Original Article

Elevated antinuclear antibodies and unprovoked venous thromboembolism: a case-control study

Parisa Delkash[1,3], Amir Behnam Kharazmi[2]*, Zahra Tamartash[3]

[1]Department of Rheumatology, School of Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Internal Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Clinical Research Development Center, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: Unprovoked venous thromboembolism (VTE) can occur without traditional risk factors, and its underlying causes remain poorly understood. This study investigates the potential role of elevated antinuclear antibody (ANA) titers as a biomarker for unprovoked VTE.

Materials and Methods: A case-control study was conducted with 189 patients diagnosed with unprovoked VTE, and 189 matched controls without VTE between 2019 and 2023. ANA titers were measured using enzyme-linked immunosorbent assay (ELISA), and the association between elevated ANA titers and unprovoked VTE was assessed.

Results: The study revealed a significant association between elevated ANA titers and unprovoked VTE. The case group had a higher proportion of patients with ANA titers >1:100 (14.3%) compared to controls (3.7%) ($p<0.001$). Laboratory analysis showed significantly higher white blood cell count ($p<0.001$), lower mean corpuscular volume ($p=0.03$), and higher creatinine levels ($p<0.001$) in the case group. No significant differences were observed in hemoglobin or platelet levels ($p=0.07$ and $p=0.89$, respectively).

Conclusion: Elevated ANA titers may serve as a useful biomarker for identifying patients at risk for unprovoked VTE. Clinicians should consider autoimmune disorders in the differential diagnosis for unprovoked VTE. Early detection of elevated ANA could lead to targeted interventions and improved patient outcomes by reducing VTE recurrence and managing underlying autoimmune conditions.

Keywords: Unprovoked venous thromboembolism, Antinuclear antibodies, Autoimmune disorders, Systemic lupus erythematosus, Antiphospholipid syndrome, Thrombotic events

***Corresponding Author:** Amir Behnam Kharazmi, MD, Department of Internal Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: drkharazmy@gmail.com

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Introduction

Venous thromboembolism (VTE) is a significant global health issue with high morbidity and mortality rates[1-5]. Unprovoked VTE, which occurs without an identifiable trigger such as trauma, surgery, or prolonged immobilization, presents a particularly complex challenge in clinical practice[6, 7]. Unlike provoked VTE, where the cause is often clear, unprovoked cases may be driven by underlying prothrombotic conditions that remain undiagnosed, including occult malignancies or autoimmune disorders[6, 8]. These cases are associated with a higher

risk of recurrence and may indicate a chronic predisposition to thromboembolic events.

Among the potential contributors to unprovoked VTE is the presence of antinuclear antibodies (ANA), which are commonly associated with autoimmune diseases[9, 10]. Elevated ANA levels are a hallmark of several autoimmune conditions, including systemic lupus erythematosus (SLE), and may reflect an underlying immune dysregulation in patients with VTE[11-13]. However, the relationship between ANA positivity and the risk of unprovoked VTE remains unclear. While some studies suggest that ANA positivity could be a marker for autoimmune-related clotting disorders, the extent of this association and its clinical significance require further exploration.

Given the potential impact of autoimmune mechanisms on the development of unprovoked VTE, this study aims to investigate the role of ANA titers in patients with unprovoked VTE compared to controls.

Methods

Study Design and Population: This case-control study was conducted at Imam Hossein Hospital, Tehran, between 2019 and 2023. It included 189 patients with unprovoked VTE as cases and 189 age-matched controls without VTE. Controls were selected from non-rheumatology patients visiting for unrelated conditions like mechanical pain or osteoarthritis.

Inclusion criteria were restricted to patients with unprovoked VTE admitted to the hospital. Exclusion criteria included acute coronary syndrome, recent stroke (within 3 months), malignancies, active infections, long-term anticoagulation for non-VTE reasons (e.g., arrhythmias, valve replacement), pregnancy or recent postpartum, stage 5 chronic kidney disease, and autoimmune disorders like antiphospholipid syndrome. Cases resulting from trauma, surgery, or hormone therapy were excluded. Written informed consent was obtained from all participants (IR.SBMU.MSP.REC.1402.521).

Data Collection: Demographic data and past medical history (PMH) were extracted from patient records, while laboratory data, including paraclinical test results, were obtained from the hospital's laboratory system. Data was collected by an internal medicine resident under the supervision of the primary investigator and academic advisors, using a researcher-designed checklist. The study variables included age, gender, radiologic findings for pulmonary embolism or deep vein thrombosis, and laboratory results such as ANA titer, white blood cell count (WBC), mean corpuscular volume (MCV), hemoglobin (Hb), and platelet count (Plt). ANA titers were measured using enzyme-linked immunosorbent assay (ELISA), and a titer of ≥1:100 was considered positive for elevated ANA levels[14].

Statistical Analysis: Quantitative variables were presented as mean±standard deviation (SD) or median, and categorical variables as counts and percentages. The normality of continuous data was assessed using the Kolmogorov-Smirnov test. Depending on data distribution, independent t-tests or Mann-Whitney U tests were applied to compare continuous variables between cases and controls. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Statistical significance was set at $p<0.05$. All analyses were conducted using SPSS version 26.

Results

Demographic and Clinical Characteristics: The demographic and clinical characteristics of the patients with unprovoked venous thromboembolism and controls without thromboembolism are summarized in Table 1. There was no significant difference in age between the two groups, with cases having an average age of 49.2±15.0 years and controls 48.9±14.3 years ($p=0.82$). However, a significant difference was observed in gender distribution, with a higher proportion of males in the case group (65.1%) compared to the control group (37.6%) ($p<0.001$). In terms of PMH, cases were more likely to have a history of comorbidities (69.8%) compared to controls (56.6%) ($p=0.001$). Regarding laboratory parameters, WBC was significantly higher in the case group (9.8±3.3 × 10^9/L) compared to the control group (6.2±2.2 × 10^9/L) ($p<0.001$), while MCV was significantly lower in cases (85.2±5.8 fL) compared to controls (130.9±585.8 fL) ($p=0.03$). Creatinine levels were also significantly higher in the case group (1.1±0.3 mg/dL) compared to controls (0.9±0.2 mg/dL) ($p<0.001$). No significant differences were

found in Hb or Plt between the two groups, with p-values of 0.07 and 0.89, respectively.

Table 1. Demographic and clinical characteristics.

Characteristic		Cases (N=189)	Controls (N=189)	p-value
Age (years)		49.2 ± 15.0	48.9 ± 14.3	0.82
Gender (%)	Male	65.1% (123)	37.6% (71)	0.00
	Female	34.9% (66)	62.4% (118)	
Past Medical History (PMH) (%)	With PMH	69.8% (132)	56.6% (107)	0.00
	Without PMH	30.2% (57)	43.4% (82)	
WBC (×10⁹/L)		9.8 ± 3.3	6.2 ± 2.2	0.00
Hb (g/dL)		13.1 ± 2.2	20.4 ± 101.4	0.07
MCV (fL)		85.2 ± 5.8	130.9 ± 585.8	0.03
Plt (×10⁹/L)		226 ± 86.5	296 ± 83.6	0.89
Creatinine (mg/dL)		1.1 ± 0.3	0.9 ± 0.2	0.00

Table 2. ANA status in patients with and without unprovoked venous thromboembolism.

ANA Status	Cases (N=189)	Controls (N=189)	p-value
< 1/100	62.4% (118)	82.0% (155)	
1/100	23.3% (44)	14.3% (27)	0.00
>1/100	14.3% (27)	3.7% (7)	

ANA Status in Patients with and without Thromboembolism: Table 2 shows the ANA status in patients with unprovoked venous thromboembolism and those without thromboembolism. A significant difference was found between the two groups in terms of ANA titers.

In the case group, 62.4% (118) had an ANA titer of <1/100, while in the control group, 82.0% (155) had this titer ($p<0.001$). The ANA titer of <1/100 indicates low levels of antinuclear antibodies, which was more common in controls. The proportion of patients with an ANA titer of 1/100 was higher in the case group (23.3%) compared to the control group (14.3%). Importantly, a striking difference was observed for ANA titers >1/100, with 14.3% of the case group having higher titers, compared to only 3.7% of the control group ($p<0.001$). This suggests that elevated ANA titers may be associated with an increased risk of unprovoked venous thromboembolism.

Discussion

The main result of this study was the significant association between elevated ANA titers and unprovoked VTE. Patients with unprovoked VTE had a significantly higher proportion of elevated ANA titers (>1/100) compared to controls, with 14.3% in the case group versus 3.7% in the control group.

These findings have significant clinical implications for managing and understanding unprovoked VTE. The strong association between elevated ANA titers and unprovoked VTE suggests that autoimmune or inflammatory mechanisms could play a crucial role in the development of VTE in patients without traditional risk factors, such as trauma, surgery, or cancer. This highlights the need for clinicians to consider autoimmune disorders as a potential underlying cause in patients presenting with unprovoked VTE.

Autoimmune conditions such as SLE and antiphospholipid syndrome (APS) promote thrombotic events through various mechanisms[15-17]. In SLE, immune complexes and prothrombotic antiphospholipid antibodies (such as lupus anticoagulant and anti-cardiolipin antibodies) increase the risk of thrombosis by interfering with the clotting cascade and causing endothelial damage[18]. In APS, antiphospholipid antibodies directly induce a hypercoagulable state, leading to an increased risk of both venous and arterial thromboembolism[18]. These mechanisms emphasize the importance of elevated ANA titers as a potential biomarker for identifying patients at risk for unprovoked VTE.

Identifying elevated ANA titers in these patients could lead to more comprehensive diagnostic workups for autoimmune diseases such as SLE or APS, which are associated with increased thrombotic risk[19-23]. Early detection and diagnosis of these conditions could

inform more personalized treatment strategies, including long-term anticoagulation therapy or immunomodulatory treatments in high-risk patients, potentially reducing the risk of VTE recurrence.

Furthermore, these results suggest that routine ANA screening might be considered in patients with unprovoked VTE, particularly when other causes of thrombosis have been excluded. Such an approach could improve risk stratification and enable clinicians to implement targeted interventions earlier in the disease process. Ultimately, this could improve patient outcomes by preventing future thrombotic events and managing the underlying autoimmune disorder more effectively.

The findings also emphasize the need for multidisciplinary management involving both hematologists and rheumatologists in the care of patients with unprovoked VTE and elevated ANA titers. Collaborative care could help optimize treatment plans and provide more holistic patient management, addressing thrombotic events and associated autoimmune conditions.

The limitations of this study include some factors that may impact the generalizability and interpretation of the findings. First, the study was conducted at a single center, which may limit its external validity to other populations or healthcare settings. Second, the observational design of this case-control study cannot establish causality between elevated ANA titers and unprovoked VTE. While a significant association was observed, it remains unclear whether elevated ANA levels directly contribute to the development of thrombosis or are merely a marker of underlying autoimmune activity. Third, potential confounding factors, such as other autoimmune conditions or undiagnosed comorbidities, were not fully controlled for, which could influence the observed relationship. Additionally, the study's retrospective nature relied on existing patient records, which may have led to incomplete or missing data, particularly in relation to some laboratory parameters or medical history. Finally, the study did not assess the long-term outcomes of patients with elevated ANA titers or investigate the effectiveness of specific treatments, which could provide more insight into the clinical significance of elevated ANA levels in preventing VTE recurrence.

Conclusion

This study highlights a significant association between elevated ANA titers and the occurrence of unprovoked VTE. The findings suggest that autoimmune mechanisms, potentially mediated by elevated ANA levels, may contribute to the development of VTE in patients without traditional risk factors. These results underscore the importance of considering autoimmune disorders in the evaluation of patients with unprovoked VTE. Routine ANA screening in such patients could improve early detection and risk stratification, potentially guiding personalized treatment strategies and reducing the risk of thrombotic events. However, further studies are needed to confirm these findings, explore the underlying mechanisms in more depth, and assess the long-term outcomes and therapeutic implications of elevated ANA titers in VTE management.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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