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Venous thromboembolism in patients with dermatomyositis and polymyositis

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ABSTRACT

Objective. *To assess the incidence of venous thromboembolic events in dermatomyositis and polymyositis patients, and associated factors.*

Methods. *We retrospectively studied a cohort of 123 myositis patients (87 dermatomyositis, 36 polymyositis) from a single centre and identified cases with deep vein thrombosis and/or pulmonary embolism. Type of myositis, association with cancer, presence of thrombophilia, disease activity, and intravenous immunoglobulin therapy were analysed. Incidence rates were calculated on the basis of time to first venous thrombotic event. Patients with less than 12 months' follow-up were excluded.*

Results. *Six new first thromboembolic events occurred in 6 of 96 patients studied (6.3%), all with dermatomyositis. Median time to development of venous thromboembolism was 4.3 months (IQR, 0.8–8.8) after the dermatomyositis diagnosis. Venous thromboembolism was significantly associated with intravenous immunoglobulin therapy ($p<0.05$) and older age ($p<0.05$), but not with cancer. All events (100%) occurred during active myositis. The incidence density of venous thromboembolism among patients with dermatomyositis according to the first year of follow-up was 9.3 per 1000 person-years (95% CI, 3.4 to 20.3).*

Conclusion. *A trend toward venous thromboembolism was detected in patients with dermatomyositis.*

Introduction

The incidence of venous thromboembolism (VTE) seems high in some systemic autoimmune inflammatory disorders (1-5). An increased incidence of venous thromboembolic events has recently been reported in patients with dermatomyositis/polymyositis (DM/PM) (6). This data is clinically important because of the substantial morbidity and mortality associated with thromboembolic disease. Certain factors such intravenous immunoglobulin use, immobilisation due to disease activity, inflammation *per se*, presence of an associated neoplasm, and autoimmune thrombophilia (lupus anticoagulant or anticardiolipin antibodies), could be implicated in patients with autoimmune myositis and venous thromboembolism.

Our objective was to investigate the presence of VTE in a cohort of patients with inflammatory myopathies and determine the clinical relevance of associated factors.

Patients and methods

Patient population

A retrospective cohort study was performed of all consecutive adult Caucasian patients with PM/DM seen at Vall d'Hebron General Hospital in Barcelona, Spain between 1983 and 2010. Vall d'Hebron is a 700-bed referral and teaching hospital for a catchment population of nearly 450,000 inhabitants. All myositis patients are referred to our hospital for diagnosis and therapy, regardless of the disease severity. The study was approved by the institutional review board.

The diagnosis of DM and PM was based on the criteria of Bohan and Peter (7, 8). Only patients with definite or probable disease were included. The Sontheimer criteria were used to diagnosis amyopathic DM (9). Cancer-associated myositis (CAM) was defined according to the modified Bohan and Peter classification as cancer occurring within 3 years of the myositis diagnosis, as well as the fact that if cancer was cured, myositis was also cured (10). Patients receiving long-term anticoagulation and those with a follow-up of less than 12 months were excluded from the study.

Patients have been regularly followed-up every 3 months. Clinical data were obtained by taking a standardised medical history, conducting a physical examination, and reviewing the patients' medical records. The following data were recorded in a database: demographic information, signs and symptoms, presence of associated disorders, systemic and organ involvement, clinical course, VTE, and number and nature of the treatment courses, specifically intravenous immunoglobulin (IVIg). Disease activity was assessed with the Myositis Disease Activity Assessment Tool (MDAAT) (11, 12).

Diagnosis and documentation of venous thromboembolism

DM/PM patients were considered to have experienced VTE if the event was

clinically apparent and was confirmed by diagnostic tests, such as vascular ultrasound, ventilation-perfusion scanning, CT angiography, or conventional flebography.

Thrombophilia was investigated whenever possible in patients with venous thrombotic events, and included antiphospholipid antibodies (lupus anticoagulant and IgG or IgM anticardiolipin antibodies), factor V Leiden, prothrombin, homocysteine, antithrombin, protein C, protein S, factor VIII, and MTHFR gene mutations. A possible role of the presence of MTHFR gene mutation associated with methotrexate therapy (13) was sought in patients with VTE.

Statistical analysis

The patients included were a convenience sample. Qualitative variables are expressed as the percentage, and quantitative variables as the mean and standard deviation (SD). The median (interquartile range) was used to establish follow-up and disease-free periods. Incidence was calculated as the number of new cases of VTE divided by the total number of persons included in the study. VTE incidence density was calculated as the number of new events per years of follow-up free of thromboembolic disease for each patient, with the confidence interval (CI). Associations between presence of VTE and other factors were calculated using the chi-square or Student *t*-test. VTE-free survival time was calculated from the date of the diagnosis to the date of the first appearance of VTE. Data on patients who did not have VTE were censored at the last follow-up visit. Kaplan-Meir survival plots were used to describe time to first VTE according to cumulative probability. Variables included in analysis did not have missing values. All statistical analyses were performed with SPSS 13.0 software (SPSS, Chicago, IL). Significance was set at a *p*-value of less than 0.05. We followed the STROBE (14) statement to improve the quality of reporting of observational studies.

Results

Between 1986 and 2010, 123 consecutive patients were diagnosed with DM/PM in our department. Twenty-six were excluded from the study: 23 whose follow-up time was less than 12 months and 3 who were receiving long-term anticoagulation therapy (mitral prosthesis, pulmonary hypertension, and carotid artery thrombosis in a DM antiphospholipid syndrome overlap). The final sample included 97 patients (78 women, 19 men; mean [SD] age, 47.9 [18] years). Median follow-up time of the cohort was 6.3 years (P25-P75, 3.2–12.4).

At the end of the observation period, 9 of 97 patients (9.2%; 95% CI: 4.3 to 16.7) with DM/PM had experienced VTE at some time: 6 had first-time VTE after the DM/PM diagnosis, and 2 of these 6 patients developed a new thromboembolic event after withdrawal of anticoagulation. Altogether, patients with DM developed 8 new VTE after the diagnosis of inflammatory myopathy. Data are summarised in Table I.

The 6 new (all DM) VTE cases among the 97 patients (6.2%, 95% CI: 2.3–13.0) occurred over 816.5 person-years of observation, yielding an incidence density of 7.3 per 1000 person-years (95% CI, 2.7–16.0). Median time of VTE development was 4.3 months (IQR: 0.8–8.8) after the diagnosis of myositis. None of the 6 patients had a past history of previous events or were receiving prophylactic heparin at the time of the event.

When the data analysis was restricted to the first year of follow-up of DM patients (68 patients), 6 new cases of VTE occurred over 642.8 person-years of observation, and the incidence density increased to 9.3 per 1000 person-years (95% CI, 3.4–20.3). Figure 1 shows the time to the first VTE among patients with DM during the first year of follow-up.

We found no difference in the sex ratio between patients with a first VTE and the remainder of the series, (p=0.7), but patients with new events were significantly older than the rest of the sample (63.5 *vs*. 46.9 yrs; p<0.05). All six events (100%) occurred during active myositis (mean MYOACT score, 0.8 and mean MITAX score, 0.7; range of values from 0 to 1). DM was more frequently associated with VTE than PM, (6 of 68 *vs*. 0 of 29; p=0.11), although statistical significance was not reached. Cancer-associated myositis was present in 2 of the 6 myositis patients with a first VTE, a rate that was not statistically different from the remainder of the cohort (p=0.41). Five of 28 patients exposed to IVIg infusion developed a first VTE (p<0.05). Four of the 5 VTE patients investigated for the presence of thrombophilia showed an MTHFR gene mutation (C677T); 3 were heterozygous and 1 homozygous. The single patient who received methotrexate did not carry this mutation;

Table I. Patients with polymyositis/dermatomyositis and venous thromboembolism.

Patient	DM/PM onset age, yrs	VTE age, yrs	Relapse	Cancer*	IVIg	Thrombophilia	#DA†
1≈	DM/57	DVT/57	No	No	Yes	Negative	Yes
2	DM/73	PE/DVT/75	No	Ovarian	Yes	ND	Yes
3≈	DM/46	PE/47	No	No	No	Negative	Yes
4§	DM/74	DVT/73	No	No	No	ND	No
5§	PM/43	RSVT/42	No	No	No	ND	No
6§	DM/55	PE/DVT/53	PE/55	Breast	No	Negative	No
7	DM/46	PE/46	PE/48	Breast	Yes	Negative&	Yes
8≈	DM/81	DVT/82	DVT/83	No	Yes	Negative	Yes
9≈	DM/78	PE/78	No	No	Yes	Negative	Yes

Cancer: *paraneoplastic in nature; DA: †disease activity assessed by the Myositis Disease Activity Assessment Tool; DM: dermatomyositis; DVT: deep vein thrombosis; IVIg: intravenous immunoglobulin (venous thrombotic event within 30 days of receiving an IVIg infusion); Negative&: positivity for lupus anticoagulant not confirmed at 6 months of follow-up; PE: pulmonary embolism; PM: polymyositis; RSVT: right subclavian vein thrombosis central line related; Thrombophilia#: include determination of antiphospholipid antibodies, factor V Leiden and prothrombin gene mutation, MTHFR gene mutation, homocysteine, antithrombin, protein C, protein S and factor VIII; VTE: venous thromboembolism. §These patients were diagnosed of VTE before the DM/PM diagnosis. ≈ Time (months) of follow-up after VTE without developing cancer (patient 1: 72; patient 3: 66; patient 8: 59; patient 9: 13).

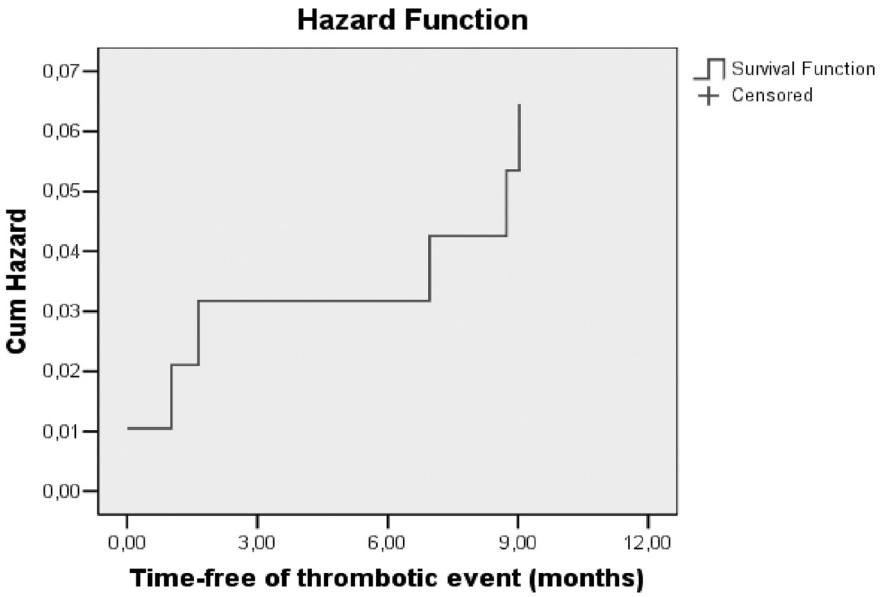

Fig. 1. Time to first venous thromboembolic event in patients with dermatomyositis.

hence, a relationship between VTE and the combined presence of MTHFR mutation and methotrexate treatment was excluded. Other hereditary or acquired factors were not found.

Discussion

In this study of a large cohort of DM/PM patients diagnosed and followed up in a single centre, VTE incidence density is established and a trend toward VTE is demonstrated in patients with DM. Although the differing characteristics of related studies make comparisons difficult, our results show a higher incidence of VTE than occurs in the general Spanish population matched for mean age (annual incidence ranges from 0.3 per 1000 person-years in women to 0.4 in men in the group aged 45 to 49 years) (15).

All new VTEs occurred during the first year following the myositis diagnosis, which supports a possible role of disease activity in the development of VTE. Microvascular endothelial injury is the pathogenic basis of DM; hence, endothelial damage caused by active disease could be the link between VTE and DM, as has been suggested to occur in antineutrophil cytoplasmic antibody-associated vasculitis (AAV) (4). Inflammation is likely a contributing factor, as has been previously reported (2-4). Although inflammation is also present in PM, vascular injury is not a pathological characteristic of PM. Furthermore, the acute onset and greater severity of weakness, occurring more frequently in DM, could lead to a higher level of disability and immobilisation. This could contribute to the development of VTE, as well as the IVIg therapy requirement in these cases. All these factors can help to explain why DM patients are more predisposed to VTE than those with PM, a finding observed in the present cohort and described in a previous report (6).

Among the myositis-associated factors that can be related to VTE in patients with myositis, both cancer and IVIg therapy warrant consideration. Administration of IVIg is a well-recognised, effective therapy in DM/PM (16), but it has been related to arterial and venous thrombotic events, perhaps due to hyperviscosity or procoagulant activity caused by the presence of factor XI in the IVIg infusion (17). Although studies addressing the incidence of VTE in this setting are lacking, our results point to a relationship between IVIg and VTE in patients with DM.

Cancer is a well-known trombophilic state. The incidence of VTE events in cancer patients is higher than in the normal population. Moreover, in nearly 15% of patients with inflammatory myopathy, mainly DM, the disease is paraneoplastic in nature (10). Therefore, when a patient presents with DM and venous thrombosis, malignant disease is highly suspected. However, our findings do not support this association. Up to 66% of our patients with DM and VTE did not develop cancer, nor was a significant association found between VTE and paraneoplastic myositis.

As is well known, VTE is considered a multistep process in which the addition of several prothrombotic factors leads to the development of thromboembolism. Factors such as disease activity and subsequent immobilisation, type of myositis (mainly DM), MTHF polymorphisms, and certain treatments, such as IVIg administration, could have an additive effect, gradually increasing the risk of VTE in these patients.

In conclusion, patients with DM seem to be predisposed to VTE, mainly during the first year after diagnosis. Associated factors such as inflammation, immobilisation due to disease activity, and IVIg therapy could play a role in these patients.

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