The Heightened Risk of Deep Venous Thrombosis and Pulmonary Embolism in Patients with Cutaneous Lupus Erythematosus

Christopher G. Gibson[1,*], Bhakti B. Chavan[2], Ruby S. Gibson[3], Benjamin Strickland[5], Adam D. Fratczak[2], Robert L. Zee[1], Stephanie J. Ott[4] and Irving L. Rosenberg[4]

[1]*Department of Internal Medicine, Fairfield Medical Center, Lancaster, Ohio, USA*

[2]*Ohio University Heritage College of Osteopathic Medicine, Dublin, OH, USA*

[3]*Long School of Medicine, University of Texas Health San Antonio, San Antonio, TX, USA*

[4]*Department of Rheumatology at the Fairfield Medical Center, Lancaster, OH, USA*

[5]*Kirksville College of Osteopathic Medicine, Kirksville, MO, USA*

Abstract: *Background*: Lupus is an inflammatory disorder that involves many different organ systems. One of these systems is coagulation cascade. This leads to increased rate of venous thromboembolism (VTE). Isolated cutaneous lupus (CLE) is typically thought to just be limited to cutaneous structures. However, there has been very little studies on evaluating the risk of VTE in patients with CLE. This paper attempts to outline whether CLE is a risk factor for VTE.

Methods: Two large databases of patient information were used, the NIS, and HCUP. Using the ICD 9-10 codes from these discharge summaries it was possible to see which patients had both an in-hospital diagnosis of VTE and CLE. Patients with other rheumatologic diseases aside from CLE were excluded.

Results: A total of 3551 patients with CLE and 35,608 with SLE were identified in the 2015-2016 population. CLE and SLE were associated with a statistically significant increased risk of VTE in adjusted and unadjusted analyses. 912 patients with SLE were diagnosed with VTE (2.6%) with a p-value of <0.001.

Conclusion: Through adjusted analysis of the discharge diagnosis it was found the 1.6% of patients also had an in hospital VTE diagnosis. This correlated with an increased risk of VTE with a p value of .0026.

Keywords: Cutaneous Lupus, Epidemiology, Inflammation, Deep Vein Thrombosis, Pulmonary Embolism.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that includes a broad spectrum of symptoms. The term 'lupus' is Latin for wolf first used several hundred years ago to describe the lesions evocative of a 'wolf's bite' [1]. SLE is a multisystem disease with many clinical phenotypes, including drug induced lupus, neonatal lupus, secondary antiphospholipid antibody syndrome and isolated cutaneous lupus (CLE). Often CLE can occur both with SLE and separately [2]. SLE is known to cause an immune-inflammatory state that has been shown to increase the risk of venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE) [3]. There has been very little research into whether or not CLE carries an increased risk of VTE. Prior to this paper, only one previously published article has investigated this issue in a study that examined a Danish cohort of patients [4]. To determine if CLE increases the risk of VTE we will examine national trends in rates of hospitalizations for VTE events in patients with CLE from 2015 to 2016.

METHODS

Data Sources and Study Population

We utilized the Healthcare Cost and Utilization Project's National Inpatient Sample (NIS) database. The NIS is the largest inpatient care database in the United States, containing demographic and clinical information from approximately 8 million hospital stays from about 1000 hospitals sampled to approximate a 20% stratified sample of U.S. community hospitals

This study utilized the 2016 Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP). Hospitals are divided into strata based on U.S. region, urban/rural location, teaching status, bed size and ownership. Sampling probabilities are proportional to the number of hospitals in each stratum. No unique patient identifiers are contained in the NIS. Information available for each hospitalization includes general hospital characteristics as well as patient information such as age, gender, race, quartile of median income based on patient ZIP code, and

*Address correspondence to this author at the Office of Graduate Medical Education, 401 N Ewing St, Lancaster, OH 43130, USA; Tel: (740) 652-4779; E-mail: drcgibson@fmchealth.org

diagnostic and procedure codes form the International Classification of Diseases (ICD).

Patients with CLE were identified by hospitalizations with the primary endpoint will be an in-hospital diagnosis of VTE. We used ICD-10 codes to identify hospitalizations of patients aged 18 years or older for which DVT or PE was the primary discharge diagnosis. For DVT, PE, and VTE we used the following ICD 10 codes I82.409, I26.9, I82.40 respectively. We identified hospitalizations for adults (age 18 or older) with CLE using the ICD-10 codes listed as any secondary discharge diagnosis. This has been previously validated as a valid administrative approach to identification of patients with SLE and CLE [6]. We excluded hospitalizations of patients with CLE if these also include discharge codes for rheumatoid arthritis, systemic sclerosis, dermatomyositis, polymyositis, or other connective tissue diseases.

Statistical Analysis

Descriptive statistics was performed to summarize and describe the distribution of study variables. Bivariate analysis was performed using chi-square (χ^2) statistic to evaluate the association between diagnosis of AMI and study characteristics. Alpha was set at 0.05. All analyses were performed using SAS version 9.4 [13]. Cutaneous Lupus status was included as a time dependent variable, age, gender, smoking status, insurance status, household income, BMI, race, were included as fixed variables.

RESULTS

A total of 3551 patients with CLE and 35,608 with SLE were identified in the 2015-2016 population (Figure **1**). CLE and SLE were associated with a statistically significant increased risk of VTE in adjusted and unadjusted analyses (Figure **1**). 57 patients diagnosed with CLE were found to have experienced VTE (1.6%) with a p value of 0.026. 912 patients with SLE were diagnosed with VTE (2.6%) with a p-value of <0.001.

DISCUSSION

In this Nationwide registry-based cohort study, CLE and SLE were significant for increased risk for VTE. Importantly, the study demonstrated an increased risk of PE and DVT in CLE students. The risk of having a composite VTE endpoint was higher for CLE and SLE, compared to the general population. Chronic, systemic inflammation is described in previous studies as a significant risk factor for developing VTE [7-9]. Numerous studies have hypothesized that the reason for the increased risk of DVT and PE in patients with SLE may be due to the chronic systemic inflammation [10]. In addition SLE patients may have antiphospholipid syndrome, renal disease, hypertension and low levels of natural antibodies such as those against phosphorylcholine [11] which all are proven risk factors for developing VTE [12]. The pathogenesis underlying the association between CLE and PE is less clear. Systemic inflammation is a likely link between these diseases, as seen in SLE and other inflammatory autoimmune diseases [13]; however, little is known about the systemic markers of inflammation in patients with CLE. Stimulation by environmental triggers such as ultraviolet (UV) irradiation induces epidermal keratinocyte apoptosis, autoantigen externalization and alteration of cytokine chemokine production such as interferon (IFN), TNF alpha, interleukin (IL)-1, IL-10 and IL-17, which may initiate a systemic inflammation (Figure **1**). The above idea of increased local cytokine production and the following systemic leak could be an explanation of the association between local cutaneous inflammation and systemic inflammation resulting in CVD. SLE, in the

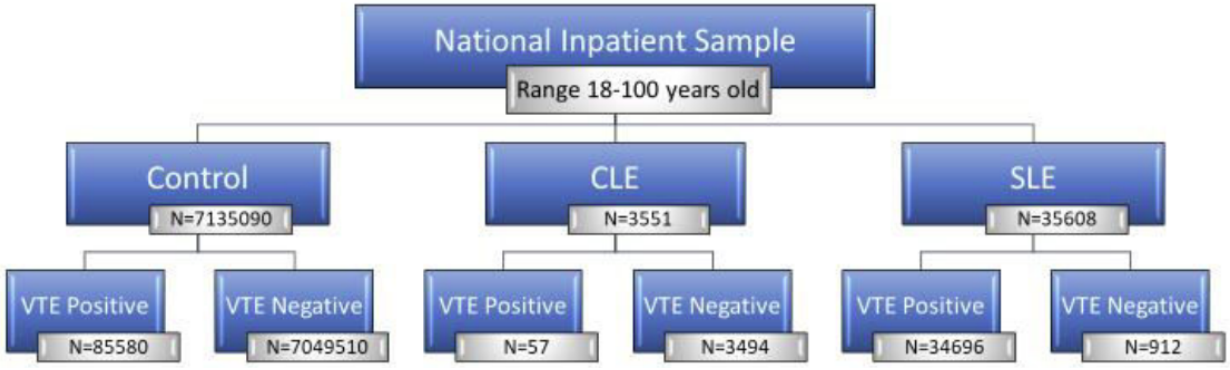

Figure 1: Flowchart of the study population selection.

published literature, is a well described cardiovascular risk factor and the risk of those patients having CVD is increased [15]. A Swedish study examined whether there was an association between hospital admission for CLE and subsequent risk of hospitalization for coronary heart disease. The risk was greatest 1–5 years after being hospitalized with CLE (standardized incidence ratio (SIR) 2.38; 95% CI 1.67–3.30) and overall, the risk was almost doubled (SIR 1.86; 95% CI 1.55–2.21) [13]. This study was limited by low numbers of participants with CLE and it only included hospitalized CLE patients; hence, it might not represent the risk of developing VTE for all CLE patients, as most patients with CLE are not hospitalized [13]. The present study does have certain strengths. This is the first study that has evaluated traditional risk factors such as body mass index (BMI), diet and smoking. Previous studies have shown that SLE patients smoke more than the general population [16] and we cannot refute residual confounding. Another limitation is that some CLE patients are followed by their private dermatologist or general practitioner, and our results cannot be generalized to these patients. It is most likely that they have a lower risk of VTE than the patients under hospital care, as they most likely are mild cases. Misclassification of patients with CLE as references would tend to bias the results towards having no differences in risk of VTE. Importantly, the impact of misclassification is likely minor, due to the very large sample size. The diagnoses of CLE and SLE in the National Inpatient Sample have not previously been validated. The large number of participants, the nationwide coverage of recorded registries, no loss to follow-up and the long duration of the follow-up period represent major strengths. The nationwide coverage minimized selection bias, compared to data obtained from highly specialized centers. Also, the use of nationwide, prospectively recorded registries eliminated recall bias. Finally, the results were supported by the sensitivity analyses accounting for pre-existing CLE and changes in co-morbidities during follow-up. CLE and SLE are associated with clinically significant VTE risk.

CONCLUSIONS

CLE and SLE were significant cardiovascular risk factors with an increased risk of PE, DVT. These results call for an increased awareness of the association between CLE and morbidity and mortality associated with CLE. Further studies are needed to investigate the pathogenesis and the clinical relevance of the association between CLE and an increased risk of DVT and PE.

CONFIDENTIALITY AND RECORDS

Any identifying information was removed, the Office of Human Research Protections for Mount Carmel Health System and the Institutional Review Board approved of this paper.

DECLARATION OF CONFLICTING INTERESTS

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