Prevalence and outcome of thrombocytopenia in systemic lupus erythematosus: single-centre cohort analysis

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Abstract

Objective

We aimed to characterise the frequency of thrombocytopenia in systemic lupus erythematosus (SLE) and determine its time of onset during the course of the disease, severity and impact on mortality.

Methods

This was a single-centre cohort analysis of 707 patients with SLE followed for up to 40 years. We reviewed the patients' clinical notes identifying the presence of thrombocytopenia, its time of onset and ascertained other clinical and serological features of the disease. Thrombocytopenia was classified as mild (100-149x10^9/L), moderate (31-99x10^9/L) or severe (≤30x10^9/L platelets). It was also classified as asymptomatic, with minor bleeding or with major bleeding.

Results

22.9% of patients (n=162) had thrombocytopenia prior to or during the course of SLE. Twenty three patients (14.2%) had isolated immune thrombocytopenia (ITP) before the diagnosis of SLE. Median follow-up time was 19 years (IQR=13). Most patients (n=67, 41.4%) had mild thrombocytopenia. More than half the patients (n=98, 60.5%) developed asymptomatic thrombocytopenia and only 6 patients (3.7%) had major bleeding events in the context of thrombocytopenia. The development of severe thrombocytopenia any time during the course of SLE was associated with an increased risk of death (HR=3.57, p=0.025). Anti-phospholipid syndrome was over twice as common in patients with thrombocytopenia in the cohort. There is an increased risk of death for male patients (HR=3.41, p=0.036) who develop thrombocytopenia and for those who present with concomitant haemolytic anaemia (HR=3.07, p=0.027).

Conclusion

The presence of severe thrombocytopenia (platelets ≤30x10^9) in patients with SLE is associated with an increased risk of death, regardless of bleeding events. Male patients with SLE and thrombocytopenia have an increased mortality risk, as have those who develop concomitant thrombocytopenia and haemolytic anaemia.

Key words

thrombocytopenia, lupus mortality, haemolytic anaemia

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Introduction

Thrombocytopenia is a common haematological feature of SLE, affecting 10–40% of patients with this disorder (1-3). It can predate other features of systemic lupus erythematosus (SLE), presenting as isolated immune thrombocytopenia (ITP) (4). Severe thrombocytopenia, however, is relatively rare (5). The presence of thrombocytopenia has been associated with other severe manifestations of SLE, such as neuropsychiatric and/or kidney involvement and haemolytic anaemia (6-8). Thrombocytopenia also appears to have an impact on the prognosis of SLE, including mortality (3, 9-11), although contradictory results have been reported (6, 12).

The aim of this study was to characterise the frequency of thrombocytopenia in SLE in a larger cohort followed for very long periods of time (up to 40 years), to determine its time of onset during the course of the disease, as well as its severity. We also aimed to characterise the impact of thrombocytopenia on morbidity – mainly in bleeding – and mortality.

Methods

All available clinical and lupus clinic notes from a cohort of 707 patients with SLE, followed since January 1979 at University College London Hospital, were reviewed. Patients with less than 5 years follow-up were excluded. Patients whose thrombocytopenia was most likely to be due to concomitant medication were excluded. We identified the patients that developed thrombocytopenia (defined as platelet count $<150x10^9$/L) any time during the course of the disease, including those that presented with isolated ITP before the diagnosis of SLE. Thrombocytopenia was classified as mild ($100\text{-}149x10^9$/L platelets), moderate ($31\text{-}99x10^9$/L platelets) or severe ($\leq 30x10^9$/L platelets). It was also classified as asymptomatic (no relation to any bleeding event), with minor bleeding (thrombocytopenia in relation with non-life-threatening bleeding events such as epistaxis or gum bleeding) or with major bleeding (thrombocytopenia in relation to life-threatening bleeding events such as major gastro-intestinal haemorrhage or haemorrhagic stroke). Other clinical features of the disease were noted: age at diagnosis, time elapsed since the diagnosis of SLE to the appearance of thrombocytopenia (or between the diagnosis of ITP and the diagnosis of SLE), the presence of mucocutaneous manifestations of SLE, such as rash, photosensitivity, alopecia or oral ulcers; joint, kidney or central nervous system (CNS) involvement, the presence of serositis or secondary Sjögren's syndrome, as well as the presence of other haematological features, such as haemolytic anaemia, leucopenia or lymphopenia. Patients with thrombocytopenia who also had concomitant anti-phospholipid antibody syndrome (APS) were noted. Serological features of the disease were also noted, namely positivity for dsDNA antibodies, anti-Sm, anti-Ro, anti-La and anti-RNP antibodies, the presence of low complement C3, Rheumatoid factor, Lupus anticoagulant and anti-cardiolipin antibodies.

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (v. 22.0). Univariable Cox proportional hazard models were conducted to screen for predictors of mortality. Multivariable Cox proportional hazard models were then applied to the predictors that showed $p<0.10$. A case-control study was also performed comparing the patients that developed thrombocytopenia with the remainder of the cohort. Chi-square tests were used for categorical variables and t-tests were used for the continuous variables. Significance was considered for 0.05. Marginally significant results ($p<0.10$) were considered for retaining variables in multivariate final models contributing for a more comprehensive data adjustment.

Results

A total of 162 patients (22.9%) were identified as having developed thrombocytopenia prior to or sometime during the course of SLE, from a cohort of 707. The mean age at diagnosis of SLE was 28.47±13.31 years, ranging from 7 to 77 years old; 148 patients (91.4%) were female and 14 (8.6%) were male. Caucasian was the most prevalent eth-

Table I. Sample characteristics.

Variable	n (%)
Sex	
Female	148 (91.4%)
Male	14 (8.6%)
Ethnic origin	
Caucasian	94 (58.0%)
Black	18 (11.1%)
Chinese	6 (3.7%)
South Asian	19 (11.7%)
Other Asian background	10 (6.2%)
Other/Mixed ethnic origin	15 (9.2%)
Thrombocytopenia	
Previous ITP	23 (14.2%)
After SLE diagnosis	139 (85.5%)
Degree of thrombocytopenia	
Mild	67 (41.4%)
Moderate	41 (25.3%)
Severe	42 (25.9%)
Unknown	12 (7.4%)
Bleeding	
Asymptomatic	98 (60.5%)
Minor bleeding	35 (21.6%)
Major bleeding	6 (3.7%)
Unknown	23 (14.2%)

nic origin (n=94; 58.0%). Twenty-three patients (14.2%) had isolated ITP before the diagnosis of SLE. Sample characteristics are compiled in Table I.

The median time from diagnosis of SLE to development of thrombocytopenia was 8 years (IQR=14). Most patients (n=67, 41.4%) had mild thrombocytopenia, 41 (25.3%) moderate and 42 (25.9%) severe thrombocytopenia. More than half the patients (n=98, 60.5%) developed asymptomatic thrombocytopenia, while 35 (21.6%) presented with minor bleeding but only 6 patients (3.7%) had major bleeding events in the context of thrombocytopenia.

Twenty-nine patients (17.9%) with thrombocytopenia also had APS. Twenty-eight were female. Eleven, 7 and 9 of these patients had mild, moderate or severe thrombocytopenia respectively. Six patients with APS had thrombocytopenia as the first manifestation of lupus (diagnosed initially as isolated idiopathic thrombocytopenia). Five patients with thrombocytopenia and APS had minor bleeding, two had major bleeds and the remainder were asymptomatic.

Univariable survival analysis with Cox regression models was performed to screen for significant predictors of mortality. These were found to be older age at diagnosis (HR=1.06; $p<0.001$) and severe thrombocytopenia (HR=3.59; $p=0.019$). Thrombocytopenia diagnosed after lupus (as opposed to previous ITP) was not associated with risk of death (HR=0,45; $p=0.088$). When considering the survival rates after the development of thrombocytopenia, higher death risk was found for older patients at time of diagnosis (HR=1.02; $p=0.047$), males (HR=3.77; $p=0.020$), patients with concomitant haemolytic anaemia (HR=2.73; $p=0.037$) and concomitant serositis (HR=2.33; $p=0.040$). No significant association was found with increased DNA binding (HR=2.58; $p=0.085$). There was no association found between bleeding events (of any severity) and mortality. When a multivariable survival analysis was performed, higher age at diagnosis (HR=1.07; $p<0.001$) and the development of severe thrombocytopenia (HR=3.57; $p=0.025$) were confirmed as associated with an increased risk of death. Regarding survival time after the development of thrombocytopenia, results confirmed increased mortality risk for older patients at diagnosis of SLE (HR=1.03; $p=0.015$), males (HR=3.41; $p=0.036$) and those with concomitant haemolytic anaemia (HR=3.07; $p=0.027$). These results are summarised in Table II.

Table II. Multivariable survival analysis.

	Lupus → death/last contact		Thrombocytopenia → death/last contact	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at diagnosis	1.07 (1.03;1.10)	**<0.001**	1.03 (1.01; 1.06)	**0.015**
Sex				
Female	-	-	1 1	
Male	-	-	3.41 (1.08; 10.73)	**0.036**
Thrombocytopenia				
Previous ITP	1	1	-	-
After SLE diagnosis	1.23 (0.34;4.51)	0.751	-	-
Degree of thrombocytopenia				
Mild	1	1		
Moderate	0.98 (0.27;3.54)	0.970		
Severe	3.57 (1.18;10.81)	**0.025**		
Unknown	1.88 (0.49;7.15)	0.355		
Haemolytic anaemia				
No	-	-	1	1
Yes	-	-	3.07 (1.614; 4.54)	**0.027**
Serositis				
No	-	-	1	1
Yes	-	-	2.05 (0.91; 4.63)	0.084
DNA				
No	-	-	2.45 (0.76; 7.91)	0.136
Yes	-	-		

Table III. Sample characteristics comparison (thrombocytopenia *vs*. control group).

Variable	Thrombocytopenia n (%) (n=162)	Control n (%) (n=545)	*p*-value
Sex			0.893
Female	148 (91.4%)	500 (91.7%)	
Male	14 (8.6%)	45 (8.3%)	
Ethnic origin			**<0.001**
Caucasian	94 (58.0%)	314 (57.6%)	
Black	18 (1.0%)	42 (7.7%)	
Chinese	6 (3.7%)	29 (5.3%)	
South Asian	19 (11.7%)	15 (2.8%)	
Other Asian	10 (6.2%)	48 (8.8%)	
Others	15 (9.2%)	97 (17.8%)	

A case control analysis was conducted, using the patients in the lupus cohort that did not develop thrombocytopenia as a control group (n=545). Mean age in the control group was 29.15±13.33 years, ranging from 7 to 75 years old; 500 patients (91.4%) were female and 45 (8.3%) were male. Caucasian was the most prevalent ethnic group (n=314; 57.6%). Sample characteristics comparison is presented in Table III.

Sex prevalence distribution was very close in both groups, with more than 90% of females (p=0.893). Significant differences were found for ethnic group (p<0.001) with higher prevalence of South Asian in the disease group (11.7% *vs*. 2.8%) and higher prevalence of Caucasians in the control group (57.6% *vs*. 47.7%). No significant differences were found regarding age at diagnosis (p=0.483).

Regarding the comparison of predictors between groups, haemolytic anaemia (p<0.001), leucopoenia (p=0.002), and kidney involvement (p<0.001) were more prevalent in the disease group. Positive Rheumatoid Factor (p=0.019), low complement C3 (=0.022) and non-erosive joint involvement (p<0.001) were more prevalent in the control group. These characteristics are summarised in Table IV.

A logistic regression was applied, with thrombocytopenia as outcome (results summarised in Table V). Patients of South Asian ethnicity have an increased risk for the development of thrombocytopenia (OR=5.54) when compared with Caucasian patients (p=0.004). Haemolytic anaemia (OR=18.09; p<0.001), leucopenia (OR=2.63, p=0.024) and positive lupus anticoagulant (OR=4.11; p<0.001) are also associated with increased risk of developing thrombocytopenia.

Table IV. Predictors comparison (thrombocytopenia *vs*. control group).

	Thrombocytopenia		Control		*p*-value
Predictor	n	%	n	%	
Haemolytic anaemia	25	15.4%	15	2.8%	**<0.001**
Leucopenia	61	37.7%	137	25.2%	**0.002**
Lymphopenia	123	75.9%	403	74.1%	0.636
Rash	106	65.4%	357	65.6%	0.964
Photosens	60	37.0%	217	40.0%	0.503
Alopecia	43	26.5%	127	23.3%	0.397
Oral ulcers	40	24.7%	145	26.8%	0.601
Serositis	61	37.7%	203	37.2%	0.925
Kidney	72	44.4%	158	29.0%	**<0.001**
CNS	42	25.9%	112	20.6%	0.152
Sjögren	12	7.4%	54	10.0%	0.318
RF	26	16.0%	131	24.9%	**0.019**
SM	26	16.1%	96	17.7%	0.652
RNP	51	31.5%	160	29.4%	0.604
RO	61	37.7%	217	39.9%	0.609
LA	17	10.5%	87	16.0%	0.083
DNA	114	70.4%	335	62.4%	0.063
C3	91	56.5%	251	46.2%	**0.022**
Joint					**<0.001**
No joint involvement	20	12.9%	55	10.1%	
Non-erosive	135	87.1%	490	89.9%	

Table V. Logistic regression with thrombocytopenia as outcome.

Predictor	OR	*p*-value	95% CI
Ethnic origin			
Caucasian	1	1	
Other Asian	3.06	0.106	(0.79; 11.91)
Black	2.04	0.235	(0.63; 6.60)
Chinese	4.49	0.086	(0.81; 24.92)
South Asian	5.54	**0.004**	(1.75; 17.54)
Others	0.26	0.071	(0.06; 1.12)
Haemolytic anaemia			
No	1	1	
Yes	18.09	**<0.001**	(6.74; 48.58)
Leucopenia			
No	1	1	
Yes	2.63	**0.024**	(1.13; 6.11)
Alopecia			
No	1	1	
Yes	5.62	**0.002**	(1.86; 16.98)
LA			
No	1	1	
Yes	4.11	**<0.001**	(1.92; 8.81)

Discussion

Twenty-three percent of patients in our cohort of 707 patients developed thrombocytopenia sometime during the course of SLE. This is in line with previously published prevalence data (1-3). Of these 162 patients, 23 (14.2%) had thrombocytopenia as a first manifestation of SLE (initially diagnosed as ITP). Also in accordance with previously published results (13, 14), Most patients (n=67, 41.4%) in our cohort developed only mild thrombocytopenia ($100x10^9$-$149x10^9$/L platelets). Twenty-five percent of patients (n=41) had moderate thrombocytopenia ($31x10^9$-$99x10^9$/L platelets) and 25.9% (n=42) had severe thrombocytopenia (≤$30x10^9$ platelets/L).

More than half the patients in this cohort (n=98, 60.5%) developed asymptomatic thrombocytopenia. Only 6 patients (3.7%) had major bleeding events in the context of thrombocytopenia and only one patient died as a direct complication of thrombocytopenia. These results are also in line with previous reports (14-16). Although thrombocytopenia is a common feature of SLE, symptomatic thrombocytopenia is rare. The presence of severe thrombocytopenia (platelets ≤$30x10^9$) in patients with SLE is associated with an increased risk of death, in this cohort. This is independent of bleeding events. Several authors (5-7, 9-11) tried to establish

prognostic value for the severity of thrombocytopenia in SLE with varied results. Jung *et al*. (16) found a similar association between severe thrombocytopenia and mortality in a cohort of 230 patients. Our greater numbers and longer follow-up time permit us to confirm these results.

Male patients with SLE who develop thrombocytopenia (any degree) appear to have an increased mortality risk in our cohort. The simultaneous appearance of other severe haematological abnormalities, namely haemolytic anaemia carries an increased mortality risk in patients with lupus thrombocytopenia.

Predictors for the development of thrombocytopenia, in our cohort, include, as in other cohorts (5, 13, 14), the presence of haemolytic anaemia, leucopenia and positive lupus anticoagulant. We found no association with neuropsychiatric involvement as reported by Sultan *et al*. (13). Besides these commonly described predictors, we also found an increased risk for the development of thrombocytopenia in patients of South Asian ethnicity (5.5 fold increase in risk in this population). 17.9% of our thrombocytopaenic patients had APS and this is over twice as many as we have previously reported in the cohort as a whole (7%) (17).

The real strength of this study is that the careful observations on a large number of patients (platelets being tested at every outpatient visit) over periods of up to 40 years allow us, we believe, to suggest that the trial adds significantly to the previous literature with some new observations. Its weaknesses include that the changing nature of our formal clinical activity assessments in clinic from the pre-BILAG (British Isles Lupus Activity Assessment) to the classic BILAG to the BILAG-2004 methods (reviewed elsewhere (18) make it very difficult to make accurate statements about links between thromboctyopaenia and lupus activity overall. However, we have not seen (apart from patients who present with a seemingly idiopathic thrombocytopenia who later develop SLE) moderate/major thrombocytopenia as an isolated clinical feature of lupus activity. Thus an important practice point is that in an established SLE patient, the isolated development of thrombocytopenia is likely to be due to something other than lupus activity. There were also too many gaps in our recording of damage in the cohort as a whole to present compelling data about links between damage and thrombocytopenia in the cohort as a whole. The damage index proposed by the Systemic Lupus Collaborating Clinics (18) was not proposed until 17 years after we began our SLE clinic.

In summary, although a common manifestation of SLE, thrombocytopenia may be a marker of severe disease as it is associated with other organ involvement, namely with lupus nephritis and other haematological complications, such as haemolytic anaemia. These patients require close monitoring, especially those who develop severe thrombocytopenia, as this finding is, by itself linked with higher mortality risk.

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