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Risk of acute leukemia and myelodysplastic syndromes in patients with monoclonal gammopathy of undetermined significance (MGUS): a population-based study of 17 315 patients

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Abstract

The purpose of this study was to determine if there is an increased risk of acute leukemia and myelodysplastic syndromes (MDS) in persons with monoclonal gammopathy of undetermined significance (MGUS). We used a large population-based cohort of individuals systematically screened for the presence or absence of MGUS. MGUS status was then linked to the diagnosis of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and MDS. A total of 17 315 patients age 50 and older (605 MGUS and 16 710 controls) with a cumulative 435 021 person-years of follow-up were studied. MGUS patients had a significantly higher risk of developing MDS compared with controls, hazard ratio 2.4 (95% CI 1.08, 5.32), $P = 0.031$. There was no statistically significant increase in the risk of AML (RR 1.36 $P = 0.675$), and no increased risk of developing ALL.

Keywords

monoclonal gammopathy of undetermined significance; MGUS; acute leukemias; myelodysplastic syndromes; population-based screening

INTRODUCTION

An increased risk of developing myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) has been observed for over 40 years in patients with multiple myeloma.[1] Treatment for multiple myeloma, specifically with melphalan, and more recently, lenalidomide maintenance, has been implicated as the major cause of this phenomenon.[2–8] However, it is possible that some of this excess risk is due to an inherent predisposition to

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LER, RAK and SVR designed the research, wrote and edited the manuscript. DRL analyzed the data. SK and AD participated in data interpretation, reviewed the manuscript and provided critical comments. All authors reviewed and approved the final manuscript.

acute leukemia and MDS associated with clonal plasma cell proliferation, as well as a combination of other related host, environmental and behavioral factors.[9,10]

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder present in 3% of the population over 50 years of age.[11] Patients with MGUS have a serum monoclonal immunoglobulin (Ig) concentration of 3 g/dl or less, less than 10% plasma cells in the bone marrow, and do not have lytic bone lesions, hypercalcemia, anemia or renal insufficiency related to monoclonal plasma cell proliferation.[12–14] Unlike patients with multiple myeloma, those with MGUS require no therapy, and represent an ideal population to study in order to determine if there is any inherent increased risk of acute leukemia or MDS associated with clonal plasma cell disorders.

To comment on a true association between MGUS and acute leukemia/MDS, ascertainment bias must be eliminated by a screening study in which all subjects in the cohort are uniformly tested for the presence or absence of MGUS. In this report, we studied the association of MGUS with acute lymphoblastic leukemia (ALL), AML and MDS in the Olmsted County population- based screening cohort in which 77% of the general population living in a defined geographic distribution was systematically screened for MGUS with sensitive laboratory techniques.[11]

MATERIALS AND METHODS

Study cohort

Methods for the assembly of this cohort and the screening procedures to determine the presence or absence of MGUS have been previously described.[11] Briefly, all residents of Olmsted County, Minnesota who were 50 years old or older as of 1 January 1995 were eligible for inclusion. Serum samples were collected and tested from 77% of residents (21 463 of 28 038). All serum samples were tested for monoclonal protein with electrophoresis on agarose gel (REP; Helena Laboratories, Beaumont, TX, USA). A technician and one of the authors (RAK) examined each strip for a discrete or localized band; strips with discrete bands underwent immunofixation (Hydrasys and Hydragel; Sebia Inc., Norcross, GA, USA) in order to detect MGUS. Of 21 463 patients studied in the original cohort, patients who were blinded due to lack of informed consent were excluded, leaving a cohort of 17 315 eligible for study. The study was approved by the Mayo Clinic Institutional Review Board.

Disease associations and statistical analysis

In the 17 315 patients who comprised the study cohort, MGUS status was linked to diagnosis of other associated diseases entered in the Mayo Clinic Medical Index from 1 January 1975 to last follow up or 31 May 2006, as previously described.[15] Diseases were classified by Hospital Adaptation of the International Classification of Diseases, Eighth Edition (H-ICDA-2). We then reviewed all diagnosis codes, and grouped appropriate codes into MDS, AML and ALL. The medical record was reviewed to confirm a diagnosis for all patients with a diagnostic code for MDS, AML and ALL. For any patient who progressed to develop another plasma cell proliferative process, including multiple myeloma and amyloidosis, only diagnoses of acute leukemia or MDS made before progression were considered. The total occurrences of ALL, AML and MDS and the number of person-years were determined for each stratum. Using the generalized linear mode and MASS packages provided in the base system of R, 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. Risk ratios with 95% confidence intervals were then calculated.

RESULTS

The study included 17 315 Olmsted County residents greater than 50 years old as of 1 January 1995. This cohort represents 435 021 person-years of follow-up. Patient characteristics are given on Table 1. The MGUS cohort consisted of 605 individuals. The mean age at MGUS diagnosis was 69.7 years (range, 39.0–98.0). Controls consisted of 16 710 persons tested and found to be negative for the presence of a monoclonal protein. The MGUS cohort was older (mean age 70.4 for MGUS, 68.5 for controls, $P<0.0001$) and a larger proportion was male (51.1% for MGUS, 44.8% for controls, $P = 0.002$) than controls. Follow up was similar for the MGUS cohort and controls.

MGUS patients had a 2.4-fold significantly increased risk of developing MDS over the general population ($P = 0.031$, 95% CI 1.08, 5.32). There was a slightly increased risk of AML (RR 1.36), though the increased risk was not significant ($P = 0.675$). There were no cases of ALL in the MGUS cohort. Overall, MGUS patients had a higher risk of developing acute leukemia (ALL or AML) or MDS compared with controls, risk ratio 1.83 ($P = 0.105$) (Table 2).

Seven of the 605 MGUS patients were diagnosed with MDS and two were diagnosed with AML. One patient who developed AML had antecedent MDS, so there were a total of eight patients diagnosed with MDS or AML. There was a 1.96-fold increased risk of developing MDS or AML over the general population, though this increase did not reach statistical significance ($P = 0.072$, 95% CI 0.94, 4.08). The risk of developing MDS was statistically significant (RR 2.40, $P = 0.031$). However, MGUS patients had no significantly increased risk of developing AML over the general population (RR 1.36, $P = 0.675$, 95% CI 0.32–5.74).

In subset analysis, MDS was observed in patients with IgA/IgG and IgM isotypes, though AML was observed only in patients with IgA/IgG isotypes ($n = 2/484$). The risk ratio for patients with IgA/IgG MGUS for MDS or AML was 2.16 over controls ($P = 0.052$). Patients with an IgM M spike had a 1.85-fold increased risk of developing MDS over controls ($P = 0.542$), but patients with MDS and this isotype did not develop AML (Table 3).

DISCUSSION

Our population-based study was prompted by the gravity of the implication that MGUS may be inherently associated with acute leukemia and MDS. Our goal was to determine whether such a risk could be detected after eliminating ascertainment bias by screening a well-defined population for the presence or absence of MGUS. We also sought to clarify the magnitude of the excess risk, if one was present.

This large population-based cohort analysis shows that MGUS patients have a 2.4-fold increased risk of developing MDS compared with controls. Our study did not show that MGUS patients are at an increased risk of developing AML. However, the limited number of AML cases in MGUS patients restricts the ability to draw firm conclusions. There were no cases of ALL in the MGUS cohort, suggesting that MGUS patients are not at an increased risk of developing ALL.

Overall, our study shows that when MDS and AML are considered together, there is a 2.0-fold increased risk compared with the general population, which is considerably lower than the 8.01-fold increased risk suggested in a recent report.[16] This Swedish study compared patients found to have MGUS through a clinical workup that included serum protein electrophoresis (SPEP). However, the rest of the population was not systematically screened for the presence or absence of MGUS. Thus, the reported hazard ratio could have merely

reflected the circumstances, in which an SPEP was ordered, rather than the result of the test. Such biases are hard to overcome by adjusting for confounders. In other words, the eightfold increased risk may be inflated, as patients with symptoms requiring a medical workup with SPEP testing are more likely to have underlying pathology than those who never presented to the medical system and were not tested. The smaller risk ratios in our study are likely related to our population-based cohort design with universal screening, which avoided ascertainment bias that occurs when testing for MGUS is done in response to illness in hospital or clinical setting. As a result, we feel that our study is more likely to accurately approximate the true increase in risk.

Our finding of no increased risk of ALL in MGUS patients is consistent with the Swedish study.[16] This finding is especially interesting since ALL has been reported in lenalidomide maintenance trials.[6–8] If patients with MGUS, and in turn multiple myeloma, have no inherent increased risk of developing ALL, treatment effects may be responsible for the observed increase in development of ALL following lenalidomide maintenance.

Unlike the Swedish study,[16] we did not find that MDS and AML were isolated to IgA/IgG isotypes. Although MDS was found in MGUS patients with IgA, IgG and IgM M spikes, excess risk of MDS was isolated to patients with IgA/IgG M spikes. IgA/IgG MGUS patients had a 2.60-fold increased risk of developing MDS ($P = 0.028$) compared with controls, while patients with an IgM M spike did not have a significant increased risk of developing MDS (RR = 1.85, $P = 0.542$). Although the increased risk of developing MDS in patients with IgM isotype was not significant, it does suggest that the association of MDS or AML with MGUS may not be isolated to patients with IgA or IgG isotypes.

Our findings confirm the Swedish study[16] and support the hypothesis that there is an inherent increased risk of MDS in patients with plasma cell disorders that is independent of therapy for myeloma. Our study also suggests that the risk is smaller than previously reported with a risk ratio of 2.0 for AML and MDS. Whether MGUS is a biomarker of patients who have an inherent increased risk of developing hematologic disorders, including myeloma and MDS, or the clonal plasma cell has a causal role in the development of acute leukemia is yet to be elucidated.

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Table 1

Patient characteristics

	Controls (*n* = 16710)	MGUS (*n* = 605)
Age in years (as of 1 January 1995), mean (s.d.)	64.5 (10.6)	70.4 (11.1)
Age in years at MGUS diagnosis, mean (s.d.)	NA	69.7 (11.0)
Gender, female %	55.2	48.9
Follow-up in years, mean (range)	25.14 (0.01–31.4)	24.64 (0.11–30.57)
Total follow up, person-years	420116.37	14904.25
Type of monoclonal protein, no. of patients (%)		
IgA		67 (11.1%)
IgG		417 (68.9%)
IgM		103 (17.0%)
Biclonal		17 (2.8%)
Unknown		1 (0.2%)

Abbreviation: MGUS, monoclonal gammopathy of undetermined significance; NA, not applicable

Table 2

Association with MDS and acute leukemia, MGUS patients versus controls

Outcome	MGUS		Controls		Risk ratio** (95% CI)	*P*-value
	Cases	Rate[a]	Cases	Rate[a]		
MDS	7	0.49	56	0.20	2.40 (1.08, 5.32)	0.031
AML	2	0.74	32	0.54	1.36 (0.32, 5.74)	0.675
AML or MDS	8	1.02	82	0.52	1.96 (0.94, 4.08)	0.072
ALL	0	0.00	6	0.06	0.00 (0, Inf)	0.995
Acute leukemia	2	0.68	38	0.61	1.12 (0.27, 4.68)	0.877
Acute leukemia or MDS	8	0.95	87	0.52	1.83 (0.88, 3.80)	0.105

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndromes; MGUS, monoclonal gammopathy of undetermined significance.

** Compared with controls.

[a] Rate per 100 000 person-years, age- and sex-adjusted.

Table 3

Association with MDS and acute leukemia by isotype

Outcome	IgA or IgG isotype		IgM isotype	
	Cases	Risk ratio[a] (*P*-value)	Cases	Risk ratio[a] (*P*-value)
MDS	6	2.60 0.028	1	1.85 0.542
AML	2	1.71 0.463	0	0 0.993
AML or MDS	7	2.16 0.052	1	1.35 0.765
ALL	0	0.00 0.995	0	0 0.996
Acute leukemia	2	1.42 0.634	0	0 0.993
Acute leukemia or MDS	7	2.02 0.076	1	1.26 0.82

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndromes; Ig, immunoglobulin.

[a]Compared with controls.