Venous thromboembolism during systemic inflammatory and autoimmune diseases associated with myelodysplastic syndromes, chronic myelomonocytic leukaemia and myelodysplastic/myeloproliferative neoplasms: a French multicentre retrospective case-control study

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Abstract

Objective

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML) are associated with systemic inflammatory and autoimmune diseases (SIADs) in 10–30% of cases. The aims of this study were (i) to evaluate the prevalence of venous thromboembolism VTE in patients presenting with both MDS/CMML and SIADs, (ii) to describe risk factors associated with thrombosis, and (iii) to analyse the impact of VTE on overall survival and transformation to acute myeloid leukaemia in comparison to patients with MDS/CMML-associated SIADs without VTE.

Methods

This retrospective multicentre case-control study was conducted among patients with MDS/CMML and dysimmune disorders and featured in the French retrospective database of the French Network of Dysimmune Disorders Associated with Hemopathies (MINHEMON), diagnosed with MDS/CMML and dysimmune disorders.

Results

During a median follow-up of 16 months (5–48) VTE occurred in 35 patients (21.6 %) whereas 127 patients did not. Among those with VTE, 8 patients (22.9%) experienced two or more VTE. Common prothrombotic risk factors were not significantly different in patients with or without VTE. CMML was more frequent in patients without VTE (37 % vs. 14.3%, p=0.01), whereas myelodysplasic/myeloproliferative neoplasm (MDS/MPN) was higher in VTE patients (20 % vs. 5.5 %, p=0.01). In a multivariate analysis, only MDS/CMML progression at the time of VTE (odds ratio 28.82, 95 % CI (5.52–530.70) was significantly associated with VTE. When treated with an anticoagulation therapy, bleeding occurred in 19.4% of cases (6/31). Overall survival was not significantly different between patients with and without VTE (p=0.68). Leukaemia-free survival between groups was not significantly different (p=0.83).

Conclusion

VTE is a common complication in MDS/CMML-associated SIADSs with an increased risk of bleeding when treated by anticoagulants. In the MDS/CMML subgroup, SIADS flares and MDS/CMML progression seem to be prothrombotic risk factors.

Key words

venous thromboembolism, myelodysplastic syndrome, chronic myelomonocytic leukaemia, autoimmune diseases

Affiliations on page 1342.

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Introduction

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML) are haematopoietic stem cell neoplasms characterised by cytopenia and a risk of progression to acute myeloid leukaemia (AML). Systemic inflammatory and autoimmune diseases (SIADs) occur in 10–30% of MDS and CMML (1-3, 4). Abnormal secretion of inflammatory cytokines, deregulated cellular immunity, increased lymphocyte apoptosis could be some of the pathophysiological mechanisms underlying the dysimmune features in MDS/CMML (5).

MDS/CMML are associated with a risk of venous thromboembolism (VTE), myocardial infarction and stroke, which could be explained by patients' age and comorbidities (6). The risk of venous thrombosis is increased in various idiopathic autoimmune diseases, such as autoimmune haemolytic anaemia (AIHA), immune thrombocytopenic purpura (ITP), rheumatoid arthritis (RA), vasculitis and systemic lupus erythematosus (SLE) (7). A 6.38% (95% CI 6·19–6·57) overall risk of pulmonary embolism was found during the first year after diagnosis of the autoimmune disorders in a group of 33 autoimmune diseases (8). Thus, the probability of a thrombotic event could potentially be increased in patients presenting both MDS/CMML and SIADs. However, the prevalence and risk factors of VTE in this particular subgroup was not evaluated.

The aims of this study were i) to evaluate the prevalence of VTE in patients presenting both MDS/CMML and dysimmune disorders, ii) to describe risk factors associated with VTE, and finally iii) to analyse the impact of VTE on overall survival and progression to acute myeloid leukaemia in comparison to patients with MDS/CMML-associated SIADs without VTE.

Patients and methods

Patients' selection

This retrospective multicentre case-control study was conducted between May 2015 and December 2019. Patients from the retrospective database of the French Network of Dysimmune Disorders Associated with Hemopathies (MINHEMON) and, diagnosed with both MDS/CMML and related dysimmune disorders, were included. Inclusion criterias were i) MDS or CMML diagnosis, based on blood and bone marrow examinations, according to the 2016 World Health Organisation classification (9); ii) SIADSs according to the usual international classification criteria for each disease (*i.e.* 2019 EULAR/ACR criteria for SLE, 2012 Chapel Hill vasculitides criteria for systemic vasculitis, Michet criteria for relapsing polychondritis, ACR/EULAR criteria for Sjögrens' syndrome, Von Den Driesch criteria for Sweet's syndrome, Yamaguchi criteria for Still's disease, 2012 ACR/EULAR criteria for giant cell arteritis and polymyalgia rheumatica, 2006 Sydney criteria for antiphospholipid syndrome and 1990 ACR criteria for polyarteritis nodosa). Seronegative polyarthritis was defined as polyarthritis without any immunological marker and which does not fulfill any classification criteria for SIADSs. Flare of the SIADs is defined as the recurrence of symptoms according to each type of autoimmune disease, concomitant with usual acute phase reactants and/or immunological analysis specific to each disease, not related to another conditions (for example, infectious, haematologic malignancies or metabolic abnormalities). (3) Pulmonary embolism (PE) confirmed by intraluminal filling defect on computer tomography (CT) pulmonary angiography, pulmonary angiogram or ventilation/perfusion lung scan (VQ scan). The diagnosis of deep venous thrombosis (DVT) required the evidence of one or more filling defects on compression ultrasonography, with the involvement of at least the popliteal vein or a more proximal vein. In this paper, venous thromboembolism (VTE) was considered as the occurrence of pulmonary embolism and/or DVT.

A control group of patients diagnosed with MDS/CMML-associated SIADs without VTE from the French observational database of MINHEMON was used for the case-control study.

Data collection

For each patient the following data were recorded: elapsed time between VTE

Table I. Characteristics and outcome of patients with MDS/CMML associated SIADs with and without VTE.

	MDS/CMML-VTE n=35	MDS/CMML without VTE n=127	Odds ratio, IC95%	*p*-value
Age at diagnosis, mean (SD)	71.3 (11.1)	70.8 (11.7)	– 0.62	
Female sex, n (%)	11 (31.4)	34 (26.8)	1.3 (0.6–2.8)	0.67
Median follow up, months (IQR)	16 (5–48)	19 (4–45)	– 0.96	
MDS/CMML features				
MDS, n (%)	23 (65.7)	73 (57.5)	1. (0.7–3.2)	0.44
Refractory cytopenia with single lineage dysplasia, n (%)	3 (13.0)	17 (23.3)	0.49 (0.14–1.72)	0.39
Refractory cytopenia with multilineage dysplasia, n (%)	12 (52.2)	34 (46.6)	1.25 (0.49–3.28)	0.81
Refractory anaemia with excess blasts (AREB), n (%)	5 (21.7)	19 (26.0)	0.79 (0.29–2.45)	0.79
MDS with isolated del (5q), n (%)	1 (4.3)	1 (1.4)	3.27 (0.17–62.87)	0.42
Unclassified MDS, n (%)	2 (8.8)	2 (2.7)	3.38 (0.50–22.23)	0.24
CMML, n (%)	5 (14.3)	47 (37)	**0.28 (0.11–0.74)**	**0.01**
MDS/MPN n (%)	7 (20)	7 (5.5)	**4.28 (1.49–12.14)**	**0.01**
IPSS-low risk, n (%)	8/15 (53.3)	21/43 (48.8)	1.20 (0.40–3.79)	1
IPSS-intermediate risk, n (%)	6/15 (40)	20/43 (46.5)	0.77 (0.21–2.37)	0.77
IPSS-high risk, n (%)	1/15 (6.7)	2/43 (4.7)	1.46 (0.09–13.24)	1
R-IPSS-very low risk, n (%)	7/15 (46.7)	13/41 (31.7)	1.89 (0.56–6.03)	0.35
R-IPSS-low risk, n (%)	8/15 (53.3)	19/41 (46.3)	1.32 (0.44–4.26)	0.77
R-IPSS-intermediate risk, n (%)	0	4/41 (9.8)	0 (0–2.94)	0.56
R-IPSS-high risk, n (%)	0	2/41 (4.9)	0 (0–5.95)	1
R-IPSS-very high risk, n (%)	0	3/41 (7.3)	0 (0–3.16)	0.56
First line MDS treatment (except EPO and blood transfusion), n (%)	7/17 (41.2)	28/83 (33.7)	1.38 (0.52–3.82)	0.58
Features of SIADs				
Vasculitis, n (%)	24/40 (60)	59/133 (44.4)	1.88 (0.91–3.85)	0.10
Hypocomplementaemic urticarial vasculitis, n (%)	0	2 (3.4)	0 (0–5.33)	1
IgA vasculitis, n (%)	1 (4.2)	1 (1.7)	2.52 (0.13–48.6)	0.5
Cryoglobulinaemic vasculitis, n (%)	1 (4.2)	2 (3.4)	1.24 (0.08–11.03)	1
ANCA-associated small-vessel vasculitis, n (%)	3 (12.5)	6 (10.2)	1.26 (0.32–4.70)	0.71
Polyarteritis nodosa, n (%)	1 (4.2)	5 (8.5)	0.47 (0.04–3.89)	0.67
Giant cell arteritis, n (%)	2 (8.3)	10 (16.9)	0.45 (0.09–1.93)	0.49
Takayashu arteritis, n (%)	0	1 (1.7)	0 (0–22.13)	1
Behcet's disease, n (%)	2 (8.3)	6 (10.2)	0.8 (0.16–3.61)	1
Unclassified vasculitis, n (%)	4 (16.6)	11 (18.6)	0.87 (0.28–3.08)	1
Relapsing polychondritis, n (%)	10 (41.7)	15 (25.4)	2.1 (0.81–5.56)	0.19
Other AID, n (%)	8/40 (20)	26/133 (19.5)	1.03 (0.44–2.55)	1
Sweet's syndrome, n (%)	3 (37.5)	5 (19.2)	2.52 (0.51–11.54)	0.36
Still's disease, n (%)	2 (25)	0	NC	**0.05**
Systemic lupus erythematosus, n (%)	0	2 (7.7)	0 (0–7.16)	1
Anti phospholipid syndrome, n (%)	1 (12.5)	1 (3.8)	3.57 (0.17–70.01)	0.42
Seronegative polyarthritis , n (%)	1 (12.5)	8 (30.8)	0.32 (0.03–2.80)	0.40
Polymyalgia rheumatica, n (%)	0	4 (15.4)	0 (0–3.82)	0.55
Pyoderma gangrenosum, n (%)	0	1 (3.8)	0 (0–29.25)	1
Myositis, n (%)	1 (12.5)	5 (19.3)	0.6 (0.05–4.36)	1
Auto immune cytopenia	8/40 (20)	48/133 (36.1)	0.44 (0.20–1.01)	0.08
ITP, n (%)	8 (100)	46 (95.8)	NC	1
AIHA, n (%)	0	2 (4.2)	0 (0–13.38)	1
Including various associated SIAD	5	5	–	–
Therapeutic management				
Pulmonary embolism, n (%)	5 (14.3)	–	–	–
Deep venous thrombosis (DVT), n (%)	21 (60)	–	–	–
Deep venous thrombosis and pulmonary embolism, n (%)	9 (25.7)	–	–	–
Recurrent VTE (Over 2 VTE), n (%)	8 (22.9)	–	–	–
Number of relapses, mean (range)	2.13 (2–3)	–	–	–
Time between MDS/CMML diagnosis and VTE, mean (range) months	46.22 (0–516)	–	–	–
Time between diagnosis of SIAD and VTE, mean (range) months	40 (0–516)	–	–	–
Anticoagulation, n (%)	29/30 (96.7)	–	–	–
LMWH and UH, n (%)	14 (48.30)	–	–	–
Direct oral anticoagulants, n (%)	7 (24.10)	–	–	–
Vitamin K antagonists, n (%)	8 (27.60)	–	–	–
Bleeding under therapy, n (%)	6/29 (20.70)	–	–	–
Life-threatening bleeding, n (%)	5/6 (83.33)	–	–	–
Non severe bleeding, n (%)	1/6 (16.67)	–	–	–
Outcome				
AML progression, n (%)	3 (8.57)	12 (9.4)	0.90 (0.26–3.14)	1
Deaths, n (%)	7 (20)	22 (17.3)	1.19 (0.47–3.03)	0.80
MDS progression, n (%)	15/16 (93.75)	38/111 (34.23)	**28.82 (4.3–308.1)**	**<0.0001**
Flare of the SAIDs, n (%)	24/28 (68.57)	42/110 (38.2)	**9.71 (3.14–27.04)**	**<0.0001**

MDS: myelodysplastic syndrome; MDS-SLD: myelodysplastic syndrome with single lineage dysplasia; MDS-EB: myelodysplastic syndrome with excess blasts; MDS-MLD: myelodysplastic syndrome with multilineage dysplasia; CMML: chronic myelomonocytic leukaemia; MDS/MPN: myelodysplastic/myeloproliferative neoplasm; R-IPSS: revised international index prognostic scoring system; IPSS: international index prognostic scoring system; ESA erythropoiesis stimulating agents; ANCA: anti neutrophils cytoplasmic antibodies; ITP immune thrombocytopenic purpura; AIHA: autoimmune haemolytic anaemia; AML: acute myeloid leukaemia; SIAD: systemic inflammatory and autoimmune diseases; UH: unfractioned heparin.

and MDS/CMML associated to SIADS diagnosis, age, sex, MDS/CMML features (OMS type, International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (R-IPSS), treatments received), SIADS type, location, number and type of VTE (pulmonary embolism, deep venous thrombosis), anticoagulation (VKA, LMWH, DOAC, others) and bleeding onset under therapy. Additional information about the risk factors contributing to thrombosis at the time of thrombosis event were also recorded such as the presence of an SIADS flare, immobilisation, concurrent neoplasm, recent surgery, medications such as Imids (thalidomide, lenalidomide) and Erythropoietin-stimulating agents, obesity, and active infections. Laboratory data from thrombophilia screening were recorded: protein C, protein S, antithrombin levels, factor V and II mutation status, antiphospholipid antibodies and JAK2/calreticulin mutations. MDS/CMML progression were reported at time of VTE and at the last date of follow-up in patients with and without VTE, respectively.

This study was conducted in compliance with the Helsinki Declaration, on a database of patients treated according to standard care under the MR04 methodology; therefore, no ethics approval was necessary according to French law. The database was declared to the Commission Nationale de l'Informatique et des Libertés (CNIL), with registration number 2218061 v. 0.

Statistical analysis

Quantitative variables are expressed as means ± SD or medians (quartile 25 and 75). Continuous variables were compared by a Student t-test. Qualitative variables are presented as numbers (%) and were compared by chi-square and Fisher exact test. The overall survivals (OS) were calculated from the date of MDS/CMML diagnosis to death or until last date of follow up. Leukaemia-free survival (LFS) was calculated from the date of MDS/CMML diagnosis to the date of acute myeloid leukaemia transformation. OS and LFS were estimated by a Kaplan-Meier analysis and compared using a Geihan-Breslow-Wilcoxon test. To analyse the factors associated with VTE, a multivariate analysis was performed including variables with a p-value <0.05 in univariate analyses. A p-value <0. 05 was considered as statistically significant. All the statistical analyses were performed with Graphpad software, LLC v. 8.4.3 2020 (GraphPad Software™, La Jolla, CA, USA).

Results

MDS/CMML and SIADSs characteristics of patients with VTE

One hundred and sixty-two patients with MDS/CMML associated to SIADs were included. During a median follow-up of 16 months (IQR, 5–48), 35 patients (21.6%) presented one or more venous thromboembolisms (VTE), mean age 71.3 (11.1) (Table I). In all cases, CMML patients were CMML-1. In most cases, patients had low or intermediate IPSS risk or low-very low R-IPSS risk MDS. Among those 40 diagnosed, vasculitis and auto immune cytopenia were the most frequent SIADS, respectively 24 and 8 cases. Focusing in these two groups, relapsing chondritis (10/40) and ITP (8/40) had highest proportion.

Thrombosis features and risk factors of MDS/CMML-associated SIADs patients with VTE

VTE occurred in 35 patients (21.6%) whereas 127 patients did not. Pulmonary embolism, deep venous thrombosis and both pulmonary embolism and DVT occurred in 5 (14.3%), 21 (60%) and 9 (25.7%) cases respectively. In isolated DVT, VTE affected lower limb in 17 cases (above or below popliteal in 12 and 5 cases respectively), upper limb in 3 cases and a splenic vein in one case. Eight patients (22.9%) experienced recurrent VTE, isolated DVT in 75% (6/8) with mean 2.13 (2–3) relapses. Relapse occur within the following three years. At least, one prothrombotic factor was identified in 17 (17/33, 51.5%) cases of VTE. In patients without VTE, one was under -imid medication and 9 under erythropoietin-stimulating agent whereas in patients with VTE, 2 were under imid and none under erythropoietin-stimulating agent. However, risk factor of VTE were not significantly different between patients with and without VTE. VTE remained unexplained in 16 patients (16/33, 48.50%) (Table III).

Case-control study of MDS/CMML-associated SIADs patients with and without VTE

In the univariate analysis, MDS/MPN (OR of 4.28, 95 % CI [1.49–12.14]), MDS progression (OR of 28.82, 95% CI [4.34–308.1]), and flare of the SIADs (OR of 9.71, 95% CI [3.14–27.04]) were risk factors of VTE whereas CMML (OR of 0.28, 95% CI [0.11–0.74]) were protective factors. Age, sex, other MDS subtypes, IPSS and R-IPSS scores, and previ-

Table II. Univariate and multivariate analysis of risk factors associated with VTE.

	MDS/CMML with VTE n=35	MDS/CMML without VTE n=127	Univariate analysis		Multivariate analysis	
			Odds ratio (CI95%)	p-value	Odds ratio (CI95%)	p-value
MDS progression at the time of VTE	15/16 (93.75)	38/111 (34.23)	**28.82 (4.34–308.1)**	**<0.0001**	**28.82 (5.52–530.70)**	**0.0014**
Flare of the SIADs	24/28 (68.57)	42/110 (38.2)	**9.71 (3.14–27.04)**	**<0.0001**	–	–
CMML, n (%)	5 (14.3)	47 (37)	**0.28 (0.11–0.74)**	**0.01**	–	–
MDS/MPN n (%)	7 (20)	7 (5.5)	**4.28 (1.49–12.14)**	**0.01**	–	–

VTE: venous thromboembolism; CMML: chronic myelomonocytic leukaemia; MDS/MPN: myelodysplastic/myeloproliferative neoplasm; SIAD: systemic inflammatory and autoimmune disesases.

Table III. VTE risk factors in MDS/MPN patients with and without VTE.

	MDS/CMML with VTE n=35	MDS/CMML without VTE n=127	Odd ratio, IC95%	*p*-value
Presence of JAK2 mutation, n (%)	2/8 (25)	4/12 (33.3)	0.67 (0.10–4.72)	1
Anticardiolipin, n (%)	1/14 (7.14)	3/27 (11.1)	0.44 (0.03–3.33)	0.64
Lupus anticoagulant, n (%)	0/20 3/31 (9.7)	0 (0–1.75)	0.27	
B2GPI antibodies, n (%)	0/13 2/19 (10.5)	0 (0–3.13)	0.50	
Factor II and V Leiden, n (%)	2/5 (40)	2/5 (40)	0 .10 (0.10–9.98)	1
Protein C and S deficiency	0/5	0	NC	1
Antithrombine III deficiency	0/5	0	NC	1
dsDNA antibodies	0/21	0/21	NC	1
Anti-Sm antibodies	0/21	0/21	NC	1
Prolonged bed rest, n (%)	2/34 (5.88)	14/78 (17.9)	2.38 (0.36–15.53)	0.58
Current neoplasia, n (%)	3/10 (30)	7/83 (8.4)	4.65 (1.09–20.07)	0.07
Recent surgery, n (%)	2/34 (5.88)	4/81 (4.9)	1.20 (0.22–5.37)	1
Antiphospholipid syndrome, n (%)	1 (2.86)	1 (0.8)	3.71 (0.19–70.84)	0.39
Active infection, n (%)	4 (11.42)	23/105 (21.9)	0.46 (1.61–1.33)	0.22
Inducers medication, n (%)	2 (5.71)	10/98 (9.8)	0.53 (0.11–2.15)	0.73
Obesity, n (%)	1/16 (6.25)	7/36 (19.4)	0.28 (0.02–1.93)	0.41
Risk factors of thrombosis per patients, mean (range)	0.67 (0–2), 33/35	-	-	-

JAK2 mutation: Janus kinase 2 mutation; dsDNA antibodies: double strand DNA antibodies.

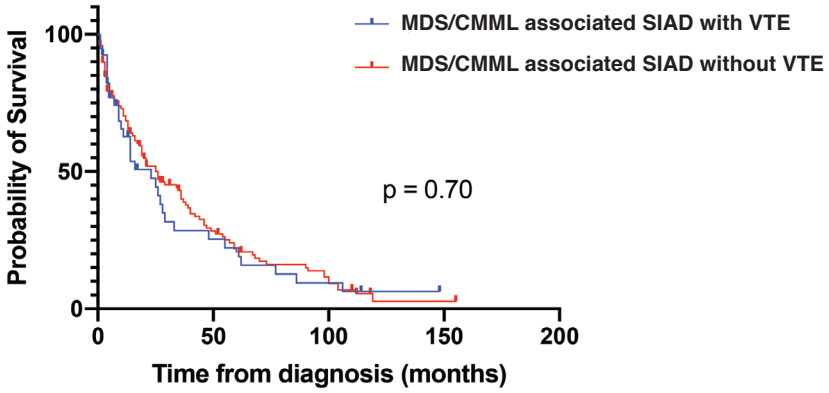

Fig. 1. Overall survival in MDS/CMML associated AID patients with and without VTE.

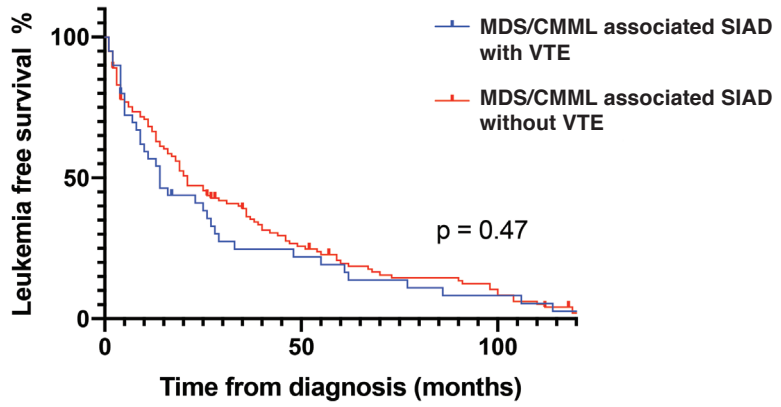

Fig. 2. Leukaemia-free survival in MDS/CMML patients with and without VTE.

ous MDS-specific associated therapies were not significantly different between both groups (Table I). In the multivariate analysis, MDS/CMML progression at time of VTE was the only factor independently associated with VTE with a 28.82 OR (95% CI [4.34–308.1]).

Therapeutic management and outcome

Thirty patients (n=29/30, 96.7%) were treated with LMWH/UH (n=14, 48.30%), DOAC (n=7, 24.10%) and VKA (n=8, 27.60%). A switch to DOAC (n=3), VKA (n=3) or Orgaran (n=1) were reported in 7 patients receiving LMWH/UH. Under anticoagulant therapy, bleeding occurred in a fifth of patients (6/29). Five patients experienced life-threatening haemorrhagic events (3 with digestive bleeding, 1 with subdural haematoma and one psoas haematoma), including one death. Low molecular weight heparin curative dose was associated with life-threating haemorrhagic event in 3 cases (60%). Among patients who experienced recurrence thrombosis, three were under long-term VKA with the Normalised Ratio index in the target area.

During a median follow-up (IQR) of 16 months (5–48) and 19 months (4–45), mortality rate was similar between MDS/CMML-SIADs patients with and without VTE (7, 20% *vs*. 22, 17.3%. *p*=0.80) and estimated median overall survival was not significantly different between both groups (114 *vs*. 112 months; *p*=0.68) (Fig. 1). AML progression was reported in 3 (8.57%) and 12 (9.4%) patients with and without VTE respectively (*p*=1) and leukaemia-free survival between groups was equivalent (148 *vs*. 118 months; *p*=0.83) (Fig. 2).

Molecular biology analysis in MDS/CMML-associated SIADs patients with VTE

Among MDS/CMML-SIADs patients with VTE, 10 (35%) underwent Next Generation Sequencing analysis. We identified somatic mutation in 6 patients (60%): 3 MDS/MPN, 2 MDS and 1 CMML. Seven mutations were encountered in one patient. Of 12 mutations encountered, the most common occurred in JAK2 (n=3, 23.1%) and DNMT3 (n=2, 16.7%) and others were rare (IDH1, Asxl1, TET2, WT1, SETBP2, NRAS, KRAS).

Discussion

This retrospective nationwide multicentre study found i) a high prevalence (21.6%) of VTE in MDS/CMML patients associated with SIADs; ii) MDS/

CMML progression as a major risk factor for thrombosis; iii) while VTE did not appear as an independent prognostic factor for transformation to AML and death.

The high prevalence of VTE in our subset of MDS/CMML-associated with SIADs is consistent with known prothrombotic factors, such as the increased risk of VTE in SIADs (7, 8), the role of comorbidities and the underlying haematological disease (10). To date, MDS/CMML is not considered to be usually associated with an increased risk of VTE. In a Danish population-based cohort study, the VTE frequency was 4.6% among 2695 MDS patients, while the frequency was higher in patients with multiple myeloma and myeloproliferative diseases (11). However, no clinical trials are available and retrospective studies are quite limited in size. On the other hand, idiopathic SIADs are known to be associated with an increased risk of VTE, in particular during the active phases of systemic diseases. Hypercoagulability is a common feature in most SIADs and it increases with the inflammatory activity of the disease. Interestingly, despite similar frequencies of prothrombotic factors in MDS/MPN-associated SIADs with and without VTE, patients with VTE presented markedly increased rates of active SIADs and MDS progression at the time of VTE. Despite this, the occurrence of VTE did not impact the overall MDS survival nor the risk of transformation to AML progression in our cohort.

On the pathophysiological level, aberrant immune activation and a dysregulation of the innate and adaptive immune systems were identified as key pathogenic drivers in MDS (5). MDS Haematopoietic stem progenitor cells (HSPC) overexpress Toll-like receptors (TLR). TLR4 stimulation results in the activation of intracellular pathways that interact with NLRP3 complexes. This results in the production of IL1β and IL18 promoting a pro inflammatory cellular death called pyroptosis (a caspase 1-dependent lytic form of cell death). Basiorka *et al*. (12) reported that pyroptosis drives cell death in MDS. Furthermore, abnormal release of inflammatory cytokines such as TNFα and IL-6 by bone marrow fibroblasts and macrophages are observed in MDS and could contribute to a hyperinflammatory, and thus prothrombotic microenvironment. Additionally, in our study, only 2 patients had antiphospholipid syndrome (1.20%), arguing the fact that other prothrombotic factors are incriminated in VTE in MDS-SAIDs patients. However, the precise mechanism of VTE in MDS/CMML-associated SIADs is still unclear.

JAK2 mutations are well-known to increase arterial and venous thrombosis risk(15). Recently, clonal expansions of mutated haematopoietic cells termed clonal haematopoiesis, commons with aging were associated with increased risk of haematologic cancers but unexpectedly with non-haematologic disorders such as veinous thrombosis (15, 16). In our MDS/CMML-associated SIADs population with VTE, we identified 12 somatic mutations in genes most commonly mutated in MDS and MPN (TET2, Asxl1, JAK2, IDH1 and DNMT3). With a lower incidence, other genes are associated with venous thrombosis.

We can hypothesise that an increase of mutated cells concomitant with MDS progression and flare of the SIADs generate a hyper inflammatory/coagulability state favouring emergence of veinous thrombosis in susceptible patients. In our study, in about half of the cases (51.5%, 17/33), SIADs preceded MDS/CMML diagnosis, and first thrombosis event occurred after the autoimmune disease onset in 54.8% (17/31). Another important feature of this study is the increased risk of bleeding under anticoagulation therapy, occurring in almost 20% of patients. This can be explained by the patients' age, underlying cytopenias and MDS-specific associated therapies. The risk of bleeding encountered in the literature is consistent with our results. Among 20 MDS/CMML patients treated with anticoagulants, Sorrigue *et al*. found a cumulative incidence of major bleeding of 21% (13). Further evaluation of the benefits and risks of anticoagulation in this particular population is necessary (14).

Missing data inherent to retrospective design make not possible to report C-reactive protein or percentage of abnormal cells which could be valuable for our study. Even important regarding last publications about MDS/CMML associated SIADs with VTE, the limited size of our cohort can explain some non-significant result in particular in multivariate analysis. A larger population are needed to confirm our results.

In conclusion, VTE is a common complication in MDS/CMML-associated SIADs possibly related to a hyper inflammatory state induced by SIADs flares and MDS/CMML progression. Its anticoagulation is associated with an increased risk of bleeding. Prospective studies are needed to better determine the risk factors of VTE in these patients.

Abbreviations

SIADs:	systemic inflammatory and autoimmune diseases
MDS:	myelodysplastic syndrome
AML:	acute myeloid leukaemia
CMML:	chronic myelomonocytic leukaemia
ACR:	American College of Rheumatology
EULAR:	European League Against Rheumatism
AIHA:	auto immune haemolytic anaemia
ITP:	immune thrombocytopenic purpura
RA:	rheumatoid arthritis
SLE:	systemic lupus erythematosus
LMWH:	low molecular weight heparin
VKA:	vitamin K antagonist
IPSS-R:	Revised International Index Prognostic scoring system
IPSS:	International Index Prognostic scoring system
RAEB:	refractory anaemia with excess blasts
ESA:	erythropoiesis stimulating agent
VTE:	venous thromboembolism
SVT:	superficial venous thrombosis
DVT:	deep venous thrombosis
TEE:	thromboembolic events
DOAC:	direct oral anti-coagulant
AT:	arterial thrombosis
TIA:	transient ischaemic attack
MDS/MPN:	myelodysplastic/myeloproliferative neoplasm
MDS-SLD:	myelodysplastic syndrome with single lineage dysplasia
MDS-EB:	myelodysplastic syndrome with excess blasts
MDS-MLD:	myelodysplastic syndrome with multilineage dysplasia
NGS:	next generation sequencing

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References

1. KOMROKJI RS, KULASEKARARAJ A, AL ALI NH *et al*.: Autoimmune diseases and myelodysplastic syndromes. *Am J Hematol* 2016; 91: E280-83.
2. MEKINIAN A, GRIGNANO E, BRAUN T *et al*.: Systemic inflammatory and autoimmune manifestations associated with myelodysplastic syndromes and chronic myelomonocytic leukaemia: a French multicentre retrospective study. *Rheumatology* (Oxford) 2016; 55: 291-300.
3. MEKINIAN A, BRAUN T, DECAUX O *et al*.: Inflammatory arthritis in patients with myelodysplastic syndromes: a multicenter retrospective study and literature review of 68 cases. *Medicine* (Baltimore) 2014; 93: 1-10.
4. FRAISON J-B, MEKINIAN A, GRIGNANO E *et al*.: Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Leuk Res* 2016; 43: 13-7.
5. BRAUN T, FENAUX P: Myelodysplastic Syndromes (MDS) and autoimmune disorders (AD): cause or consequence? *Best Pract Res Clin Haematol* 2013; 26: 327-36.
6. HORVÁTH-PUHÓ E, SUTTORP MM, FREDERIKSEN H *et al*.: Erythropoiesis-stimulating agents and cardiovascular events in patients with myelodysplastic syndrome and multiple myeloma. *Clin Epidemiol* 2018; 10: 1371-80.
7. YUSUF HR, HOOPER WC, GROSSE SD, PARKER CS, BOULET SL, ORTEL TL: Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. *Thromb Res* 2015; 135: 50-7.
8. ZÖLLER B, LI X, SUNDQUIST J, SUNDQUIST K: Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. *Lancet* 2012; 379: 244-9.
9. ARBER DA, ORAZI A, HASSERJIAN R *et al*.: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127: 2391-405.
10. LANDOLFI R, GENNARO L: Thrombosis in myeloproliferative and myelodysplastic syndromes. *Hematology* 2012; 17 (Supp1. 1): S174-6.
11. ADELBORG K, CORRAINI P, DARVALICS B *et al*.: Risk of thromboembolic and bleeding outcomes following hematological cancers: A Danish population-based cohort study. *J Thromb Haemost* 2019; 17: 1305-18.
12. BASIORKA AA, MCGRAW KL, EKSIOGLU EA *et al*.: The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. *Blood* 2016; 128: 2960-75.
13. SORIGUE M, NIETO J, SANTOS-GOMEZ M *et al*.: Indications and use of, and incidence of major bleeding with, antithrombotic agents in myelodysplastic syndrome. *Leuk Res* 2018; 73: 24-8.
14. SORIGUE M, CAÑAMERO E, SIGUENZA P, NOMDEDEU M, LÓPEZ-NÚÑEZ JJ: Recent developments and persisting challenges in the prevention and treatment of venous thromboembolism in patients with hematological malignancies. *Leuk Lymphoma* 2020; 61: 1277-91.
15. JAISWAL S: Clonal hematopoiesis and nonhematologic disorders. *Blood* 2020; 136: 1606-14.
16. WOLACH O, SELLAR RS, MARTINOD K *et al*.: Increased neutrophil extracellular trap formation promotes thrombosis in myeloproliferative neoplasms. *Sci Transl Med* 2018; 10: eaan8292.