Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study

Sigurdur Y. Kristinsson,[1] Min Tang,[2] Ruth M Pfeiffer,[3] Magnus Björkholm,[1] Lynn R. Goldin,[3] Cecilie Blimark,[4] Ulf-Henrik Mellqvist,[4] Anders Wahlin,[5] Ingemar Turesson,[6] and Ola Landgren[1,3,7]

[1]Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; [2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, and Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [4]Department of Medicine, Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden; [5]Department of Radiation Sciences Umeå University, Umeå, Sweden; [6]Department of Hematology, Skane University Hospital, Malmö, Sweden; and [7]Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

ABSTRACT

No comprehensive evaluation has been made to assess the risk of viral and bacterial infections among patients with monoclonal gammopathy of undetermined significance. Using population-based data from Sweden, we estimated risk of infections among 5,326 monoclonal gammopathy of undetermined significance patients compared to 20,161 matched controls. Patients with monoclonal gammopathy of undetermined significance had a 2-fold increased risk ($P<0.05$) of developing any infection at 5- and 10-year follow up. More specifically, patients with monoclonal gammopathy of undetermined significance had an increased risk ($P<0.05$) of bacterial (pneumonia, osteomyelitis, septicemia, pyelonephritis, cellulitis, endocarditis, and meningitis), and viral (influenza and herpes zoster) infections. Patients with monoclonal gammopathy of undetermined significance with M-protein concentrations over 2.5 g/dL at diagnosis had highest risks of infections. However, the risk was also increased ($P<0.05$) among those with concentrations below 0.5 g/dL. Patients with monoclonal gammopathy of undetermined significance who developed infections had no excess risk of developing multiple myeloma, Waldenström macroglobulinemia or related malignancy. Our findings provide novel insights into the mechanisms behind infections in patients with plasma cell dyscrasias, and may have clinical implications.

Key words: monoclonal gammopathy of undetermined significance, infections, multiple myeloma, bacteria, virus.

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Introduction

Infections are an important cause of morbidity and the leading cause of death in patients with multiple myeloma (MM).[1] Recently, much attention has been drawn to the changing spectrum of infections in MM, possibly related to the more intensive treatment and new classes of therapeutic agents of recent years.[2-4]

According to recent studies, MM is always preceded by monoclonal gammopathy of undetermined significance (MGUS).[5] While patients with MGUS are asymptomatic, they have increased morbidity and mortality compared to the general population.[6-8] The risk of infections among patients with MGUS has not been studied in great detail. Gregersen *et al.* analyzed risk of bacteremia in 1,237 MGUS patients in Denmark diagnosed from 1981 to 1993.[9] Based on 40 episodes of bacteremia, there was a 2.2-fold increase in risk compared to the general population. In another study based on screening data from Olmsted County in Minnesota, risks of several different diseases, including some infectious disorders, were analyzed among 605 MGUS patients and compared to 16,793 controls.[8] An increased risk of upper respiratory bacterial infection, spontaneous bacterial peritonitis, and mycobacterium infection was found. We previously showed that MGUS patients had a higher mortality compared to matched controls that was explained by the increased risk of several different causes of death, including infections.[6] In addition, there have been some smaller series and case reports on associations between MGUS and selected infections.[10-12] To our knowledge, there has been no systematic analysis of the risk of a broad span of bacterial and viral infections in a large population-based cohort of MGUS patients.

Using high-quality population-based data from Sweden, we assessed the risk of bacterial and viral infections and indi-

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Correspondence: Sigurdur Yngvi Kristinsson, MD, PhD, Department of Medicine, Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden. Phone: international +46.8.51771922. Fax: international +46.8.318264. E-mail: sigurdur.kristinsson@karolinska.se

vidual infections in 5,326 MGUS patients compared to 20,161 population-based matched controls.

Design and Methods

The details of the study population have been described previously.[13] We established a nationwide MGUS cohort from a national hospital network including MGUS patients diagnosed in Sweden between 1965 and 2005. All available information on MGUS subtype and concentration of the M-protein at diagnosis was included in the dataset. To minimize the influence of a potentially undetected lymphoproliferative malignancy, MGUS patients who were diagnosed with a lymphoproliferative malignancy within six months of MGUS diagnosis were excluded from the analysis. For each MGUS patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive and free of any preceding hematologic malignancy at the time of MGUS diagnosis for the corresponding case.

Information on occurrence and date of infections was obtained from the centralized Swedish Patient Registry that captures information on individual patient-based discharge diagnoses and discharge listings from inpatient (since 1964, with very high coverage from 1987) and outpatient (since 2000) care. Through linkage with the Cause of Death Register and the Register of Total Population, we collected information on vital status until December 31, 2006.

Cox's proportional hazard models (adjusted for sex, age at diagnosis and year of diagnosis) were used to compare 5- and 10-year risks of infections in MGUS patients compared to controls. Follow up started at age at diagnosis of MGUS (age at registration for controls) or January 1, 1987, if MGUS was diagnosed before that date. Censoring events were death, emigration, the end of acquisition period or diagnosis of a lymphoproliferative disorder. We excluded all infections occurring in the first six months from MGUS diagnosis (date of selection for controls). For sensitivity analyses, we excluded infections occurring within 12 months of MM diagnosis. The results were essentially the same.

Approval was obtained from the Karolinska Institutional Review Board (IRB) for this study. Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Results and Discussion

A total of 5,326 MGUS patients and 20,161 matched population-based controls were included in this study (Table 1). The median age at diagnosis was 71 years, and 50% of patients were male. The MGUS isotype was available in 61% of patients, and was IgG, IgA, and IgM in 40%, 11%, and 10% of patients, respectively. Information on the M-protein concentration at diagnosis was available in 53% of patients; of these 60% had a value above and 40% below 1.0 g/dL.

A total of 377 MGUS patients (7.1%) and 550 controls (2.7%) were diagnosed with more than one infection. The average number of infections per MGUS patient was 0.34 and 0.17 per control. Median time from MGUS diagnosis to first infection was 1,928 days.

At 5-year follow up, compared to controls, MGUS patients had a 2.1-fold (95% confidence interval (CI) 2.0-2.3) increased risk of developing any infection; at 10-year follow up, the risk was very similar (hazard ratio (HR)=2.2; 95% CI 2.0-2.3; Table 2). We further found MGUS patients to have a 2.1-fold (95% CI 1.9-2.3) and a 2.2-fold (95% CI 2.0-2.4) increased risk of developing bacterial infections at five and ten years, respectively. When we assessed risks of individual bacterial infections, at 10-year follow up, we found an increased risk of pneumonia (HR=2.4; 95% CI 2.2-2.6), osteomyelitis (HR=3.3; 95% CI 2.1-5.0), septicemia (HR=3.1; 95% CI 2.6-3.6), pyelonephritis (HR=2.5; 95% CI 2.1-3.2), cellulitis (HR=1.9; 95% CI 1.5-2.3), endocarditis (HR=2.2; 95% CI 1.2-3.9) and meningitis (HR=3.1; 95% CI 1.5-6.5) (Table 2). Our findings that MGUS patients are at a 2-fold increased risk of a broad range of bacterial infections agree with the results of the prior smaller study from Denmark,[9] and they support the hypothesis that MGUS is associated with an underlying immunodeficiency. It is clear that the major immunological defect in MM and Waldenström macroglobulinemia (WM) patients is in the humoral system, with a diminished production of polyclonal immunoglobulins which leads to a defective antibody response.[1,14,15] In MGUS, prior studies report that hypogammaglobulinemia is present in 25-28% of the cases.[9,16] Interestingly, in contrast to MM and WM, in the MGUS study from Denmark, presence of hypogammaglobulinemia was not associated with an increased risk of bacteremia.[9] A limitation of our study was the lack of quantitative data regarding immunoglobulins in the large majority of the MGUS patients.[6]

Regarding individual viral infections, compared to controls, MGUS patients had a 2.7-fold (95% CI 2.1-3.6) and 2.7-fold (95% CI 2.2-3.3) increased risk of developing viral infections at five and ten years, respectively. At 10-year follow up, MGUS patients had an increased risk of influenza (HR=2.7; 95% CI 1.9-3.9) and herpes zoster (HR=2.8; 95% CI 2.0-3.9; Table 2). To our knowledge, this is the first large population-based study that shows that

Table 1. Characteristics of patients with MGUS and their matched controls.

	MGUS patients	MGUS controls
Total, n. (%)	5,326 (20.90)	20,161 (79.10)
Gender, n. (%)		
Male	2,642 (49.61)	9,990 (49.55)
Female	2,684 (50.39)	10,171 (50.45)
Age at dx, median (range)	71 (22-100)	71 (22-100)
Age group, n. (%)		
< 40	114 (2.14)	446 (2.21)
40-49	336 (6.31)	1,310 (6.50)
50-59	765 (14.36)	2,963 (14.70)
60-69	1,210 (22.72)	4,684 (23.33)
70-79	1,779 (33.40)	6,756 (33.51)
80 ≥	1,122 (21.07)	4,002 (19.85)
MGUS subtype, n (%)		
IgG	2,146 (40.29)	-
IgA	578 (10.85)	-
IgM	530 (9.95)	-
IgD	2 (0.00)	-
Missing	2,070 (38.87)	-
M-protein concentration, n (%)		
< 10.0 g/dL	1,732 (32.52)	-
> 10.0 g/dL	1,108 (20.80)	-
Missing	2,486 (46.68)	-

- not applicable; dx: diagnosis.

MGUS patients have an increased risk of viral infections. Interestingly, this risk is similar to that we observed for bacterial infections. MM and WM patients have an increased risk of viral infections. However, this is mainly related to the therapy given, e.g. herpes zoster infections in patients treated with bortezomib.[17] In a case series, MGUS was associated with an increased frequency of Epstein-Barr infections.[18] In the study from the Mayo clinic, no increase in several viral infections (chronic hepatitis, cytomegalovirus infection, Epstein-Barr infection, hepatitis C, human immunodeficiency virus) was found among patients with MGUS.[8]

We found that the risk of infections was similar for the different MGUS isotypes (IgG, IgA and IgM; Table 3) and in an analysis stratified by M-protein concentration, the risk of infection was similar among MGUS cases with an M-protein of 1.0 g/dL and over, and less than 1.0 g/dL, respectively (Table 3). MGUS patients with M-protein concentrations over 2.5 g/dL at diagnosis had higher (P<0.005) risks of infections compared to those with concentrations less than 0.5 g/dL. However, compared to controls, the risk of infections was still significantly increased among MGUS patients with concentrations less than 0.5 g/dL. The underlying mechanisms for these findings are not clear, but it is known that higher M-proteins are associated with hypogammaglobulinemia.

When we assessed the risk of developing MM (n=187), WM or related malignancies (n=20) among MGUS patients with (*vs.* without) an infectious event, we found no statistical difference (HR=0.72; 95% CI 0.40-1.30). In a sensitivity analysis, we also excluded MGUS patients who developed myeloma and the risk estimates were similar (*data not shown*). Prior studies have found a history of infectious disease to increase the risk of developing MGUS and MM suggesting that infections may trigger MGUS or MM in susceptible patients.[19,20] Furthermore, low levels of polyclonal immunoglobulins in MGUS patients have been found to be a risk factor for progression to MM or a related lymphoproliferative malignancy.[21] Taken together, the predisposing role of infections in MGUS and MM remains for the most part unclear.

Lastly, when we stratified risk of infections by three calendar time periods of MGUS diagnosis or selection (<1987, 1988-1996, and >1997), MGUS patients had somewhat different, but consistently increased risk of infections for all calendar periods with HR=2.8 (95% CI 2.1-3.6, HR=1.9 (95% CI 1.7-2.3), and 2.1 (95% CI 1.9-2.4) for before 1987, 1988-1996, and after 1997, respectively (P heterogeneity <0.001).

Our study has several strengths, including its large sample size and the high-quality population-based data from Sweden, including a population that had access to standardized medical care during the entire study period. As reported previously,[22] the MGUS patients in our study were diagnosed at hematology/oncology outpatient units using standard criteria at the time of diagnosis. In accordance with clinical practice in Sweden, most MGUS patients typically underwent a bone marrow examination as part of the clinical workup. In a recent validation study, we have reported that ascertainment and diagnostic accuracy for lymphoproliferative disorders is very high (>90-95%) in Sweden.[23] Limitations are the lack of information on detailed clinical data including bone marrow examination and underlying diseases, and thus the observed excess risks among MGUS patients may partly reflect various underlying medical illnesses that led to the medical workup and the detection of the M-protein. To lessen the impact of this problem, we excluded MGUS patients with

Table 2. Relative risk of selected infections after a diagnosis of MGUS compared to matched controls.

Disease/grouping	5-year follow up MGUS (n=5326)	5-year follow up Ctrl (n=20,161)	5-year follow up HR* (95% CI)	10-year follow up MGUS pts	10-year follow up Ctrl	10-year follow up HR* (95% CI)
Any infection (combined)**						
All patients	789	1564	2.1 (2.0-2.3)	1282	2603	2.2 (2.1-2.3)
Males	424	894	2.0 (1.8-2.2)	679	1440	2.1 (1.9-2.3)
Females	365	670	2.3 (2.0-2.6)	603	1163	2.3 (2.1-2.5)
Specific infections						
Bacterial***	736	1468	2.1 (1.9-2.3)	1215	2451	2.2 (2.0-2.4)
Pneumonia	416	778	2.4 (2.1-2.7)	695	1309	2.4 (2.2-2.6)
Osteomyelitis	19	30	2.8 (1.5-4.9)	37	49	3.3 (2.1-5.0)
Septicemia	143	201	3.1 (2.5-3.8)	257	361	3.1 (2.6-3.6)
Pyelonephritis	84	132	2.8 (2.1-3.6)	134	231	2.5 (2.1-3.2)
Cellulitis	66	163	1.7 (1.3-2.2)	120	276	1.9 (1.5-2.3)
Meningitis	7	11	2.9 (1.1-7.6)	12	17	3.1 (1.5-6.5)
Endocarditis	10	20	2.1 (1.0-4.6)	17	34	2.2 (1.2-3.9)
Other bacterial*****	172	379	1.8 (1.5-2.2)	317	676	2.0 (1.7-2.2)
Viral****	87	132	2.7 (2.1-3.6)	145	231	2.7 (2.2-3.3)
Influenza	29	42	3.2 (2.0-5.1)	45	75	2.7 (1.9-3.9)
Herpes zoster	32	52	2.7 (1.8-4.3)	60	95	2.8 (2.0-3.9)

*HR: hazard ratio; CI: confidence interval; ctrl: controls; *Cox's proportional hazard models were used to compare 5- and 10-year risks of infections in MGUS patients compared to controls. The time metric was age. Follow up started at the later of either age at selection or January 1, 1987. Age at selection was age at MGUS diagnosis for a case and for a control it was age of diagnosis of the matched case. Infections occurring during the first six months were excluded. Follow up ended at the age of diagnosis of a specific infection event or age at censoring. Censoring events were death, emigration, the end of acquisition period (December 31, 2006) or diagnosis of a lymphoproliferative disorder. Adjusted (by sex, age at diagnosis, and year of diagnosis) HRs and 95% CIs were estimated; ** pneumonia, cellulitis, osteomyelitis, endocarditis, meningitis, septicemia, malaria, pyelonephritis, cystitis, sinusitis, tuberculosis, syphilis, gonorrhea, Chlamydia, otitis media, nasopharyngitis/pharyngitis, empyema, HIV, herpes simplex, herpes zoster, hepatitis (A-C), mononucleosis, encephalitis, pericarditis, myocarditis, and influenza; ***pneumonia, cellulitis, osteomyelitis, endocarditis, meningitis, septicemia, malaria, pyelonephritis, cystitis, sinusitis, tuberculosis, syphilis, gonorrhea, Chlamydia, otitis media, nasopharyngitis/pharyngitis, empyema; ****HIV, herpes simplex, herpes zoster, hepatitis (A-C), mononucleosis, encephalitis, pericarditis, myocarditis, and influenza.*

Table 3. Relative risk for selected infections among MGUS patients (*vs.* matched controls), stratified by MGUS subtype (IgG/IgA *vs.* IgM) and by M-protein concentration at diagnosis (above *vs.* below 1 g/dL).

	IgG/IgA subtype						IgM subtype					
	5-year follow up			10-year follow up			5-year follow up			10-year follow up		
Disease/ grouping	MGUS (n=2724)	Ctrl (n=10,348)	HR* (95% CI)	MGUS pts	Ctrl	HR* (95% CI)	MGUS (n=530)	Ctrl (n=2,017)	HR* (95% CI)	MGUS pts	Ctrl	HR* (95% CI)
Any infection**	402	731	2.3 (2.0-2.6)	662	1255	2.3 (2.1-2.5)	64	181	1.4 (1.01-1.8)	135	300	1.7 (1.4-2.1)
Bacterial***	376	686	2.3 (2.0-2.6)	633	1184	2.3 (2.1-2.5)	60	171	1.3 (0.99-1.8)	128	287	1.7 (1.4-2.1)
Viral****	41	63	2.6 (1.8-3.9)	68	109	2.5 (1.9-3.4)	5	10	2.2 (0.7-6.5)	12	18	2.7 (1.3-5.7)
	Concentration of M protein below 1g/dL						Concentration of M protein above 1g/dL					
	5-year follow up			10-year follow up			5-year follow up			10-year follow up		
Disease/ grouping	MGUS pts (n=1732)	Ctrl (n=6585)	HR* (95% CI)	MGUS pts	Ctrl	HR* (95% CI)	MGUS (n=1108)	Ctrl (n=4214)	HR* (95% CI)	MGUS pts	Ctrl	HR* (95% CI)
Any infection**	235	445	2.3 (1.9-2.6)	389	767	2.2 (2.0-2.5)	167	338	2.0 (1.6-2.4)	283	547	2.1 (1.8-2.5)
Bacterial***	218	418	2.2 (1.9-2.6)	371	724	2.2 (2.0-2.5)	155	315	1.9 (1.6-2.4)	266	514	2.1 (1.8-2.4)
Viral****	26	33	3.3 (2.0-5.6)	36	61	2.2 (1.2-4.0)	17	31	2.5 (1.6-3.8)	36	51	2.8 (1.8-4.3)

*HR: hazard ratio; CI: confidence interval; ctrl: controls; *Cox's proportional hazard models were used to compare 5- and 10-year risks of infections in MGUS patients compared to controls. The time metric was age. Follow up started at the later of either age at selection or January 1, 1987. Age at selection was age at MGUS diagnosis for a case and for a control it was age of diagnosis of the matched case. Infections occurring during the first six months were excluded. Follow up ended at the age of diagnosis of a specific infection event or age at censoring. Censoring events were death, emigration, the end of acquisition period (December 31, 2006) or diagnosis of a lymphoproliferative disorder. Adjusted (by sex, age at diagnosis, and year of diagnosis) HRs and 95% CIs were estimated; **pneumonia, cellulitis, osteomyelitis, endocarditis, meningitis, septicemia, malaria, pyelonephritis, cystitis, sinusitis, tuberculosis, syphilis, gonorrhea, Chlamydia, otitis media, nasopharyngitis/pharyngitis, empyema, HIV, herpes simplex, herpes zoster, hepatitis (A-C), mononucleosis, encephalitis, pericarditis, myocarditis, and influenza; ***pneumonia, erysipelas, osteomyelitis, endocarditis, meningitis, septicemia, malaria, pyelonephritis, cystitis, sinusitis, tuberculosis, syphilis, gonorrhea, Chlamydia, otitis media, nasopharyngitis/pharyngitis, empyema; ****HIV, herpes simplex, herpes zoster, hepatitis (A-C), mononucleosis, encephalitis, pericarditis, myocarditis, and influenza; *****all except those specified above.*

a diagnosis of a lymphoproliferative malignancy and infections diagnosed within six months following MGUS diagnosis from our analyses.[24] Since our controls were population-based and not screened for M-protein, one has to be cautious and consider possible bias. For example, given the fact that MGUS patients are followed clinically, it may have contributed to the reporting of more infections (i.e. surveillance bias). One future strategy to assess the potential influence of detection and surveillance bias may be the launching of a large record-linkage study based on a screened MGUS population. Although the risk determined in a screened MGUS population is likely to be more conservative and would also reflect the biological underpinning involved in infectious complications following MGUS, this study is based on the general clinical setting. Another limitation is that some of the controls are expected to have undiagnosed MGUS. Furthermore, there is also the potential for inaccuracy and the lack of independent validation of infectious diagnosis obtained from the centralized Patient Registry as the infections may not be microbiologically verified. However, this problem should affect MGUS cases and matched controls equally and thus any bias should be towards a null association.

In summary, we found MGUS patients from a clinic-based cohort to have a significantly increased risk of several types of both bacterial and viral infections. High M-protein concentration at diagnosis was associated with the highest risks of infections. However, the occurrence of infection was not associated with MM or lymphoproliferative disease progression. Our study provides novel insights into the underlying mechanisms behind infections in patients with plasma cell dyscrasias, and may have clinical implications for treatment strategies, prophylactic measures and vaccinations, as well as surveillance of MGUS patients.

Authorship and Disclosures

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