Sylvie Hermouet, Nicolas Mennesson, Sophie Allain-Maillet, Edith Bigot-Corbel, Andri Olafsson, Brynjar Viðarsson, Páll T. Önundarson, Bjarni A. Agnarsson, Margrét Sigurðardóttir, Ingunn Þorsteinsdóttir, Ísleifur Ólafsson, Elías Eyþórsson, Ásbjörn Jónsson, Thorvardur J. Love, Saemundur Rognvaldsson, Einar S. Björnsson, Sigrún Thorsteinsdóttir, and Sigurdur Y. Kristinsson declare that they have no conflict of interest and nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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