Personal and family history of immune-related conditions increase the risk of plasma cell disorders: a population-based study

Ebba K. Lindqvist,[1] Lynn R. Goldin,[2] Ola Landgren,[1,3] Cecilie Blimark,[4] Ulf-Henrik Mellqvist,[4] Ingemar Turesson,[5] Anders Wahlin,[6] Magnus Björkholm,[1] and Sigurdur Y. Kristinsson[1]

[1]Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD; [3]Center for Cancer Research, NCI, NIH, Bethesda, MD; [4]Department of Medicine, Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden; [5]Department of Hematology, Skåne University Hospital, Malmö, Sweden; and [6]Cancer Centre, Section of Hematology, Umeå University Hospital, Umeå, Sweden

The associations between immune-related conditions and multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS) have previously been investigated with inconsistent results. In a large population-based study, we identified 19 112 patients with MM, 5403 patients with MGUS, 96 617 matched control subjects, and 262 931 first-degree relatives. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the association of MM and MGUS with immune-related conditions by use of logistic regression. A personal history of all infections combined was associated with a significantly increased risk of MM (OR = 1.2; 95% CI, 1.1-1.3), and a personal history of all conditions in the categories infections (OR = 1.6; 95% CI, 1.5-1.7), inflammatory conditions (OR = 1.4; 95% CI, 1.2-1.5), and autoimmune diseases (OR = 2.1; 95% CI, 1.9-2.4) was associated with a significantly increased risk of MGUS. Several specific immune-related conditions elevated the risk of MM and/or MGUS. A family history of autoimmune disease was associated with a significantly increased risk of MGUS (OR = 1.1; 95% CI, 1.00-1.2), but not MM. Our findings suggest that immune-related conditions and/or their treatment are of importance in the etiology of MGUS and possibly MM. The association of both personal and family history of autoimmune disease with MGUS indicates the potential for shared susceptibility for these conditions. (*Blood*. 2011; 118(24):6284-6291)

Introduction

Multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS) are grouped together as plasma cell disorders.[1] MM is characterized by a proliferation of clonal plasma cells in the bone marrow that overproduce monoclonal protein (M-protein), resulting in tissue damage, such as osteolytic lesions, anemia, renal failure, and hypercalcemia.[1,2] MGUS is the precursor to MM and is by definition an asymptomatic, premalignant condition with an average risk of progression to MM or other lymphoproliferative disorders of 1% per year.[3-5]

The etiology of both MM and MGUS is largely unknown. Evidence for genetic factors includes increased risk of MM and MGUS in first-degree relatives of patients with one of these disorders,[6-9] as well as racial disparities in the incidence patterns of MM and MGUS.[10,11] Older age, male gender, and exposure to pesticides have also been identified as risk factors for MGUS.[12,13]

Convincing evidence shows immune dysregulation to play a major role in lymphomagenesis; however, much less is known regarding immune-related conditions and risk of plasma cell disorders.[14] Results from prior population-based studies have been inconsistent with some indicating no association between autoimmune disease and subsequent risk of MM.[15] We and others previously have found only single conditions, such as pernicious anemia and polymyalgia rheumatica, to increase the risk of MM.[7,16] Some of these associations found in previous studies were restricted to the first year preceding the MM diagnosis, suggesting a possibility of the autoimmune disease being discovered during the workup of a plasma cell disorder.[16] In addition to autoimmune diseases, recent studies suggest that a personal history of infections increases the risk of MM; however, much less is known about infections and MGUS.[17-19] Results from a retrospective study of male United States veterans with MM (n = 4641) and MGUS (n = 2046) patients showed a personal history of all autoimmune diseases combined, all infections combined, all inflammatory conditions combined, as well as several specific conditions to be associated with an increased risk of MM and MGUS.[17] Despite the study being restricted to male veterans, the results indicate a possible association between immune-related conditions and plasma cell disorders.

To increase our understanding of the impact of immune-related conditions and plasma cell disorders, we have performed the largest study to date, a population-based, case-control study, involving males and females diagnosed with MM and MGUS over a 40-year period, using high quality data from Sweden. Among 19 112 patients with MM, 5403 patients with MGUS, their 96 617 population-based controls, and 262 931 first-degree relatives of MM and MGUS cases and controls, we evaluated the association between a prior personal or family history of a broad range of autoimmune diseases, infections, and inflammatory conditions and the subsequent development of MM or MGUS.

Submitted April 14, 2011; accepted September 30, 2011. Prepublished online as *Blood* First Edition paper, October 13, 2011; DOI 10.1182/blood-2011-04-347559.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Table 1. Characteristics of MM and MGUS patients

Variable	MM patients	MM controls	MGUS patients	MGUS controls
No. in total	19 112	75 408	5403	21 209
Males, no. (%)	10 427 (55)	41 269 (55)	2677 (50)	10 537 (50)
Females, no. (%)	8685 (45)	34 139 (45)	2726 (50)	10 672 (50)
Median age at diagnosis, y (range)	71 (24-101)	—	71 (22-100)	—
Isotype, no. (%)				
Isotype IgA/IgG	—	—	2747 (51)	—
Isotype IgM	—	—	529 (10)	—
Unknown	—	—	2127 (39)	—
M-protein at diagnosis, no. (%)				
< 10 g/L	—	—	1567 (29)	—
> 10 g/L	—	—	1286 (24)	—
Unknown	—	—	2550 (47)	—

— indicates not applicable.

Methods

Registries, patients, and control subjects

In Sweden, patients with lymphoproliferative malignancies are typically diagnosed and followed clinically by physicians at hospital-based hematology or oncology centers. All pathologists/cytologists and physicians in Sweden have been required to report each case of cancer that they diagnose or treat to the nationwide Swedish Cancer Register since 1958.[20] In a recent validation study, the completeness and diagnostic accuracy of the Register were found to be very high (> 93%) for MM patients diagnosed in Sweden 1964 to 2003.[21]

Approval was obtained from the Karolinska Institutional Review Board for this study. We identified all patients with a first cancer diagnosis of MM who were diagnosed from January 1, 1965 through December 31, 2004 in the nationwide Swedish Cancer Register. Patients with MGUS are not reported to the Swedish Cancer Register; thus, information on patients with MGUS diagnosed from January 1, 1965 through December 31, 2004 was retrieved through a national network, including all outpatient units in major hematology and oncology centers in Sweden. In addition, we identified all patients with MGUS diagnosed in the same period of time reported in the Swedish Inpatient Register, which captures information on individual patient-based discharge diagnosis from inpatient (since 1964) and outpatient (since 2001) care with very high coverage and accuracy.[22,23]

For all included patients, we obtained information on sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made. When available, information on MGUS M-protein isotype and concentration of the M-protein at diagnosis was also collected.

For each MM or MGUS patient, 4 population-based control subjects matched by sex, year of birth, and county of residence were chosen randomly from the Swedish Population database. The control subjects had to be alive at the time of MM or MGUS diagnosis of the corresponding case and without preceding hematologic malignancy at the date of the corresponding case's diagnosis.

We obtained information on all first-degree relatives, denoting parents, siblings, and offspring, of case patients and control subjects, from the Swedish Multigenerational Register.[24] MM and MGUS case patients and control subjects with no identified relatives were not included in the familial part of the study.

From the Swedish Inpatient Register, we obtained information on occurrence and date of immune-related condition. The condition only had to be on the discharge list for a hospitalization episode and was not required to be the primary diagnosis for which the patient was admitted. To code diagnoses for specific autoimmune, infectious, and inflammatory conditions, we used the seventh, eighth, ninth, and tenth revisions of the International Classification of Diseases. The conditions included in the analyses were in concurrence with a previously published study (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).[25] In accord with a previous study, autoimmune conditions were categorized according to those that generally have detectable autoantibodies and those that do not.[26]

Statistical analysis

We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of MM and MGUS with immune-related conditions by adjusting for year of birth (in quartiles), year of diagnosis (in quartiles), and sex. When no MM or MGUS patients or control subjects had an immune-related condition, unadjusted *P* values that were derived from the Fisher exact test were presented. All *P* values and 95% CIs were from 2-sided statistical tests.

Analyses on personal history were made for each of the 3 categories of immune-related conditions and for the specific conditions included in each category. To avoid the possibility of immune-related conditions being discovered more often in cases than in controls because of the diagnostic workup of a plasma cell disorder (detection bias), we excluded immune-related conditions diagnosed < 1 year before diagnosis of MM or MGUS (> 1 year latency). For the conditions that were statistically associated with MM or MGUS at more than 1 year latency, analyses were also stratified by age (< 71 or ≥ 71 years), by sex, and in MGUS by M-protein concentration (<15 g/L or > 15 g/L at diagnosis), and by M-protein isotype (IgA, IgG, or IgM). A sensitivity analysis was performed where the data were stratified by longer latency (time from diagnosis of immune-related condition to subsequent date of MM or MGUS diagnosis being > 5 years).

We also examined the association between a family history of autoimmune diseases and risk of MM and MGUS, by use of unconditional logistic regression adjusted for personal history of the condition, year of birth, year of diagnosis, sex, and county.

To explore whether the results differed between MGUS patients who later develop MM and MGUS patients who do not, we also performed a subanalysis where all MGUS patients who later developed MM were excluded from the MGUS cohort.

Results

A total of 19 112 patients with MM and 5403 patients with MGUS that were diagnosed January 1, 1965 through December 31, 2004 were included in the study, and 75 408 matched control subjects for MM, and 21 209 matched control subjects for MGUS. In addition, 38 037 first-degree relatives of MM case patients, 151 797 first-degree relatives of MM controls, 14 535 first-degree relatives of MGUS case patients, and 58 164 first-degree relatives of MGUS controls were included. The median age at diagnosis was 71 years for both MM and MGUS (Table 1).

Table 2. Personal history of autoimmune diseases and risk of MM and MGUS

	MM			MGUS		
Category or condition	MM patients (n = 19 112)	Controls (n = 75 408)	OR* (95% CI) [*P*]	MGUS patients (n = 5403)	Controls (n = 21 209)	OR* (95% CI) [*P*]
Total autoimmune disease†	443	1683	1.0 (0.9-1.2)	383	741	2.1 (1.9-2.4)
Autoantibodies detectable	277	1210	0.9 (0.8-1.02)	246	472	2.1 (1.8-2.5)
Systemic involvement	148	685	0.9 (0.7-1.01)	162	272	2.4 (2.0-2.9)
Rheumatoid arthritis	111	567	0.8 (0.6-0.9)	122	224	2.2 (1.7-2.7)
Systemic sclerosis	7	40	0.7 (0.3-1.5)	7	4	6.9 (2.0-23.6)
Sjögren syndrome	4	17	0.9 (0.3-2.7)	15	13	4.5 (2.2-9.6)
Systemic lupus erythematosus	11	29	1.5 (0.7-3.0)	7	12	2.3 (0.9-5.9)
Polymyositis or dermatomyositis	4	11	1.4 (0.5-4.5)	3	5	2.3 (0.6-9.8)
Organ involvement	137	559	1.0 (0.8-1.2)	93	218	1.7 (1.3-2.2)
Hashimoto thyroiditis	5	16	1.2 (0.4-3.4)	3	2	5.9 (0.99-35.5)
Graves disease	9	52	0.7 (0.3-1.4)	4	23	0.7 (0.2-2.0)
Addison disease	4	17	0.9 (0.3-2.7)	3	17	0.7 (0.2-2.4)
Pernicious anemia	48	156	1.2 (0.9-1.7)	19	41	1.8 (1.1-3.1)
Autoimmune hemolytic anemia	4	1	15.8 (1.8-141.0)	6	0	∞ [< .05]
Immune thrombocytopenia	4	10	1.6 (0.5-5.0)	7	4	6.9 (2.0-23.7)
Primary biliary cirrhosis	1	14	0.3 (0.0-2.1)	3	4	3.0 (0.7-13.2)
Discoid lupus erythematosus	3	6	2.0 (0.5-7.9)	2	7	1.1 (0.2-5.4)
Myasthenia gravis	4	16	1.0 (0.3-2.9)	1	6	0.6 (0.1-5.4)
Polyarteritis nodosa	1	3	1.3 (0.1-12.7)	4	0	∞ [< .05]
Guillain-Barré syndrome	2	15	0.5 (0.1-2.3)	6	8	3.0 (1.03-8.5)
Diabetes type 1	0	1	0 [1.00]	0	5	0 [.59]
Celiac disease	6	12	2.0 (0.7-5.3)	6	8	3.0 (1.03-8.6)
Dressler syndrome	2	13	0.6 (0.1-2.7)	3	9	1.3 (0.4-4.8)
Chronic rheumatic heart disease	30	159	0.7 (0.5-1.1)	21	48	1.7 (1.03-2.9)
Multiple sclerosis	14	64	0.9 (0.5-1.5)	6	32	0.7 (0.3-1.8)
Amyotrophic lateral sclerosis	1	6	0.7 (0.1-5.4)	2	2	3.9 (0.6-27.8)
Autoantibodies not detectable	189	538	1.4 (1.2-1.6)	171	314	2.2 (1.8-2.6)
Rheumatic fever	9	20	1.8 (0.8-3.9)	7	12	2.3 (0.9-5.9)
Sarcoidosis	15	67	0.9 (0.5-1.5)	16	37	1.7 (0.95-3.1)
Reiter disease	1	2	2.0 (0.2-21.8)	1	5	0.8 (0.1-6.8)
Crohn disease	16	60	1.1 (0.6-1.8)	15	46	1.3 (0.7-2.3)
Ulcerative colitis	33	97	1.3 (0.9-2.0)	20	58	1.4 (0.8-2.3)
Ankylosing spondylitis	12	40	1.2 (0.6-2.3)	15	22	2.7 (1.4-5.2)
Polymyalgia rheumatica	56	116	1.9 (1.4-2.6)	58	79	2.9 (2.1-4.1)
Psoriasis	33	130	1.0 (0.7-1.5)	24	62	1.5 (0.95-2.4)
Giant cell arteritis	16	8	7.8 (3.3-18.2)	20	7	11.3 (4.8-26.7)
Aplastic anemia	9	16	2.2 (0.98-5.0)	7	1	27.4 (3.4-222.4)

*When no case patient or control subject has the specific condition, *P* values (2-sided) based on Fisher exact test are given.
†Overall category totals more than the sum of the individual categories because some of the patients have > 1 autoimmune disease.

Personal history of autoimmune diseases and risk of plasma cell disorders

A total of 443 and 383 patients had a history of autoimmune disease 1 year or more before their diagnosis of MM or MGUS, respectively (Table 2). Overall, autoimmune disease was associated with a significantly increased risk of MGUS (OR = 2.1; 95% CI, 1.9-2.4) but not with MM (OR = 1.0; 95% CI, 0.9-1.2; Table 2).

A significantly elevated risk of MM was found among persons with a personal history of all autoimmune disease without detectable autoantibody, and the specific conditions autoimmune hemolytic anemia, polymyalgia rheumatica, and giant cell arteritis (Table 2). A significantly lowered risk of MM was found among patients with rheumatoid arthritis (Table 2).

Significantly elevated risks of MGUS were found in patients with a history of all subcategories of autoimmune diseases, and the specific conditions rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, pernicious anemia, immune thrombocytopenia, Guillain-Barré syndrome, celiac disease, chronic rheumatic heart disease, ankylosing spondylitis, polymyalgia rheumatica, giant cell arteritis, and aplastic anemia (Table 2).

Family history of autoimmune diseases and risk of plasma cell disorders

Based on data from 38 037 first-degree relatives of MM case patients, 151 797 first-degree relatives of MM controls, 14 535 first-degree relatives of MGUS case patients, and 58 164 first-degree relatives of MGUS controls, family history of autoimmune disease was associated with a significantly increased risk of MGUS (OR = 1.1; 95% CI, 1.0-1.2), but not with MM (OR = 1.0; 95% CI, 1.0-1.1). We confirmed that both family history and personal history of autoimmune disease were independent predictors of risk of MGUS (results not shown).

Personal history of infections and risk of plasma cell disorders

A total of 1381 and 815 patients had a history of infection 1 year or more before their diagnosis of MM or MGUS, respectively (Table 3). Overall, infections were associated with a significantly increased risk of subsequent MM (OR = 1.2; 95% CI, 1.1-1.3) and MGUS (OR = 1.6; 95% CI, 1.5-1.7). A history of pneumonia, septicemia, herpes zoster, infectious mononucleosis, sinusitis,

Table 3. Personal history of infections and risk of MM and MGUS

	MM			MGUS		
Category or condition	MM patients (n = 19 112)	Controls (n = 75 408)	OR* (95% CI) [*P*]	MGUS patients (n = 5403)	Controls (n = 21 209)	OR* (95% CI) [*P*]
Total infections†	1381	4530	1.2 (1.1-1.3)	815	2126	1.6 (1.5-1.7)
Pneumonia	568	1509	1.5 (1.4-1.7)	266	671	1.6 (1.4-1.8)
Tuberculosis	60	267	0.9 (0.7-1.2)	18	90	0.8 (0.5-1.3)
Intestinal infection	173	668	1.0 (0.9-1.2)	154	368	1.7 (1.4-2.0)
Rickettsiosis	1	3	1.3 (0.1-12.6)	2	2	4.0 (0.6-27.2)
Syphilis	4	12	1.3 (0.4-4.1)	0	3	0 [1.00]
Gonorrhea	5	21	0.9 (0.4-2.5)	8	12	2.7 (1.1-6.5)
Chlamydia	1	0	∞ [0.20]	0	0	
Septicemia	89	238	1.5 (1.2-1.9)	51	116	1.7 (1.2-2.4)
Herpes simplex	11	40	1.1 (0.6-2.1)	7	17	1.6 (0.7-3.9)
Herpes zoster	62	179	1.4 (1.02-1.8)	29	71	1.6 (1.03-2.5)
Viral hepatitis A	0	6	0 [.61]	0	5	0 [.59]
Viral hepatitis B	1	4	1.0 (0.1-8.9)	0	2	0 [1.00]
Viral hepatitis C	5	10	2.0 (0.7-5.8)	2	5	1.6 (0.3-8.2)
Infectious mononucleosis	7	10	2.8 (1.1-7.4)	3	9	1.3 (0.4-4.9)
Pyelonephritis	104	353	1.2 (0.9-1.4)	81	168	1.9 (1.5-2.5)
Cystitis	131	575	0.9 (0.7-1.1)	90	246	1.4 (1.1-1.8)
Sinusitis	53	142	1.5 (1.1-2.0)	37	90	1.6 (1.1-2.4)
Otitis media	71	260	1.1 (0.8-1.4)	43	137	1.2 (0.9-1.7)
Rhinitis	9	40	0.9 (0.4-1.8)	14	28	2.0 (1.1-3.8)
Nasopharyngitis/laryngitis	44	151	1.1 (0.8-1.6)	25	82	1.2 (0.8-1.9)
Influenza	62	188	1.3 (0.97-1.7)	37	96	1.5 (1.03-2.2)
Encephalitis	9	37	1.0 (0.5-2.0)	4	21	0.8 (0.3-2.2)
Malaria	0	8	0 [.37]	2	2	4.0 (0.6-28.2)
Meningitis	21	45	1.8 (1.1-3.1)	15	29	2.1 (1.1-3.8)
Lyme disease	14	55	1.0 (0.6-1.8)	22	27	3.2 (1.8-5.7)
Pericarditis	21	82	1.0 (0.6-1.6)	19	39	1.9 (1.1-3.3)
Myocarditis	14	21	2.1 (1.1-3.9)	13	26	2.0 (1.02-3.9)
Endocarditis	37	139	1.0 (0.7-1.5)	25	52	1.9 (1.2-3.0)
Osteomyelitis	17	93	0.7 (0.4-1.2)	15	40	1.5 (0.8-2.7)
Cytomegalovirus	4	4	3.9 (0.98-15.7)	3	5	2.4 (0.6-10.0)
Epstein-Barr virus	0	1	0 [1.00]	0	1	0 [1.00]
Helicobacter pylori	0	0		0	0	
HIV	1	0	∞ [.20]	0	1	0 [1.00]
Gingivitis or periodontitis	1	17	0.2 (0.0-1.7)	5	10	2.0 (0.7-5.8)
Tonsillitis	23	84	1.1 (0.7-1.7)	9	50	0.7 (0.4-1.5)
Empyema	4	26	0.6 (0.2-1.7)	10	11	3.6 (1.5-8.4)
Erysipelas (cellulitis)	149	530	1.1 (0.9-1.3)	107	229	1.8 (1.5-2.3)
Fasciitis	6	16	1.5 (0.6-3.8)	1	6	1.7 (0.1-5.4)

*When no case patient or control subject has the specific condition, *P* values (2-sided) based on Fisher exact test are given.
†Overall category totals more than the sum of the individual categories because some of the patients have > 1 autoimmune disease.

meningitis, and myocarditis was associated with a significantly increased risk of MM. A significantly elevated risk of MGUS was found in patients with a history of pneumonia, intestinal infection, gonorrhea, septicemia, herpes zoster, pyelonephritis, cystitis, sinusitis, rhinitis, influenza, meningitis, Lyme disease, pericarditis, myocarditis, endocarditis, empyema, and erysipelas (Table 3).

Personal history of inflammatory conditions and risk of plasma cell disorders

A total of 1079 and 617 patients had a history of inflammatory conditions 1 year or more before their diagnosis of MM or MGUS, respectively (Table 4). Overall, inflammatory conditions were associated with a significantly increased risk of subsequent MGUS (OR = 1.4; 95% CI, 1.2-1.5) but not with MM (OR = 1.1; 95% CI, 1.0-1.1). A history of nephrotic syndrome, chronic osteoarthritis, and diverticulitis was associated with a significantly increased risk of MM. A significantly decreased risk of MM was found in patients with a history of chronic bronchitis. A significantly elevated risk of MGUS was found in patients with a history of nephrotic syndrome, chronic glomerulonephritis, acute nephritis, chronic osteoarthritis, and diverticulitis (Table 4).

Subgroup and latency analyses

Analyses were also stratified by age, sex, year of diagnosis, and for MGUS patients M-protein isotype and M-protein concentration at diagnosis, and the results were virtually the same (data not shown). The risk of MM and MGUS that was associated with these autoimmune diseases, infections, and inflammatory conditions remained statistically significant for most conditions at > 5 years of latency (Tables 5-8). In a subanalysis where all MGUS patients who later developed MM were excluded from the MGUS cohort, the results were essentially the same (data not shown).

Table 4. Personal history of inflammatory conditions and risk of MM and MGUS

	MM			MGUS		
Category or condition	MM patients (n = 19 112)	Controls (n = 75 408)	OR (95% CI)	MGUS patients (n = 5403)	Controls (n = 21 209)	OR (95% CI)
Total inflammatory conditions*	1079	4021	1.1 (0.99-1.1)	617	1843	1.4 (1.2-1.5)
Chronic bronchitis	115	572	0.8 (0.6-0.96)	69	259	1.0 (0.8-1.4)
Nephrotic syndrome	13	14	3.7 (1.7-7.8)	12	10	4.7 (2.1-11.0)
Chronic glomerulonephritis	20	59	1.3 (0.8-2.2)	19	32	2.4 (1.3-4.2)
Chronic prostatitis	10	55	0.7 (0.4-1.4)	11	25	1.7 (0.9-3.5)
Dermatitis herpetiformis	3	8	1.5 (0.4-5.6)	1	5	0.8 (0.1-6.7)
Pemphigus	1	11	0.4 (0.0-2.8)	2	1	7.8 (0.7-85.4)
Chronic atrophic gastritis	2	22	0.4 (0.1-1.5)	5	11	1.8 (0.6-5.1)
Pancreatitis	76	346	0.9 (0.7-1.1)	42	166	1.0 (0.7-1.4)
Acute nephritis	8	17	1.9 (0.8-4.3)	10	17	2.3 (1.1-5.1)
Chronic osteoarthritis	695	2499	1.1 (1.00-1.2)	383	1117	1.4 (1.2-1.6)
Diverticulitis	186	617	1.2 (1.00-1.4)	108	322	1.3 (1.1-1.6)

*Overall category totals more than the sum of the individual categories because some of the patients have > 1 type of inflammatory condition.

Discussion

In this large population-based, case-control study that included almost 20 000 MM patients, > 5000 MGUS patients, and nearly 100 000 matched controls, we found that a personal history of several specific immune-related conditions was associated with an increased risk of MM and MGUS. Interestingly, we also found that a family history of autoimmune disease increases the risk of MGUS, and not MM. This implies that immune-related conditions or the treatment of them are of importance in the pathogenesis of MGUS and possibly MM.

We found a personal history of all autoimmune diseases combined to be significantly associated with MGUS but not with MM and several specific autoimmune diseases to significantly increase the risk of both MGUS and MM. Our findings that autoimmunity overall increases the risk of MGUS and that some specific autoimmune conditions increase the risk of MM and MGUS are consistent with a retrospective study of United States veterans[17] and in contrast to a smaller Swedish population-based study where no increased risk of MM was found in patients with a personal history of certain specific autoimmune diseases.[15] In contrast to the study of United States veterans, our population-based study did not show an increased risk of MM after a personal history of all autoimmune diseases or inflammatory conditions.[17] Considering that the incidence of plasma cell disorders is higher in black people[10] and MGUS is more common in men compared with women,[13] the difference in our results and the study of United States veterans (all male and large proportion of blacks) may be the result of population differences. Our finding that a family history of any autoimmune disease is associated with an increased subsequent risk of MGUS is, to our knowledge, novel and implies that there is a shared susceptibility for these conditions.

Interestingly, a personal history of polymyalgia rheumatica and giant cell arteritis was associated with an increased risk of both MM (OR = 7.8 and 1.9 for giant cell arteritis and polymyalgia rheumatica, respectively) and, for the first time, MGUS (OR = 11.3 and 2.9 for giant cell arteritis and polymyalgia rheumatica, respectively). Polymyalgia rheumatica and giant cell arteritis have recently been associated with lymphoplasmacytic lymphoma and Waldenström macroglobulinemia.[25] In addition, a family history of these disorders was associated with an increased risk of MGUS (data not shown). The underlying mechanisms for these findings are not clear but may involve shared susceptibility or an effect of chronic immune stimulation. As these disorders are generally only treated with glucocorticoids, it is unlikely that it is driven by treatment.[27] Future studies are required to evaluate this issue in more detail.

Among patients with rheumatoid arthritis, we found a significantly lowered risk of MM but a significantly elevated risk of MGUS. Some investigators have previously found an increased risk of MM in patients with rheumatoid arthritis,[28-30] whereas others have found no such association.[7,17] In recent years, TNF inhibitors have been increasingly used for autoimmune diseases (most commonly rheumatoid arthritis).[31] Previous studies have not shown these agents to further increase the already elevated lymphoma risk in rheumatoid arthritis. We found no difference in trends based on patients diagnosed in early versus late calendar periods. In addition, we found that the associations with autoimmune diseases were consistently stronger (higher ORs) for MGUS than for MM. One possible explanation for this is that MGUS is a biologically heterogeneous condition that can progress to several different lymphoproliferative disorders. Another explanation for the discrepancy in risk magnitude between MM and MGUS could be that there is a difference in the biology of MGUS in patients with a previous history of immune-related conditions compared with MGUS in patients without such history. Further studies are needed to determine the impact of a previous history of immune-related conditions on progression of MGUS.

Table 5. Personal history of autoimmune diseases and risk of MM with more than 5 years' latency

Category or condition	MM patients (n = 19 112)	MM controls (n = 75 408)	OR* (95% CI) [*P*]
Autoantibodies detectable	171	788	0.8 (0.72-1.00)
Systemic involvement	96	467	0.8 (0.6-1.00)
Rheumatoid arthritis	72	388	0.7 (0.6-0.9)
Autoimmune hemolytic anemia	0	0	
Autoantibodies not detectable	111	366	1.2 (0.96-1.5)
Polymyalgia rheumatica	29	44	2.6 (1.6-4.1)
Giant cell arteritis	6	3	7.7 (1.9-31.0)

*When no case patient or control subject has the specific condition, *P* values (2-sided) based on Fisher exact test are given.

Table 6. Personal history of autoimmune diseases and risk of MGUS with more than 5 years' latency

Category or condition	MGUS patients (n = 5403)	MGUS controls (n = 21 209)	OR* (95% CI) [*P*]
Total autoimmune disease	247	499	2.0 (1.7-2.3)
Autoantibodies detectable	156	313	2.0 (1.6-2.4)
Systemic involvement	106	189	2.2 (1.7-2.8)
Rheumatoid arthritis	84	155	2.1 (1.6-2.8)
Systemic sclerosis	3	3	3.9 (0.8-19.5)
Sjögren syndrome	4	6	2.6 (0.7-9.3)
Organ involvement	55	134	1.6 (1.2-2.2)
Pernicious anemia	9	20	1.8 (0.8-3.8)
Autoimmune hemolytic anemia	1	0	∞ [.20]
Immune thrombocytopenia	5	2	9.9 (1.9-51.2)
Polyarteritis nodosa	3	0	∞ [< .05]
Guillain-Barré syndrome	3	4	3.0 (0.7-13.2)
Celiac disease	3	5	2.4 (0.6-10.0)
Chronic rheumatic heart disease	14	35	1.6 (0.9-2.92)
Autoantibodies not detectable	110	215	2.0 (1.6-2.6)
Ankylosing spondylitis	12	17	2.8 (1.3-5.9)
Polymyalgia rheumatica	30	36	3.3 (2.0-5.3)
Giant cell arteritis	10	2	19.5 (4.3-89.2)
Aplastic anemia	3	0	∞ [< .05]

*When no case patient or control subject has the specific condition, *P* values (2-sided) based on Fisher exact test are given.

Taken together, our findings that a personal history of specific as well as broad categories of autoimmune diseases increase the risk of MGUS, and to some extent MM, as has been shown in lymphoma,[16] are interesting because they imply that chronic antigen stimulation may trigger the development of a plasma cell disorder or that treatment of autoimmune disease is associated with the development of a plasma cell disorder, alternatively that there is a common genetic or environmental susceptibility. Our findings that a family history of autoimmune diseases also increases the risk of MGUS support the theory of common genetic susceptibility.

Our findings of an increased risk of MM and MGUS after a broad category of infections and inflammatory conditions as well as several specific conditions (eg, pneumonia, septicemia, herpes zoster, meningitis, and chronic osteoarthritis) confirm and expand on the findings by Brown et al.[17] Other investigators have also found that a personal history of pneumonia and meningitis increases the risk of MM.[17-19] A majority of the associations we found were statistically significant even more than 5 years before diagnosis of plasma cell disorder and suggest that certain infections and inflammatory conditions can trigger the development of MGUS or MM. Approximately one-half of MGUS patients have clonal plasma cells carrying translocations that involve a locus considered to be of importance for initiation and support of clonal proliferation.[32,33] It has previously been proposed that infections could be the trigger event for these translocations and thereby generate clonal proliferation, and our findings support this.[32]

A possible explanation for the observed association between immune-related conditions and MM and MGUS is reverse causality. Undetected MM may manifest with symptoms that mimic other diseases, and undetected MM or MGUS may increase the risk of infections and other conditions. However, a majority of the MM patients in our study were diagnosed when the median survival of MM was only 2 to 3 years, and we observed significantly elevated risks of MM 5 or more years after a diagnosis of an immune-related condition.[34] Finally, we cannot fully rule out that immune-related conditions are markers for an immune dysregulation as an early manifestation of a plasma cell disorder.

Our study has several strengths, the most important ones being its large size and high-quality data from Sweden. The data derive from a stable population with access to standardized medical health

Table 7. Personal history of infections and risk of MM with more than 5 years' latency

Category or condition	MM patients (n = 19 112)	MM controls (n = 75 408)	OR (95% CI)
Total infections	753	2779	1.1 (0.98-1.2)
Pneumonia	243	792	1.2 (1.04-1.4)
Septicemia	39	106	1.4 (1.00-2.1)
Herpes zoster	34	100	1.3 (0.9-2.0)
Infectious mononucleosis	7	9	3.1 (1.2-8.3)
Sinusitis	34	94	1.4 (0.96-2.1)
Meningitis	16	32	2.0 (1.1-3.6)
Myocarditis	11	23	1.9 (0.9-3.9)

Table 8. Personal history of infections and risk of MGUS with more than 5 years' latency

Category or condition	MGUS patients (n = 5403)	MGUS controls (n = 21 209)	OR (95% CI)
Total infections	665	1751	1.6 (1.4-1.7)
Pneumonia	192	505	1.6 (1.3-1.9)
Intestinal infection	120	307	1.5 (1.2-1.9)
Gonorrhea	8	12	2.7 (1.1-6.5)
Septicemia	37	82	1.6 (0.99-2.5)
Herpes zoster	22	55	2.0 (1.2-3.5)
Pyelonephritis	62	137	1.9 (1.4-2.7)
Cystitis	61	173	1.5 (1.1-2.1)
Sinusitis	34	77	2.0 (1.3-3.1)
Rhinitis	10	23	1.2 (0.8-1.7)
Influenza	25	71	0.8 (0.4-1.6)
Meningitis	13	27	2.1 (1.03-4.2)
Lyme disease	22	27	3.2 (1.8-5.7)
Pericarditis	16	35	2.3 (1.2-4.5)
Myocarditis	11	24	1.9 (0.9-3.9)
Endocarditis	22	42	2.5 (1.4-4.2)
Empyema	8	11	2.4 (0.8-7.5)
Erysipelas (cellulitis)	80	191	1.6 (1.2-2.2)

care during the entire study period. Using the nationwide, register-based, case-control design, we were able to rule out recall bias. The population-based setting ensures a generalizability of our findings.

Our study has some limitations. Because of the large study size, we were not able to validate individual medical records. In addition, considering the nature of this hypothesis-generating study, one has to interpret our findings with caution because of the many conditions analyzed. The use of inpatient data would be expected to lead to under-ascertainment of less severe forms of chronic immune-related conditions. Thus, our findings may apply mainly to severe forms of immune-related conditions; however, we did not require these conditions to be the primary diagnosis. Finally, because personal history of immune stimulatory conditions was assessed similarly among the patients with MM/MGUS and control subjects, any under-diagnosis should be nondifferential and any bias should be toward the null. As MGUS is asymptomatic and not the subject of universal screening, our MGUS cohort represents only a selected proportion of MGUS in the population, and a significant minority of the MGUS matched controls could have an undetected MGUS. We have previously conducted a large nationwide study on the registration of lymphoproliferative malignancies diagnosed in Sweden and found the diagnostic accuracy and completeness to be $> 93\%$.[22]

In conclusion, we found that a personal and a family history of all autoimmune diseases combined are associated with an increased risk of MGUS and that a personal history of specific as well as categories of infections and inflammatory conditions is associated with an increased risk of MM and MGUS. Our findings that a family history of autoimmune diseases increases the risk of MGUS suggest that there is a common susceptibility for immune-related conditions and precursor conditions. We have speculated that this susceptibility may be the result of genetic or environmental factors, or a combination of the 2. Alternatively, one may conjecture that secondary chronic antigen stimulation or therapy related to immune-related conditions may be of importance. Future studies are needed to better understand underlying mechanisms of the observed associations.

Acknowledgments

The authors thank Ms Shiva Ayobi, the National Board of Health and Welfare, Stockholm, Sweden; Ms Susanne Dahllöf, Statistics Sweden, Orebro, Sweden; Ms Emily Steplowski, Information Management Services, Silver Spring, MD; and Ms Charlotta Ekstrand, Ms Molly Collin, and Ms Lisa Camner, Karolinska Institutet, Stockholm, Sweden for important efforts in the development of this database.

This work was supported by the Swedish Cancer Society, the Stockholm County Council, the Karolinska Institutet Foundations, the Intramural Research Program of the National Institutes of Health, National Cancer Institute, and Roche Diagnostics (unrestricted grant).

Authorship

Contribution: S.Y.K., E.K.L., L.R.G., O.L., and M.B. designed the study; S.Y.K., O.L., C.B., A.W., I.T., and U.-H.M. obtained data; L.R.G. performed the statistical analyses; E.K.L. and S.Y.K. wrote the report; and all the authors were involved in analyses and the interpretation of the results; read, gave comments, and approved the final version of the manuscript; had full access to the data in the study; and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Sigurdur Y. Kristinsson, Department of Medicine, Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden; e-mail: sigurdur.kristinsson@karolinska.se.

References

1. Swerdlow S, Campo E, Harris N, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (4th ed). Lyon, France: IARC; 2008.
2. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003;78(1):21-33.
3. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002;346(8):564-569.
4. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009;113(22):5412-5417.
5. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood.* 2009; 113(22):5418-5422.
6. Vachon CM, Kyle RA, Therneau TM, et al. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood.* 2009;114(4): 785-790.
7. Landgren O, Linet MS, McMaster ML, Gridley G, Hemminki K, Goldin LR. Familial characteristics of autoimmune and hematologic disorders in 8406 multiple myeloma patients: a population-based case-control study. *Int J Cancer.* 2006; 118(12):3095-3098.
8. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood.* 2009; 114(4):791-795.
9. Kristinsson SY, Bjorkholm M, Goldin LR, et al. Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. *Int J Cancer.* 2009;125(9):2147-2150.
10. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. *Leukemia.* 2009;23(10):1691-1697.
11. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood.* 2006;107(3):904-906.
12. Landgren O, Kyle RA, Hoppin JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood.* 2009;113(25):6386-6391.
13. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006; 354(13):1362-1369.
14. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. *Int J Cancer.* 2007;120(suppl 12):1-39.
15. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. *Eur J Cancer.* 2006;42(17):3028-3033.
16. Anderson LA, Gadalla S, Morton LM, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int J Cancer.* 2009;125(2):398-405.
17. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. *Blood.* 2008;111(7):3388-3394.
18. Landgren O, Rapkin JS, Mellemkjaer L, Gridley G, Goldin LR, Engels EA. Respiratory tract infections in the pathway to multiple myeloma: a population-based study in Scandinavia. *Haematologica.* 2006; 91(12):1697-1700.
19. Gregersen H, Pedersen G, Svendsen N, Thulstrup AM, Sorensen HT, Schonheyder HC. Multiple myeloma following an episode of community-acquired pneumococcal bacteraemia or meningitis. *APMIS.* 2001;109(11):797-800.
20. Swedish National Board of Health. *Svenska cancerregistret.* Stockholm, Sweden: Socialstyrelsen; 2008.

21. Turesson I, Linet MS, Bjorkholm M, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. *Int J Cancer.* 2007;121(10):2260-2266.
22. Nilsson A, Spetz C, Carsjo K, Nightingale R, Smedby B. Slutenvårdsregistrets tillförlitlighet. *Läkartidningen.* 1994;91(7):598-605.
23. Swedish National Board of Health. *Patientregistret*. Stockholm, Sweden: Socialstyrelsen; 2008.
24. Skarle A. *Flergenerationsregistret*. Stockholm, Sweden: Statistics Sweden, Population Statistics; 2008.
25. Kristinsson SY, Koshiol J, Bjorkholm M, et al. Immune-related and inflammatory conditions and risk of lymphoplasmacytic lymphoma or Waldenstrom macroglobulinemia. *J Natl Cancer Inst.* 2010;102(8):557-567.
26. Landgren O, Engels EA, Pfeiffer RM, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case-control study in Scandinavia. *J Natl Cancer Inst.* 2006;98(18):1321-1330.
27. Askling J, Klareskog L, Hjalgrim H, Baecklund E, Bjorkholm M, Ekbom A. Do steroids increase lymphoma risk? A case-control study of lymphoma risk in polymyalgia rheumatica/giant cell arteritis. *Ann Rheum Dis.* 2005;64(12):1765-1768.
28. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. *Eur J Cancer.* 1996;32A(10):1753-1757.
29. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. *Int J Cancer.* 2000;88(3):497-502.
30. Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chronic Dis.* 1978;31(11):691-696.
31. Neovius M, Sundstrom A, Simard J, et al. Small-area variations in sales of TNF inhibitors in Sweden between 2000 and 2009. *Scand J Rheumatol.* 2011;40(1):8-15.
32. Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. *Cancer Res.* 2004;64(4):1546-1558.
33. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood.* 2005;106(1):296-303.
34. MacLennan IC, Chapman C, Dunn J, Kelly K. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis: the Medical Research Council Working Party for Leukaemia in Adults. *Lancet.* 1992;339(8787):200-205.