Original Study

Serum Free Light Chain Difference and β_2 Microglobulin Levels Are Risk Factors for Thromboembolic Events in Patients With AL Amyloidosis

Hyunkyung Park,[1,2] Ji-Won Kim,[3] Jeonghwan Youk,[1] Youngil Koh,[1,2,4] Jeong-Ok Lee,[3] Ki Hwan Kim,[5] Soo-Mee Bang,[3] Inho Kim,[1,2,4] Seonyang Park,[1,2,4] Sung-Soo Yoon[1,2,4]

Abstract

AL amyloidosis might increase the risk of thromboembolism and other plasma cell dyscrasias. Therefore, we evaluated the features of thromboembolism in AL amyloidosis. The incidence of thromboembolism was substantial (12.3%); most events developed within the first year after the diagnosis, and arterial thromboembolism occurred frequently. In particular, patients with risk factors might require close monitoring for thromboembolism.

Background: AL amyloidosis might increase the risk of thromboembolism and other plasma cell dyscrasias; however, only a few reports have described the clinical features of thromboembolism. The present study aimed to elucidate the clinical features of thromboembolic events and to identify the risk factors for these events. **Materials and Methods:** The medical records were retrospectively reviewed to define the clinically significant thromboembolic events. **Results:** A total of 106 patients with biopsy-proven AL amyloidosis were included. During a median follow-up of 18.1 months (range, 0.4-166.9 months), 13 thromboembolism events were identified in 13 patients. Of the 13 patients, 9 (8.5%) experienced acute cerebral infarction, 2 (1.9%) experienced pulmonary embolism, and 2 (1.9%) experienced deep vein thrombosis. Patients with a higher serum free light chain (FLC) difference ($\geq$ 172.4 mg/L) or β_2-microglobulin (β2MG) levels ($\geq$ 2.78 mg/L) experienced significantly more thromboembolic events compared with those with a lower value according to multivariable analysis (for FLC difference: hazard ratio, 4.309; 95% confidence interval, 1.158-16.032; $P = .029$; for β2MG: hazard ratio, 9.739; 95% confidence interval, 1.127-84.174; $P = .039$). Most thromboembolic events (11 of 13; 84.6%) occurred within the first year after the AL amyloidosis diagnosis. **Conclusion:** The incidence of thromboembolism was substantial in those with AL amyloidosis. A greater FLC difference and for β2MG levels were risk factors for thromboembolic events.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■ © 2018 Published by Elsevier Inc.
Keywords: β2MG, Cerebral infarction, Plasma cell dyscrasia, Risk factors, Thromboembolism

Introduction

Amyloidosis is a disorder characterized by the abnormal deposition of fibrillar proteins. This disorder results in various clinical manifestations that are dependent on the involved organs.[1] According to the origin of the abnormal proteins that cause the disorder, amyloidosis can be classified as either AL amyloidosis, which is derived from immunoglobulin light chains, or AA amyloidosis, which is secondary to chronic inflammation.[1] Of these,

H.P. and J.-W.K. contributed equally.

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2]Cancer Research Institute, Seoul National University, Seoul, Korea
[3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[4]Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea
[5]Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea

Submitted: Jan 17, 2018; Revised: Mar 3, 2018; Accepted: Mar 9, 2018

Address for correspondence: Sung-Soo Yoon, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
E-mail contact: ssysmc@snu.ac.kr

2152-2650/$ - see frontmatter © 2018 Published by Elsevier Inc.
https://doi.org/10.1016/j.clml.2018.03.005

AL amyloidosis develops owing to underlying plasma cell dyscrasia and is the most common type of systemic amyloidosis, with an occurrence rate of 9 cases per 1 million persons annually in Western countries.[2]

Previous studies have revealed that plasma cell dyscrasias, such as multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS), and Waldenström's macroglobulinemia (WM)/lymphoplasmacytic lymphoma, increase the risk of thromboembolism. In MM, the incidence of thromboembolism has been reported to be 2.4% to 28%.[3] This increased risk results from the characteristics of the disease itself. The cytokines and small molecules produced by MM cells increase the activity of the procoagulant factors von Willebrand factor, factor VIII, and fibrinogen, resulting in the upregulation of coagulation pathways.[4] In addition, therapeutic drugs, such as dexamethasone/thalidomide and dexamethasone/lenalidomide, increase the risk of thromboembolism to 8% to 26% compared with dexamethasone alone.[3,5] MGUS also increases the risk of thromboembolism by 6.1% to 8.0%.[6,7] A population-based study performed in Sweden reported a hazard ratio (HR) for arterial and venous thrombosis of 1.8 (95% confidence interval [CI], 1.7-1.9) and 1.4 (95% CI, 1.4-1.5) for patients with MM and those with MGUS compared with matched controls during a 10-year follow-up period.[8] Patients with WM/lymphoplasmacytic lymphoma also had an increased risk of thromboembolism compared with matched controls during a 10-year follow-up period (HR, 2.0; 95% CI, 1.6-2.5), with the greatest risk observed during the first year after the diagnosis (HR, 4.0; 95% CI, 2.5-6.4; $P < .001$).[9]

A few studies have reported the incidence of thromboembolism in amyloidosis. A retrospective study found that thromboembolic events occurred in ~1.9% (40 of 2132) of patients with amyloidosis. Of these 40 patients, 29 (73%) experienced venous thrombosis and 11 (28%) experienced arterial thrombosis.[10] In addition, thromboembolic events were reported in 33% of patients with cardiac amyloidosis.[11] The cumulative incidence and risk factors for thromboembolic events, however, remain to be elucidated in patients with AL amyloidosis. Thus, the goals of the present study were to elucidate the clinical features of thromboembolic events and to identify the risk factors for these events in patients with AL amyloidosis.

Materials and Methods

Patient Enrollment

The present study enrolled patients from 3 hospitals in Korea: Seoul National University Hospital, Seoul National University Bundang Hospital, and SMG-SNU Boramae Medical Center. We searched the electronic medical records using the term of "amyloidosis" on the pathology report. Next, we manually selected patients with AL amyloidosis according to the inclusion and exclusion criteria. Patients with pathologically proven AL amyloidosis were eligible for the present study. AL amyloidosis was diagnosed microscopically by the presence of an apple-green

Figure 1 Diagram of Patient Selection