Disease Associations With Monoclonal Gammopathy of Undetermined Significance: A Population-Based Study of 17,398 Patients

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OBJECTIVE: **To systematically study the association of monoclonal gammopathy of undetermined significance (MGUS) with all diseases in a population-based cohort of 17,398 patients, all of whom were uniformly tested for the presence or absence of MGUS.**

PATIENTS AND METHODS: **Serum samples were obtained from 77% (21,463) of the 28,038 enumerated residents in Olmsted County, Minnesota. Informed consent was obtained from patients to study 17,398 samples. Among 17,398 samples tested, 605 cases of MGUS and 16,793 negative controls were identified. The computerized Mayo Medical Index was used to obtain information on all diagnoses entered between January 1, 1975, and May 31, 2006, for a total of 422,663 person-years of observations. To identify and confirm previously reported associations, these diagnostic codes were analyzed using stratified Poisson regression, adjusting for age, sex, and total person-years of observation.**

RESULTS: **We confirmed a significant association in 14 (19%) of 75 previously reported disease associations with MGUS, including vertebral and hip fractures and osteoporosis. Systematic analysis of all 16,062 diagnostic disease codes found additional previously unreported associations, including mycobacterium infection and superficial thrombophlebitis.**

CONCLUSION: **These results have major implications both for confirmed associations and for 61 diseases in which the association with MGUS is likely coincidental.**

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HDL = high-density lipoprotein; *H-ICDA-2* = *Hospital Adaptation of the International Classification of Diseases, Eighth Edition*; MGUS = monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell disorder, occurring in 3% of the population older than 50 years.[1] MGUS is an asymptomatic premalignant disorder, defined by a serum monoclonal immunoglobulin concentration of 3 g/dL or less and a proportion of plasma cells in the bone marrow of 10% or less in the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the proliferation of monoclonal plasma cells.

MGUS is a known precursor of more serious diseases, such as multiple myeloma, primary amyloidosis, and Waldenström macroglobulinemia,[2] but most patients with MGUS do not develop a plasma cell malignancy. However, numerous reports suggest an association of MGUS with a wide variety of other malignant and nonmalignant diseases.[3-6] Some pathogenetically important associations probably exist; however, given the relatively high prevalence of MGUS in the general population (3%), most reported disease associations are likely coincidental. The prevalence of MGUS increases with age, from 1.7% in patients aged 50 to 59 years to more than 6.6% in patients aged 80 years and older.[1] The screening test for MGUS, serum protein electrophoresis, is commonly performed in patients who present with a wide variety of clinical symptoms. Therefore, associations can occur coincidentally because the serum protein electrophoresis is performed more frequently in patients with certain clinical presentations (ascertainment bias).

Identification of true disease associations with MGUS is of major importance because it sheds light on the pathogenesis of both MGUS and the associated disorder. The only method to definitively address this is to screen all persons in a geographic population for the presence or absence of MGUS and then determine the diseases that are significantly associated with MGUS. To our knowledge, we report the first systematic study to determine the association of MGUS with all diseases in a large population-based cohort screened for the presence or absence of MGUS.

PATIENTS AND METHODS

Details on assembly of the study cohort and testing for MGUS have been previously reported.[1] Beginning with a list of all residents of Olmsted County, Minnesota, who were aged 50 years or older as of January 1, 1995, we obtained unused serum after routine clinical tests in the Mayo Clinic Laboratory Central Processing Area, which receives all serum samples from Mayo Clinic outpatients in Rochester, MN, as well as from patients at Mayo-affiliated

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Saint Marys and Rochester Methodist hospitals. A letter, approved by the Mayo Clinic Institutional Review Board, was then sent to these patients asking for permission to study their serum sample. Serum samples were obtained from 77% (21,463) of the 28,038 enumerated residents in Olmsted County.[1] Informed consent was obtained from patients to study 17,398 samples. The study was approved by the Mayo Clinic Institutional Review Board.

Laboratory Testing for MGUS

Electrophoresis was performed on agarose gel (Helena REP, Beaumont, TX) to test for monoclonal protein. The agarose strip was inspected by a technician and one of the authors (R.A.K.). Any serum with a discrete band or a suspect localized band was subjected to immunofixation (Sebia HYDRASYS/HYDRAGEL system, Norcross, GA).[7] On the basis of serum protein electrophoresis and immunofixation, 605 MGUS cases and 16,793 negative controls were identified.

Disease Associations With MGUS and Statistical Analyses

The Mayo Clinic Medical Index was used to obtain information on all diagnoses entered between January 1, 1975, and May 31, 2006, for the identified cases and controls, for a total of 422,663 person-years of observations. Diagnoses were obtained from a Mayo extension of the *Hospital Adaptation of the International Classification of Diseases, Eighth Edition* (*H-ICDA-2*) that includes additional levels of detail in each classification rubric.[8] If MGUS progressed to multiple myeloma, amyloidosis, or other plasma cell proliferative disorder, only the diagnoses up to and including the date of progression were considered.

First, we conducted a literature search and identified 75 previously reported potential disease associations.[9-103] The *H-ICDA-2* codes were grouped into a single diagnostic code to represent each of the previously reported associations. The patient population was stratified by age rounded to the nearest decade, sex, and MGUS diagnosis. The total occurrences of a diagnostic code and the number of person-years were determined for each stratum. Using the GLM and MASS packages provided in the base system of R,[104] the number of occurrences was modeled with Poisson regression adjusting for age and sex, with the log of the total person-years as an offset. From the resulting model, incidence rates per 100,000 years were estimated assuming equal observation across all strata, regardless of the age or sex specificity of the diagnostic code. The risk ratios (MGUS cases vs controls) with 95% confidence intervals are reported.

To identify new associations previously unreported in the literature, we analyzed all *H-ICDA-2* diagnostic codes at the 6th-digit level (N=16,062 codes) with the same analysis outlined previously and an additional Bonferroni correction of *P* values to adjust for multiple comparisons.

RESULTS

The MGUS cohort consisted of 309 men and 296 women, with a mean age at diagnosis of 70 years (range, 39-99 years). Mean follow-up (ie, the first diagnosis date to the last) was 24 years (range, 0-31 years), for a total of 14,373 person-years. The serum M component was 12% IgA, 70% IgG, 15% IgM, and 3% biclonal, and the median M protein level was 0.5 g/dL. The controls consisted of 7520 men and 9273 women, with mean follow-up of 25 years (range, 0-30 years), for a total of 408,290 person-years. Their mean age at the date of sample was 68 years (range, 52-105 years).

Previously Reported Disease Associations With MGUS

The 75 diagnoses for which a potential association with MGUS has been reported previously in the published literature are listed in Table 1 and Table 2. Of these 75 listed diagnoses, we were able to confirm a significant disease association in 14 (Table 1). As expected, 5 of the 14 disease associations were disorders known to evolve from MGUS, namely multiple myeloma, amyloidosis, lymphoproliferative disorders, macroglobulinemia, and other unclassified plasma cell proliferative disorders. More importantly, we confirmed that disorders of the bone, such as hip and vertebral fractures, osteoporosis, and hypercalcemia, are all significantly increased with MGUS, even in the absence of progression to multiple myeloma. We also confirmed known associations of MGUS with chronic inflammatory demyelinating neuropathy (relative risk, 5.9; 95% confidence interval, 1.2-28.4) and autonomic neuropathy.

We found no significant association with MGUS in the 61 remaining disease diagnoses, an indication that most of these previously reported associations are either coincidental or clinically insignificant (Table 2).

New Disease Associations With MGUS

We conducted a systematic analysis of all 16,062 diagnostic codes in a screening strategy for new disease associations (see eAppendix online linked to this article). We found 5 significant associations after Bonferroni correction for 16,062 comparisons being done. Of these, 4 were for known associations that we have previously confirmed, including multiple myeloma, lymphoproliferative disease, other dysproteinemias, and plasma proliferative disorders. We also identified a new previously unreported association of MGUS with hyperlipidemia (relative risk, 0.7; 95% confidence interval, 0.6-0.8). Patients with MGUS and hyperlipidemia had a distribution of monoclonal serum proteins similar to

TABLE 1. **Previously Published Disease Associations in Which a Significant Disease Association With MGUS Was Confirmed Among Olmsted County, Minnesota, Residents**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	*P* value[c]
Macroglobulinemia[9,19,20]	5	55.1	1	0.6	96.2 (11.0-836.5)	<.001
Multiple myeloma[9]	29	257.4	19	7.9	32.6 (18.1-58.7)	<.001
Plasma cell proliferative disorder[9]	11	87.1	9	3.1	28.0 (11.4-68.7)	<.001
Amyloidosis[9]	7	85.2	18	11.8	7.2 (3.0-17.4)	<.001
CIDP[21,22]	2	14.9	8	2.5	5.9 (1.2-28.4)	.03
Liver transplant[23]	2	13.9	10	2.6	5.4 (1.2-25.3)	.03
Kidney transplant[24-27]	5	34.6	38	9.8	3.5 (1.4-9.1)	.01
Lymphoproliferative disease[28]	17	161.2	105	48.0	3.4 (2.0-5.6)	<.001
Autonomic neuropathy[29]	5	35.8	39	11.0	3.2 (1.3-8.3)	.01
Vertebral fracture[17]	46	511.1	478	263.9	1.9 (1.4-2.6)	<.001
Hip fracture[17]	36	581.6	388	377.1	1.5 (1.1-2.2)	.01
Hypercalcemia[30]	40	297.5	736	214.9	1.4 (1.0-1.9)	.05
Osteoporosis[31]	153	1701.1	3013	1407.7	1.2 (1.0-1.4)	.02
Urticaria[32-34]	20	144.8	1003	242.9	0.6 (0.4-0.9)	.02

[a] CI = confidence interval; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; MGUS = monoclonal gammopathy of undetermined significance.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted *P* values are reported.

that of the overall MGUS population, with 11% having IgA; 74%, IgG; 11%, IgM; and 4%, biclonal.

Table 3 lists 20 previously unreported associations that were significant based on the *P* value obtained from the systematic analysis of all diseases. Similarly, Table 4 lists 20 previously unreported associations that had the most positive associations based on the hazard ratio with a $P<.05$ and 10 or more total cases and controls from the systematic analysis of all diseases. Although many of the diseases listed in Table 3 and Table 4 were not statistically significant after the stringent Bonferroni correction method, they may be clinically important, previously unrecognized new associations that merit further study. Diseases such as mycobacterium infection and superficial venous thrombophlebitis are of particular interest.

DISCUSSION

Throughout the years, numerous diseases have been reported to be associated with MGUS.[9] Because of the high prevalence of MGUS in the general population and the inherent bias of testing for MGUS only in patients with certain clinical symptoms, it is difficult to distinguish true pathogenetic relationships from coincidental associations. In fact, approximately 3% of patients with any given disease will be found to have MGUS based on coincidence. Therefore, the presence or absence of a true association can be determined only if the association of a disease with MGUS is significantly different from that expected in the general population. This requires screening of all persons in a geographic population for the presence or absence of MGUS and a determination of all diseases that occurred in each person over time. Moreover, because MGUS is associated with age and sex, associations need to be adjusted for these variables to eliminate bias.

The current study is based on prior screening of an entire geographically defined population for MGUS, which captured 77% of the enumerated population older than 50 years in Olmsted County.[1] The study was performed with this well-defined cohort after excluding the blinded population of patients who did not provide informed consent to test passively collected serum samples. We systematically screened for association with all previously reported MGUS-disease associations in the literature, as well as all 16,062 disease diagnostic codes. Because testing for MGUS had been performed in all the study participants, ascertainment bias (which occurs in hospital- or clinical practice–based studies in which testing for presence or absence of MGUS is performed preferentially in persons with certain diseases) is not a concern.

As expected, our study shows that clonal plasma cell proliferative disorders such as myeloma, lymphoproliferative disorders, macroglobulinemia, and amyloidosis are significantly increased because they are direct progression events in patients with MGUS.[9] We also found that a well-studied and suspected association between MGUS and neuropathy needs further examination. Kelly et al[10] reported an MGUS prevalence of 6.7% among referred patients with idiopathic neuropathy. Many other studies have found underlying pathologic associations between neuropathies and MGUS.[11-13] A direct interaction of the monoclonal protein (anti–myelin-associated glycoprotein; MAG anti-

TABLE 2. **Previously Published Disease Associations That Were Not Confirmed Among Olmsted County, Minnesota, Residents With MGUS**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	*P* value[c]
Infections and parasitic diseases						
Chronic hepatitis[35]	4	27.85	46	11.23	2.48 (0.89-6.94)	.08
Cytomegalovirus infection (includes congenital)[36]	1	7.31	13	3.83	1.91 (0.25-14.73)	.54
Epstein-Barr infection[37]	0	0	8	1.98	…	>.99
Hepatitis C[35,38,39]	3	21.39	42	12.02	1.78 (0.55-5.77)	.34
Infectious pneumonitis[40]	91	796.01	1863	706.73	1.13 (0.91-1.39)	.27
Pulmonary tuberculosis[41]	1	8.98	14	5.96	1.51 (0.2-11.56)	.69
Sarcoidosis[42]	3	24.75	68	16.16	1.53 (0.48-4.89)	.47
Neoplasms						
Acute leukemia[43]	1	7.54	3	0.94	8.05 (0.81-80.3)	.08
Chronic lymphocytic leukemia[5,9,44]	6	53.59	115	48.44	1.11 (0.49-2.52)	.81
Hairy cell leukemia[45]	1	8.64	9	3.69	2.34 (0.29-18.66)	.42
Colon cancer[46]	20	246.43	288	193.08	1.28 (0.81-2.01)	.29
Sézary syndrome[47,48]	1	7.56	10	3.18	2.38 (0.3-18.81)	.41
Thymoma[49]	0	0	8	2.88	…	>.99
Endocrine, nutritional, and metabolic diseases						
AIDS[50,51]	0	0	2	0.55	…	>.99
C1 esterase inhibitor deficiency[32,52]	0	0	1	0.23	…	>.99
Diabetic neuropathy[53]	28	243.7	559	223.16	1.09 (0.75-1.6)	.65
Hashimoto thyroiditis[54]	10	76.42	381	87.01	0.88 (0.47-1.65)	.69
Hemosiderosis[55]	1	7.11	17	4.78	1.49 (0.2-11.27)	.71
Hyperparathyroidism[56-60]	9	72.34	184	65.14	1.11 (0.57-2.17)	.76
Xanthogranuloma[61-63]	1	7.28	7	1.64	4.44 (0.53-36.84)	.17
Xanthoma[61]	1	7.34	29	6.98	1.05 (0.14-7.76)	.96
Diseases of blood and blood-forming organs						
Lupus, anti-inhibitor/anticoagulants[64-66]	0	0	23	7.85	…	>.99
Pernicious anemia[40]	8	84.64	147	80.14	1.06 (0.52-2.16)	.88
Red cell aplasia[6,7,68]	0	0	1	0.35	…	>.99
Refractory anemia[69]	8	104.86	74	54.04	1.94 (0.93-4.04)	.08
Thromboembolism[70,71]	32	349.75	599	334.94	1.04 (0.73-1.49)	.81
von Willebrand disease[72]	0	0	2	0.51	…	>.99
Diseases of the nervous system and sensing organs						
Cerebellar ataxia[73]	6	64.71	54	29.6	2.19 (0.94-5.1)	.07
Demyelinating disease (CNS)[74]	3	22.2	35	8.11	2.74 (0.84-8.98)	.10
Gravis myasthenia[49]	1	7.49	18	5.63	1.33 (0.18-10.04)	.78
Multiple system atrophy (CNS) + MND[75]	1	9.47	30	13.84	0.68 (0.09-5.03)	.71
Muscular atrophy	6	45.96	84	27.25	1.69 (0.73-3.88)	.22
Peripheral neuropathy[3,29,76]	68	672.56	1389	652.87	1.03 (0.81-1.32)	.81
Sclerosis + MND[75,77,78]	0	0	19	6.91	…	>.99
Diseases of the digestive system						
Chronic active liver disease[79]	0	0	11	2.87	…	>.99
Cirrhosis[80,81]	6	45.89	78	25.46	1.8 (0.78-4.15)	.17
Liver disease[79,81]	4	29.72	73	22.41	1.33 (0.48-3.64)	.58
Diseases of the genitourinary system						
Proliferative glomerulonephritis[82]	1	7.46	8	2.53	2.95 (0.36-23.91)	.31
Diseases of the skin and subcutaneous tissue						
Angioneurotic edema[6]	1	9.77	18	4.84	2.02 (0.27-15.25)	.50
Dermal mucinosis[6]	1	6.93	31	7.85	0.88 (0.12-6.5)	.90
Erythematosus lupus[65,83,84]	1	6.96	46	10.99	0.63 (0.09-4.61)	.65
Psoriasis[85]	20	143.06	636	157.73	0.9 (0.58-1.42)	.67
Pustular subcorneal dermatosis[86-89]	0	0	6	1.74	…	>.99
Myxedematous lichen[90,91]	1	6.93	31	7.85	0.88 (0.12-6.5)	.90
Pyoderma[92-95]	1	7.87	46	11.17	0.7 (0.1-5.13)	.73
Pyoderma gangrenosum[93]	0	0	2	1.2	…	>.99

Continued on next page

TABLE 2. **Continued**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Risk ratio (95% CI)	*P* value[c]
Diseases of the musculoskeletal system and connective tissue						
Ankylosing spondylitis[40,96,97]	1	7.53	35	8.91	0.84 (0.12-6.19)	.87
Connective tissue disorders[98]	27	192	547	139.55	1.38 (0.93-2.03)	.11
Connective tissue disorders except RA[98]	3	20.81	85	20.83	1.0 (0.31-3.17)	>.99
Polymyositis[99,100]	1	9.68	9	4.42	2.19 (0.27-17.5)	.46
RA[98]	24	170.33	468	119.26	1.43 (0.95-2.16)	.09
Scleredema[101-103]	0	0	3	0.72	…	>.99
Scleroderma[98]	1	7.05	31	7.07	1.0 (0.14-7.35)	>.99
Septic arthritis[105,106]	1	8.66	18	7.23	1.2 (0.16-9.03)	.86
Seronegative polyarthritis[107]	2	15.85	47	16.19	0.98 (0.24-4.05)	.98
Sjögren syndrome[108]	3	21.67	56	15.93	1.36 (0.42-4.37)	.61
Symptoms, signs, and ill-defined conditions						
Antibody-antigen reactions (antinuclear antibodies)[98]	1	6.99	78	20.28	0.34 (0.05-2.48)	.29
Fracture long bone[17,109]	120	1055.44	2658	973.76	1.08 (0.90-1.30)	.39
Hyperlipoproteinemia[110]	2	15.08	96	23.64	0.64 (0.16-2.59)	.53
Bone marrow/peripheral blood stem transplant[111]	0	0	10	2.54	…	>.99
HIV positive[112,113]	0	0	3	0.75	…	>.99

[a] CI = confidence interval; CNS = central nervous system; HIV = human immunodeficiency virus; MGUS = monoclonal gammopathy of undetermined significance; MND = motor neuron disease; RA = rheumatoid arthritis.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted *P* values are reported.

body) with the peripheral nerve has been described.[14] Similarly, in patients with amyloidosis, there is a direct effect of monoclonal protein–derived fibrils (amyloid fibrils) on the peripheral nerve.[3] Studies have shown that treatment of the underlying plasma cell dyscrasia in patients with neuropathy results in patient improvement.[15,16] Except in

TABLE 3. **Top 20 Previously Unpublished Associations Among Olmsted County, Minnesota, Residents With MGUS, by Significance in Systematic Analysis of Diagnostic Codes**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Relative risk (95% CI)	*P* value[c]
Hyperlipidemia[d]	247	2205.1	8653	3321.7	0.7 (0.6-0.8)	<.001
Uterus retroversion	6	347.9	36	32.6	10.7 (4.5-25.4)	<.001
Chalazion	44	336.9	695	170.7	1.97 (1.5-2.7)	<.001
Clavicle fracture	4	27.8	7	1.7	15.9 (4.6-55.9)	<.001
Upper respiratory bacterial infection	4	30.4	11	2.4	12.6 (3.9-40.5)	<.001
Small intestine diverticulum	4	32.6	5	1.8	18.0 (4.7-68.6)	<.001
Acute depression	13	183.2	172	54.4	3.4 (1.9-5.9)	<.001
Vitreous degeneration	6	47.2	31	7.3	6.5 (2.7-15.7)	<.001
Aphakic detachment	3	22.9	3	0.8	29.5 (5.8-150.4)	<.001
Vertebral fracture	26	301.8	217	130.8	2.3 (1.5-3.5)	<.001
Ventricle hypertrophy due to hypertension	9	69.8	54	17.7	3.9 (1.9-8.0)	<.001
Spontaneous bacterial peritonitis	3	20.8	5	1.3	16.7 (3.9-72.3)	<.001
Peritoneum cyst	4	28.3	14	3.2	8.8 (2.8-27.2)	<.001
Group I hypertension	16	119.4	188	44.5	2.7 (1.6-4.5)	<.001
Sural phlebitis	4	29.3	13	3.3	8.8 (2.8-27.3)	<.001
Mycobacterium infection	4	29.3	11	3.2	9.1 (2.8-29.0)	<.001
Hypercholesterolemia	68	501.2	2835	782.4	0.6 (0.5-0.8)	<.001
Sigmoid diverticulum with diverticulitis	10	71.1	80	21.5	3.3 (1.7-6.4)	<.001
Hyperglycemia	48	386.9	1871	647.7	0.6 (0.5-0.8)	<.001
Subconjunctival hematoma	3	21.6	8	1.9	11.2 (2.9-43.0)	<.001

[a] CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted *P* values are reported.
[d] *P* value was significant after Bonferroni correction for 16,062 comparisons.

TABLE 4. **Top 20 Previously Unpublished Associations Among Olmsted County, Minnesota, Residents With MGUS, by Hazard Ratio With *P*<.05 and 10 or More Total Cases and Controls in Systematic Analysis of Diagnostic Codes**[a]

Description	Positive MGUS cases	Case rate[b]	Positive controls	Control rate[b]	Relative risk (95% CI)	*P* value[c]
Benign cervix neoplasm	2	26.1	8	2.2	11.8 (2.5-56.8)	.002
Esophageal bleeding	3	21.0	8	2.2	9.7 (2.5-37.3)	.001
Peritoneum cyst	4	28.3	14	3.2	8.8 (2.8-27.2)	<.001
Sural phlebitis	4	29.3	13	3.3	8.8 (2.8-27.3)	<.001
Tympanosclerosis	3	22.6	11	2.7	8.4 (2.3-30.7)	<.001
Popliteal artery embolism	3	38.1	7	4.9	7.8 (2.0-30.7)	.003
Inhalation of fumes	5	39.1	20	5.0	7.8 (2.9-21.0)	<.001
Open wound, buttock	3	21.5	10	2.8	7.7 (2.1-28.7)	.002
Neck injury, musculoskeletal	2	15.0	9	2.0	7.4 (1.6-35.1)	.01
Fracture plate removal	2	14.7	9	2.1	7.1 (1.5-33.8)	.01
Angiomyolipoma	2	13.8	8	1.9	7.1 (1.5-34.4)	.01
Marginal gingivitis	3	23.7	14	3.3	7.1 (2.0-25.1)	.002
Femoral artery embolism	3	26.7	9	3.8	7.1 (1.9-26.6)	.004
Clavicle fracture, acromial end	3	24.9	14	3.5	7.0 (2.0-24.8)	.002
Bone marrow hyperplasia	3	27.5	9	4.0	6.9 (1.8-25.8)	.004
Ruptured ligament, shoulder	2	13.8	8	2.0	6.9 (1.4-33.0)	.02
Vitelliform dystrophy	3	24.9	10	3.7	6.7 (1.8-24.7)	.004
Postvagotomy syndrome	2	13.9	8	2.1	6.6 (1.4-31.9)	.02
Pelvolithiasis	3	21.6	13	3.2	6.6 (1.9-23.7)	.003

[a] CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance.
[b] Rates per 100,000 person-years; age and sex adjusted.
[c] Unadjusted *P* values are reported.

patients with chronic inflammatory demyelinating neuropathy and autonomic neuropathy, our results show that the vast majority of peripheral neuropathies occurred in similar frequencies in patients with and without MGUS. Because of the number of affected patients with neuropathies, this negative result is unlikely to be a result of inadequate sample size. Instead, it shows that the true proportion of cases of neuropathy that can be causally attributed to MGUS is likely to be very low.

We previously reported that the frequency of osteoporosis and bone fractures is increased in patients with MGUS, independent of progression to myeloma.[17] In the current study, we confirmed that the occurrence of hip and vertebral fractures, osteoporosis, and hypercalcemia are all significantly increased with MGUS, even in the absence of progression to multiple myeloma. This has major relevance because the progression of these bony disorders may be amenable to bisphosphonates.

The reduced risk of hyperlipidemia with MGUS observed in the current study may be explained by the assays used to measure lipids. Before 1999, high-density lipoprotein (HDL) testing at Mayo Clinic was performed using a precipitation method. Apo B–containing lipoproteins were precipitated with dextran sulfate and calcium, and cholesterol concentration in the supernatant (containing only HDL lipoproteins) was measured. Since 1999, HDL cholesterol levels have been measured on the Hitachi 912 chemistry analyzer using direct HDL-cholesterol plus reagent (Roche Diagnostics, Indianapolis, IN). The reduced risk of hyperlipidemia in patients with MGUS might be explained by falsely low HDL and low-density lipoprotein concentrations reported by each assay.[18]

We found no significant association between MGUS and a number of other disorders that have previously been reported to be associated with MGUS (Table 2). The fact that we did not demonstrate a significant disease association with MGUS in such a large sample size is of major importance because it implies that these associations are likely not true associations, but rather coincidental ones. This has important therapeutic implications, because in some settings therapy has been administered to eradicate the monoclonal protein in the hopes that the associated disorder would be alleviated. Our study suggests that caution is needed. Some previously reported disease associations (eg, rheumatoid arthritis) that were not confirmed may still merit further study if there is continued biologic rationale for a true association to exist. Despite its large sample size, our study is limited by the fact that many diseases in which prior associations have been reported are relatively rare events, and hence it is not possible to truly exclude a statistically insignificant association with MGUS and 1 or more of the disorders listed in Table 2.

Many important new disease associations that merit further testing, such as sural thrombophlebitis and mycobacterium infection, are listed in Table 3 and Table 4. For instance, the risk of deep venous thrombosis is increased in patients with

myeloma, and thrombosis is an important complication of therapy for myeloma. Studies have suggested that thrombosis is increased even in patients with MGUS.[19,20] We found no association of MGUS with thromboembolism, but we did find a possible association with superficial thrombophlebitis. Similarly, there is strong rationale that chronic infection and immune stimulation may play an etiologic role in MGUS. Thus, the association of MGUS with mycobacterial infection is particularly interesting.

The current study has some specific limitations related to the use of *H-ICDA-2* codes. We relied on *H-ICDA-2* diagnostic codes for disease definitions, and given the sample size involved, it was not possible to verify the accuracy of the coding by manual chart review. Furthermore, there is substantial overlap in diseases classified by *H-ICDA-2* codes, limiting our ability to verify or refute disease associations in many instances. A given disease may be classified by several different *H-ICDA-2* codes, and the decision to merge closely related *H-ICDA-2* codes is subjective. Therefore, any suspected association (or lack thereof) not discussed in this article needs further examination. This can be done by careful analysis of the eAppendix, which provides the case (MGUS) and control rate for each of the 16,062 *H-ICDA-2* diagnostic codes or by performing new focused studies that involve more accurate ascertainment of disease by detailed chart review.

CONCLUSION

Our study confirms several known associations of MGUS with disorders such as vertebral and hip fractures and osteoporosis, as well as provides a list of important new associations. It refutes the reported association of MGUS with numerous other disorders as likely coincidental, a finding that may have important therapeutic implications. The positive associations will be of value in the pathogenesis of myeloma, and they provide biologic insights into mechanisms of disease. The eAppendix that has the incidence of each of the 16,062 disease codes in patients with MGUS and in controls, along with relative risks and confidence intervals, will be of immense value to investigators in various fields who study these diseases.

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