Venous Thromboembolism in Patients With Monoclonal Gammopathy of Undetermined Significance

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Abstract: Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a serum M-protein at a concentration of 3 g/dL or less, with less than 10% plasma cells in the bone marrow, and the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell proliferative process. The annual risk of MGUS progressing to a symptomatic plasma cell proliferation or other related malignancy is approximately 1%. The association between malignancy and venous thromboembolism (VTE) is well recognized. In this retrospective study of MGUS patients, VTE was seen in 8% (9/112) of patients, a rate that is 22.8-fold higher than that in the general population ($P<.001$). Although many studies have identified VTE as a marker for subsequent malignancy, we did not find a significant difference in the incidence of VTE as a function of the risk factor group.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is the most common of the plasma cell dyscrasias. It is defined by the presence of a serum monoclonal protein (M-protein)—immunoglobulin (Ig) G, IgA, or IgM—at a concentration of 3 g/dL or less, with less than 10% plasma cells in the bone marrow, and the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell proliferative process.[1,2] The incidence of MGUS increases with age; the prevalence is 1–2% in adults older than 50 years[3,4] and up to 5.3% in those older than 70 years.[5] MGUS is usually asymptomatic at the time of diagnosis and ordinarily detected after routine blood testing reveals an elevation of total protein with a monoclonal spike on subsequent serum protein electrophoresis. The risk that MGUS will progress to a symptomatic plasma cell proliferation or other related malignancy is approximately 1% per year.[6] Such conditions include multiple myeloma and the related disorders of plasma cell leukemia, light chain deposition disease in patients with IgG- or IgA-type MGUS;

or lymphoproliferative disorders, such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, amyloidosis, or Waldenström macroglobulinemia (in patients with IgM-type MGUS).[7] Because of the potential for these transformations, MGUS is considered to be a premalignant condition necessitating regular follow-up.

The association between malignancy and venous thromboembolism (VTE) is well recognized.[8] Occasionally, VTE occurs before the diagnosis of the malignancy. Consequently, it has been suggested that VTE may be predictive of the subsequent diagnosis of malignancy. Indeed, several studies have reported that patients who present with idiopathic VTE are at increased risk for the subsequent diagnosis of malignancy.[9-12] Additional studies have identified VTE as a marker for a prevalence of subsequent malignancy in 2.2–12% of patients with idiopathic (unprovoked) thrombosis.[13-17] Furthermore, some data have suggested that there is an association between hypercoagulation and progressive neoplastic activity.[18,19]

We have therefore conducted a retrospective study to evaluate the incidence of VTE among MGUS patients in the absence of malignant transformation and have compared this rate with the incidence in the general population. We sought to correlate this incidence with the different risk classification used to predict the likelihood that a subsequent malignancy will develop. We also aimed to determine the time to a VTE event as a function of the risk group assignment.

Methods

The complete medical records of all MGUS patients treated at the Cleveland Clinic Cancer Center (Moll Pavilion) in Cleveland, OH, from June 2005 to June 2008 were retrospectively reviewed. We identified 112 patients (65 men, 47 women) who were eligible for our study. These patients were divided into 2 risk groups: low risk/low-intermediate risk (LR/LIR; n=78) and high-intermediate risk/high risk (HIR/HR; n=34). We used a risk stratification model based on 3 adverse predictors: a serum M-protein level at or exceeding 1.5 gm/dL, non-IgG MGUS, and an abnormal kappa/lambda (K/L) free-light chain ratio (Table 1).[20] Only patients with at least 12 months follow-up were included. Exclusion criteria included history of inherited thrombophilia, a previous episode of VTE or anticoagulant treatment, thrombocytosis, malignancy, and renal impairment (because the normal K/L ratio has been determined in patients with normal renal function). Risk factors for VTE were identified, and patients were categorized into 4 groups: 0 risk factors (RF); 1 RF; 2 RF; and more than 2 RF. Risk factors included immobilization for longer than 48 hours, surgery in the past 3 months, current hospitalization at the time of VTE occurrence, oral contraceptive use, and congestive heart failure. Cases of VTE were confirmed by contrast venography or Doppler ultrasound for venous thrombosis (upper-lower extremities) and by chest computed tomography, ventilation/perfusion scan, or pulmonary angiography for pulmonary embolism.

Table 1. Risk Stratification Model

MGUS	Number of Risk Factors*	Risk of Progression in a 20-Year Period
High risk	3	58%
High-intermediate risk	2	37%
Low-intermediate risk	1	21%
Low risk	0	5%

*M-protein level ≥1.5 gm/dL, non-immunoglobulin G monoclonal gammopathy of undetermined significance, and an abnormal kappa/lambda free-light chain (K/L) ratio (laboratory reference ranges: serum M-protein, 0 gm/dL; free kappa light chains, 3.30–19.40 mg/L; free lambda light chains, 5.71–26.30 mg/L; K/L ratio, 0.26–1.65.)

Adapted from the risk stratification model for MGUS progression into malignancy proposed by Rajkumar et al. *Blood*. 2005;106: 812-817.

Objectives

The objectives of this study were to:

- Compare the proportion of patients with MGUS who developed VTE to the proportion of patients in the general population who developed VTE over a 3-year period.
- Compare VTE incidence between the 2 risk groups: LR/LIR and HIR/HR.
- Assess the association between the time to VTE event and the group assignment.
- Assess the effect of recognized risk factors for VTE on the observed rate found in our study of 112 MGUS patients.

Statistical Methods

A binomial test was performed to analyze whether the observed VTE proportion of the MGUS patients differed from the VTE proportion of the general population over the specified 3-year time period. The 95% confidence interval (CI) for the VTE proportion of the eligible

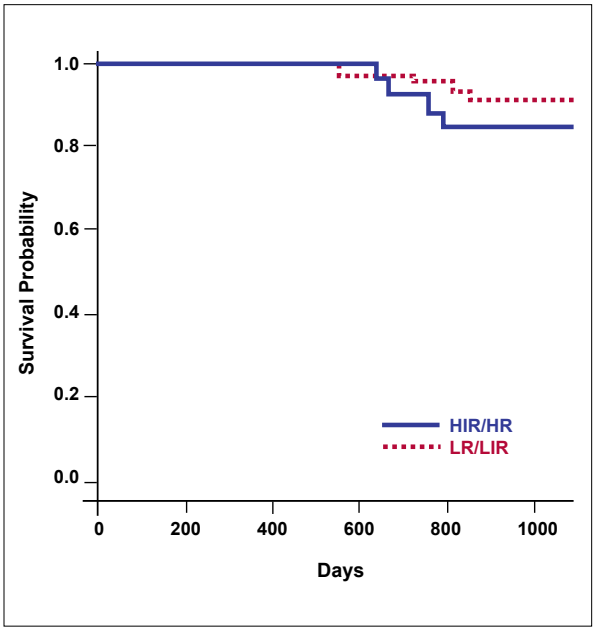

Figure 1. Kaplan-Meier survival curves by group. The y-axis is the survival probability (patients free of venous thromboembolism), and the x-axis represents time (days).

HIR/HR=high-intermediate risk/high risk; LR/LIR=low risk/low-intermediate risk.

MGUS patients was calculated. Data regarding number of follow-up days, age at diagnosis of MGUS, and time to event for those diagnosed with VTE within each group were obtained. Fisher's exact test was used to analyze the group difference in VTE rates considering the rare event occurrences. The Mantel-Haenszel test was then used to reanalyze the difference in the VTE rates between the groups after controlling for the number of risk factors. Kaplan-Meier estimates of VTE were calculated by group and presented for selected time points. Cox proportional hazards models were used to estimate the hazard ratios between the groups without adjustment for the number of risk factors. The Cox proportional hazards model was then refitted with adjustment for the number of risk factors. The time origin for the analysis of time to VTE was defined as the date of diagnosis of MGUS.

All analyses were performed using SAS software (Cary, NC), unless otherwise stated. Statistical significance was defined as $P \leq .05$. Plots were created using R 2.5.1 software.

Results

During the study period, 9 patients (8.0%) with MGUS experienced VTE. Six developed lower extremity deep venous thrombosis (DVT), 2 developed pulmonary embolism, and 1 developed upper extremity DVT. The median follow-up for the 112 patients was 867 days (range, 365–1,096 days), and the median age at the time of diagnosis of MGUS was 69.2 years (range, 48.4–89.1 years). The median time to VTE for those diagnosed with VTE was 730 days (range, 549–852 days) in the LR/LIR group (n=5) and 715 days (range, 640–791 days) in the HIR/HR group (n=4), an insignificant difference. Kaplan-Meier survival curves by group are shown in Figure 1.

Discussion

It has been reported that patients with plasma cell dyscrasias are at increased risk for VTE. This risk is further increased by the treatment of this condition, particularly in multiple myeloma patients. However, although patients with MGUS ordinarily do not receive any specific treatment, they are still at increased risk of VTE.[21] This risk has been thought to be due to ongoing clonal plasma cell activities, including secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tissue necrosis factor.[22]

Data on the association of VTE and MGUS are limited. In one prospective study, 6.1% of 310 MGUS patients developed VTE, with a median time from the diagnosis of MGUS until the diagnosis of VTE of 23 months (range, 17–35 months).[23] A further retrospective study reported that 7.5% of 174 MGUS patients developed VTE, with a median time from the diagnosis of MGUS to the development of VTE of 4 months (range, 0–67 months).[24] In a more recent and larger study of 2,374 patients evaluated by Kristinsson and colleagues, MGUS patients had a 3.3-fold increased risk of DVT and a stable excess DVT risk over time during follow-up of up to 16 years (median, 3 years) compared with the general population.[25]

With respect to the incidence of VTE among MGUS patients and progression to malignancy, Sallah and coworkers reported that MGUS patients who developed VTE had a relative risk of 4.2 of progressing to a lymphoproliferative malignant disorder compared with MGUS patients without VTE (95% CI, 1.64–10.7; P=.003).[23] In contrast, Kristinsson and colleagues reported no statistical association between DVT and the risk of transformation to multiple myeloma.[25] These studies, however, did not exclude patients with a previous personal or family history of VTE or other risk factors such as immobilization, surgery, previous malignancy, and thrombocytosis. In our study, we excluded these confounding factors and focused solely on MGUS as a risk factor for VTE. The overall average age- and sex-adjusted annual incidence of VTE is 117 per 100,000 persons in the general population.[26]

Table 2. Comparison of Event Rates in MGUS Patients and the General Population

Number of MGUS Patients	Number of Patients With VTE	VTE Proportion (standard error)	95% CI	VTE Proportion in General Population*	*P* Value
112	9	0.080 (0.026)	0.030–0.131	0.0035	<.001

*The VTE proportion for the general population over a 3-year time period.

CI=confidence interval; MGUS=monoclonal gammopathy of undetermined significance; VTE=venous thromboembolism.

Therefore, the proportion of patients developing VTE over 3 years is 0.0035 (117 per 100,000 × 3). Among the eligible MGUS patients in our study, 8% (9 of 112) developed VTE during the follow-up period (maximum of 3 years), a rate that is 22.8-fold higher than that in the general population (*P*<.001; Table 2).

The actual difference may be even greater. Some patients in the study were not followed for the full 3-year period; the median follow-up was 2.37 years. It is therefore very likely that the observed VTE proportion over 3 years (8%) was underestimated. In addition, known risk factors for VTE in the general population are independent of MGUS and contribute to the overall incidence, whereas in our analysis of MGUS patients, we did not include confounding risk factors.

The increased risk of VTE in MGUS may be related to increased secretion of pro-inflammatory cytokines such as interleukin 6 (IL-6) and tissue necrosis factor. These agents have been noted to increase in MGUS patients, and both can activate coagulation pathways, leading to increased VTE occurrence.[27] IL-6 has been shown to promote coagulation by activating the coagulation cascade through tissue factor stimulation and increased transcription of factor VIII, and it upregulates transcription of fibrinogen, increases von Willebrand factor, and decreases protein S levels.[6,28]

An increased incidence of VTE in patients with MGUS has been correlated with a high concentration of M-protein,[23] a decrease in the serum albumin level, and an increased leukocyte count.[29] The correlation between the increased incidence of VTE and the increased leukocyte count and decreased albumin level can be attributed to the effects of IL-6, which has been shown to cause leukocytosis.[30,31] Furthermore, IL-6 is a potent mediator of inflammatory processes, and it decreases the serum albumin level.[32]

Patients with IgG-type MGUS have a lower incidence of VTE than do patients with either the IgA or IgM types.[6,24] Interestingly, a high concentration of serum M-protein,[29,33,34] IgM-, or IgA-type MGUS,[6] and an abnormal K/L ratio[35] are all associated with a higher risk that MGUS will progress to malignancy.

Increased viscosity reduces blood flow to tissues, and the threshold for symptoms secondary to increased viscosity is directly related to the M-protein concentration. This symptom threshold is lowest for IgM pentamers, followed by IgA pentamers and IgG3 dimers, and then by IgG monomers.[36] Paraproteins also reduce red cell deformability and induce rouleaux formation, further increasing whole blood viscosity. Furthermore, M proteins interfere with the fibrin structure, causing the formation of thin gel fibers and subsequent clot production.[37,38]

Rajkumar and associates have constructed a risk-stratification model using all previous risk parameters to predict the risk that MGUS will progress to malignancy.[20] Our retrospective study—in addition to comparing the incidence of VTE between MGUS patients and the general population—sought to correlate this increased incidence with the risk for malignancy.

There was no difference in VTE incidence between the 2 groups (LR/LIR vs HIR/HR; Cox proportional model, *P*=.38), after adjusting for risk factors. Similarly, there was no significant difference in the risk of VTE among different levels of risk factors (*P*=.96; Table 3). The Kaplan-Meier estimate of the proportion of patients free of VTE at 24 months is 0.96 for the LR/LIR group and 0.93 for the HIR/HR group. Comparison of the VTE rates between the 2 groups without adjustment for the number of VTE risk factors revealed no significant difference (Fisher's exact test, *P*=.45).The comparison, after controlling for the number of risk factors using the Mantel-Haenszel test, likewise showed no evidence of a significant difference in the VTE rate between the 2 risk groups (*P*=.79). However, our study showed that MGUS patients in the HIR/HR group had a higher rate of VTE events (11.8%) than the patients in the LR/LIR group (6.4%). This difference failed to reach statistical significance, perhaps due to the overall low number of VTE events among patients in both risk groups.

Table 3. Association Between Risk Group and Time to VTE After Adjustment for Risk Factors

Variable	Level	N	Percent Free of VTE at 18 Months (95% CI)	Percent Free of VTE at 24 Months (95% CI)	Percent Free of VTE at 30 Months (95% CI)	Hazard Ratio (95% CI)	*P* Value*	
							Versus Reference	Overall
Risk Group	LR/LIR	78	100 (100–100)	96 (87–99)	91 (80–96)	1.00		.38
	HIR/HR	34	100 (100–100)	93 (74–98)	84 (63–94)	1.81 (0.48–6.91)	.38	
Number of Risk Factors	0	38	100 (100–100)	93 (75–98)	93 (75–98)	1.00		.96
	1	43	100 (100–100)	95 (80–99)	88 (72–96)	1.74 (0.16–19.48)	.65	
	2	23	100 (100–100)	96 (73–99)	89 (63–97)	1.41 (0.19–10.29)	.73	
	>2	8	100 (100–100)	100 (100–100)	75 (13–96)	1.48 (0.27–8.11)	.65	

**P* values are from Cox proportional hazard models.

CI=confidence interval; HIR/HR=high-intermediate risk/high risk; LR/LIR=low risk/low-intermediate risk; VTE=venous thromboembolism.

Conclusions

The rate of VTE is significantly higher—by at least 22.8 times—in patients with MGUS as compared with the general population, even after adjustment for recognized risk factors. Although many studies have identified VTE as a marker for subsequent malignancy, we did not find a significant difference in the incidence of VTE as a function of the risk factor group. Similarly, we found no significant difference in the time to onset of VTE between the 2 risk groups. The number of patients was small and the period of follow-up was relatively short, and therefore a prospective cohort study is needed to verify our results.

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