Risk factors for venous thromboembolism in immunoglobulin light chain amyloidosis

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ABSTRACT

Patients with immunoglobulin light chain amyloidosis are at risk for both thrombotic and bleeding complications. While the hemostatic defects have been extensively studied, less is known about thrombotic complications in this disease. This retrospective study examined the frequency of venous thromboembolism in 929 patients with immunoglobulin light chain amyloidosis presenting to a single referral center, correlated risk of venous thromboembolism with clinical and laboratory factors, and examined complications of anticoagulation in this population. Sixty-five patients (7%) were documented as having at least one venous thromboembolic event. Eighty percent of these patients had events within one year prior to or following diagnosis. Lower serum albumin was associated with increased risk of VTE, with a hazard ratio of 4.30 (CI 1.60-11.55; *P*=0.0038) for serum albumin less than 3 g/dL compared to serum albumin greater than 4 g/dL. Severe bleeding complications were observed in 5 out of 57 patients with venous thromboembolism undergoing treatment with anticoagulation. Prospective investigation should be undertaken to better risk stratify these patients and to determine the optimal strategies for prophylaxis against and management of venous thromboembolism.

Introduction

Immunoglobulin light chain amyloidosis (AL) is a rare systemic disorder resulting from organ deposition of amyloid fibrils comprised of immunoglobulin light chains, typically associated with an underlying clonal plasma cell or lymphoproliferative disorder.

AL is known to affect hemostasis with both severe thrombotic and bleeding complications reported.[1-5] The predilection for bleeding complications has been attributed to acquired factor X deficiency, acquired von Willebrand syndrome, and vascular fragility due to amyloid fibril deposition in small capillaries.[2,4,6-9] The last is primarily responsible for the periorbital ecchymoses considered pathognomonic of the disease. The etiology, risk, and optimal management of thrombotic complications in AL have not been established. The nephrotic syndrome, a common presentation of AL, is associated with hypercoagulability and may contribute to the risk of venous thromboembolism (VTE) in this population.[10-15] Other potential contributors to thromboembolic risk include monoclonal gammopathy and plasma cell dyscrasia[16] as well as AL treatments, specifically immunomodulatory agents (IMiDs)[17-23] and those requiring central venous catheters. A means of risk stratification of VTE in this population is needed to guide prophylaxis and treatment strategies.

In this study, we retrospectively examined the frequency of VTE events among patients with AL presenting to a single referral center, and determined specific factors that may influence the risk of VTE in this disease.

Table 1. Base-line clinical characteristics.

Characteristic	VTE (n=46)	All (n=824)
Median age at diagnosis in years (range)	60 (26-80)	61 (26-90)
N. female (%)	13 (28)	308 (37)
N. non-white (%)	3 (6.5)	99 (12)
Tobacco history in years, n. (%)		
None	18 (39)	388 (47)
<10	4 (8.7)	45 (5.5)
10-30	15 (33)	142 (17)
30-50	2 (4.3)	90 (11)
>50	0 (0)	5 (0.6)
Unknown	7 (15)	154 (19)
Primary organ involvement years, n. (%)		
Renal	27 (59)	392 (48)
Cardiac	11 (24)	225 (27)
Liver	2 (4.3)	34 (4.1)
Gastrointestinal	3 (6.5)	50 (6)
Nervous system	1 (2.2)	27 (3.3)
Pulmonary	0 (0)	11 (1.3)
Other/unknown	2 (4.3)	85 (10)
Treatment history years, n. (%)		
Any IMiD	17 (37)	151 (18)
Any ASCT	29 (63)	286 (35)
Serum albumin (g/dL)		
>4	21 (35)	175
3-4	20 (33)	421
<3	5 (8.3)	228
Urine protein (g/day)		
≤1	11 (18)	319 (39)
1-3.5	7 (12)	145 (56)
3.5-8	12 (20)	196 (24)
>8	15 (25)	164 (20)

N: number at risk; VTE: venous thromboembolism; IMiD: immunomodulatory agent; ASCT: autologous stem cell transplantation.

Table 2. Description of events.

Characteristic	Number
VTE type	
DVT	40
PE	23
DVT/PE	4
Portal vein thrombosis	1
Unknown	3
Treatment associated	
IMiD	15
ASCT	16
Other (bortezomib, melphalan, bendamustine, VAD)	11
No or unknown	29
CVC associated	
Yes	17
No or unknown	54

VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism; UTP: urine total protein; IMiD: immunomodulatory agent; ASCT: autologous stem cell transplantation; VAD: vincristine, adriamycin, dexamethasone; CVC: central venous catheter.

Methods

Study population

Clinical and laboratory data were collected prospectively on patients presenting to the Amyloid Clinic at the Boston University Medical Center through an Institutional Review Board-approved protocol. All patients gave written informed consent in accordance with the Declaration of Helsinki. Patients typically returned at least annually for re-evaluation and repeat laboratory testing but generally received care at other institutions. Patients with AL who presented between January 2003 and September 2013 were included in this study.

Cases of VTE were determined by searching the electronic medical record for the co-occurrence of "AL amyloidosis" along with terms related to VTE, including "thrombosis", "DVT", "PE", and "embolism" in the above patients' charts. Cases of VTE were verified by chart review. Only VTEs occurring within one year prior to diagnosis or at any time following the diagnosis of AL were included. Cases of arterial thrombosis and embolic cerebrovascular accidents were not included in this analysis.

Bleeding events complicating anticoagulation treatments were identified by chart review in patients with confirmed VTE. Significant bleeding events were defined as bleeding requiring hospitalization, fatal bleeding, symptomatic bleeding into a critical area or organ, or bleeding requiring transfusion.

Laboratory data from the initial evaluation at the Amyloid Clinic were used in this analysis. Urinary protein excretion was measured by 24-h collection when available. Urine protein to creatinine ratio was used to estimate proteinuria if 24-h collection was not available. Due to modification of the D-dimer assay during the period of study, the D-dimer result was converted to a binary positive or negative result based on the normal range established by the clinical laboratory at the Boston University Medical Center at the time. An intermediate result by the qualitative assay was considered to be positive. Data at the time of VTE were not available as the majority of events happened at other institutions.

Statistical analysis

Patients' characteristics were summarized by median and range for continuous variables, frequency and proportion for categorical variables (Tables 1 and 2). Time-dependent individual risk factors and the set of final models were assessed by Cox's regression model (Table 3). $P<0.05$ was considered statistically significant. The analysis was conducted by SAS 9.3.

Results

Patients' characteristics

A total of 929 patients with AL were identified on initial medical record search and included in the descriptive analysis. Of these, 105 patients were excluded from the statistical analysis because of incomplete data, including poor follow up, or because VTE occurred prior to diagnosis. Therefore, 824 patients were included in the final statistical analysis. Base-line characteristics of this group are described in Table 1.

Frequency of and description of events

Out of 929 patients who underwent evaluation, 65 patients (7%) had at least one occurrence of VTE less than one year prior to or following diagnosis of AL. Among the 65 patients identified, there were a total of 71 VTEs diagnosed; 40 deep venous thromboses (DVTs), 23 pulmonary emboli (PEs), one portal vein thrombosis, and 4 occurrences of simultaneous DVT and PE. In 3 cases, the type of VTE could not be determined. Seventeen VTEs (23.9%)

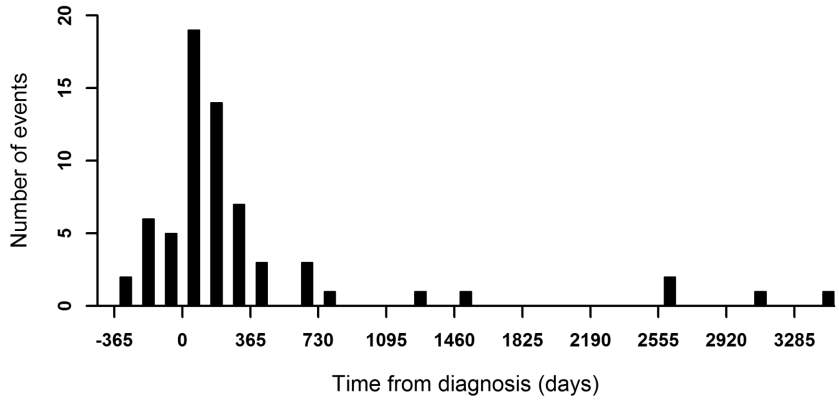

Figure 1. Number of venous thromboembolic events according to time from diagnosis.

occurred in the setting of indwelling central venous catheter (CVC) and 15 (21.1%) occurred within 100 days of IMiD therapy (Table 2). Patients undergoing treatment with IMiD therapy were taking full-dose aspirin prophylaxis or were on therapeutic anticoagulation unless contraindicated. Sixteen events (22.5%) occurred within 100 days of autologous stem cell transplantation (ASCT), of which 6 events were CVC associated. Of the twenty events (29%) that were not in the setting of indwelling CVC or treatment, 14 of these occurred in patients with nephrotic-range proteinuria.

Fifty-two patients (80%) had events occurring within one year of diagnosis (Figure 1). VTE preceded the diagnosis of AL in 12 patients. These patients were included in the descriptive analysis on the presumption that the VTE occurred in the presence of undiagnosed disease, but excluded from statistical analysis. An additional 7 patients were excluded from further analysis because they did not return for follow up after the initial visit or because laboratory data were incomplete.

Risk of VTE in AL

The results of univariate analysis of clinical and laboratory data and risk of VTE are shown in Table 3. An increasing risk of VTE with lower serum albumin was observed, with hazard ratio of 2.16 for serum albumin of 3-4g/dL (CI 0.80-5.81; *P*=0.13), and a hazard ratio of 4.30 in patients with serum albumin of less than 3 g/dL (CI 1.60-11.55; *P*=0.0038) (Figure 2). Increasing proteinuria was also associated with increased risk of VTE, with a hazard ratio of 1.84 for urine protein of 1-3.5 g per day (CI 0.74-4.57; *P*=0.19), 1.94 for urine protein of 3.5-8 g per day (CI 0.85-4.41, *P*=0.11), and 2.60 for urine protein of greater than 8 g per day (CI 1.19-5.72, *P*=0.017). Levels of serum albumin and proteinuria were correlated in this analysis, and thus urine protein was not included in final analysis. Age at diagnosis, sex, non-white race, fibrinogen, D-dimer, and partial thromboplastin time (PTT) were not significantly associated with an increased risk of VTE.

VTE among patients with nephrotic range proteinuria

To determine the specific risk factors for VTE in the setting of nephrotic-range proteinuria, we examined the 382 patients with proteinuria of more than 3.5 g per day. In this subgroup, 37 patients (9.7%) had at least one documented episode of VTE within one year prior to or anytime following the diagnosis of AL. Univariate analysis of PTT, fibrinogen, D-dimer, urine protein excretion greater

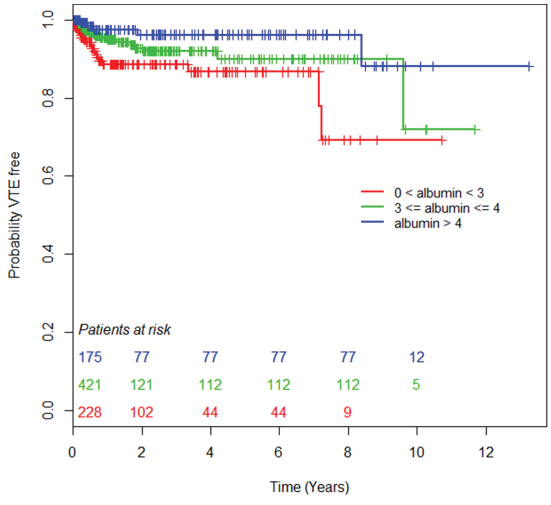

Figure 2. Kaplan-Meier estimates of VTE-free survival for individuals with serum albumin less than 3g/dL (red), greater than or equal to 3g/dL and less than or equal to 4g/dL (green), and serum albumin greater than 4 g/dL (blue).

Table 3. Univariate analysis of risk factors associated with VTE.

	Hazard ratio (95% CI)	P
Age	0.98 (0.95-1.01)	0.12
Sex	0.64 (0.34-1.21)	0.17
Race		
White	1.81 (0.56-5.83)	0.32
Non-white	1.00	
Partial thromboplastin time	1.02 (0.98-1.02)	0.33
Fibrinogen	1.00 (1.00-1.003)	0.17
D-dimer		
Normal	1.00	
Elevated	1.68 (0.93-3.04)	0.086
Albumin (g/dL)		
>4	1.00	
3-4	2.16 (0.80-5.81)	0.13
Less than 3	4.30 (1.60-11.55)	0.0038
Urine protein (g/day)		
1	1.00	
1-3.5	1.84 (0.74-4.57)	0.19
3.5-8	1.94 (0.85-4.41)	0.11
>8	2.60 (1.19-5.72)	0.017

N: number at risk; CI: confidence interval.

Table 4. Bleeding events in patients with VTE.

Event	Type of bleeding event	Anticoagulation type	ASCT-related	Transfusion required	Death from bleeding
1	Intraperitoneal bleed	UFH drip, thrombolysis	Yes	Yes	Yes
2	Intraorbital, GIB	Warfarin	No	Unknown	No
3	Hematuria	Warfarin	No	Unknown	No
4	Lower GIB	Warfarin	No	Yes	No
5	Lower GIB	Warfarin	No	Unknown	Yes

ASCT: autologous stem cell transplantation; GIB: gastrointestinal bleed; UFH: unfractionated heparin.

than 8 g per day, and albumin did not reveal any significant associations with risk of VTE in this subgroup.

Bleeding complications

The incidence of bleeding complications among the cohort of patients with a documented VTE was assessed by chart review. Fifty-seven of the 65 patients with documented VTE had a treatment history which could be verified by chart review. Of those, 5 patients were documented as experiencing at least one episode of major bleeding related to anticoagulation (Table 4). In 2 of these cases, transfusion support was required. Of note, one patient was treated with thrombolysis followed by unfractionated heparin drip for high clot-burden pulmonary emboli on day 25 following ASCT; he developed intraperitoneal hemorrhage 21 days after thrombolysis leading to PEA arrest and death.

Discussion

Venous thromboembolism and its treatment are associated with significant morbidity and mortality in AL. A better understanding of how often VTEs occur and in which patients is of extreme importance in guiding clinicians in the optimal management of these patients.

Venous thromboembolism occurred in 7% of AL patients presenting to our center, and the risk of VTE was strongly associated with low serum albumin. The frequency of VTE observed in this study is consistent with what has previously been described in the nephrotic syndrome associated with membranous nephropathy[11,12] and with what has been reported in AL and multiple myeloma.[5,24,25] Interestingly, no renal vein thromboses were documented in this group; this may reflect the often clinically silent nature of these events, which have been observed in as many as 40-50% of patients with nephrotic syndrome,[15] but were not screened for in our population. The majority of observed events occurred during treatment of the disease with chemotherapy, IMiDs, ASCT, or in the setting of an indwelling CVC. Among the events unrelated to treatment, 14 out of 20 occurred in patients with nephrotic-range proteinuria.

The hypercoagulable state of nephrotic syndrome is thought to be multifactorial and, in part, a result of the imbalance of antithrombotic and prothrombotic factors involved in the coagulation cascade.[26-29] The association between low serum albumin and risk of VTE has been previously described in nephrotic syndrome.[11,12,14,30] Serum albumin is inversely correlated with the degree of urinary protein loss, and may be a surrogate marker for loss of endogenous antithrombotic proteins such as antithrombin III and plasminogen. Serum albumin levels may have direct effects on hemostasis and platelet aggregation[26] and in addition levels may be decreased in critical illness and thus correlate with more advanced disease. Low serum albumin should be a consideration in risk-stratifying patients during treatment of AL and further prospective studies are warranted to determine the benefits of prophylactic anticoagulation in this high-risk group. Given the high rate of bleeding complications in these patients, prophylactic anticoagulation cannot be recommended without a prospective randomized trial. In particular, the role of novel oral anticoagulants should be investigated given the potential better bleeding profile of these agents.

Measures of the coagulation cascade or fibrinolysis such as PTT, fibrinogen and D-dimer were not associated with risk of VTE in this study. This may in part be explained by the fact that these data were collected at the time of initial presentation and not at the time of VTE diagnosis. Data on antithrombin III and factor VIII levels were not available at the time of this analysis, but have been demonstrated in some studies to correlate with risk of VTE.[29,31] Prospective collection of these data may have value in further risk stratifying patients.

The vast majority of documented VTEs in our cohort occurred within one year of diagnosis. Although this may be in part due to the median follow up of 2.3 years, it is consistent with reports of other studies of VTE in nephrotic syndrome patients[11,14] and in MGUS/myeloma patients.[16] The etiology of this increased incidence closer to the time of diagnosis is uncertain, but may reflect an increased risk of VTE associated with various treatments of the disease or a decrease in hypercoagulable state with treatment of the underlying disease. This may have therapeutic implications, particularly in decisions regarding duration of anticoagulation.

This study is complimentary to others examining the incidence of VTE in AL patients, and, to our knowledge, is the first to correlate risk with serum albumin in this disease state. Our study was strengthened by the large number of patients with AL presenting to our center and the breadth of laboratory and clinical data available on these patients. Limitations of the study include its retrospective design and reliance on clinician documentation of venous thromboembolic events. The majority of patients presented to our center for consultation and received treatment elsewhere, and details of the circumstances surrounding the event, such as disease-specific treatment, immobility, surgery and infections, were therefore limited. The analysis was limited by the duration of patient follow up, which varied widely from less than one month to 13.2 years in the entire cohort. Median follow up was longer in the VTE cohort (2.36 years) than the controls (9.72 months); therefore, the observed incidence of VTE may be underestimated. Laboratory data were taken from the initial visit, and may not reflect the state of the patient at the time of VTE. In addition, complete data on treatment and

response in these patients were not available to correlate with the occurrence of VTE.

In summary, VTE is a frequent complication of AL and the majority of VTEs occurred within one year of diagnosis and most often in the setting of treatment of the disease. Decisions regarding treatment duration should take this into consideration. Serum albumin is strongly correlated with risk of VTE in patients with AL and may be a consideration in determining the optimal treatment for these patients. Further prospective trials are needed to determine the risk/benefit ratio of prophylactic anticoagulation, as major bleeding complications in AL patients on anticoagulation were observed, including death in one patient receiving thrombolytics.

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