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Thrombophilia Screening in Autoimmune Hemolytic Anemia: A Single-Center Cross-Sectional Study

Nicola Cecchi, MD^{1,2}, Marco Capecchi, MD^{3,4}, Juri Alessandro Giannotta, MD⁴, Maria Abbattista⁴, Cristina Novembrino⁴, Massimo Boscolo⁴, Wilma Barcellini, MD², Bruno Fattizzo, MD²

¹Department of Oncology and Oncohaematology, University of Milan, Milan, Italy

²Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

³Clinica Moncucco, Division of Hematology, Lugano, Switzerland

⁴Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Background

Autoimmune hemolytic anemia (AIHA) is characterized by an increased rate of thrombosis, whose predictors are not completely clarified, although an association with active hemolysis (i.e., LDH >1.5 x ULN), anemia severity and previous splenectomy has been reported. Moreover, antithrombotic prophylaxis and its duration are not standardized in this patient-population. The value of thrombophilia screening, including congenital and acquired abnormalities, has not been established yet.

Aim

To investigate the prevalence of inherited and acquired thrombophilia abnormalities in a cohort of AIHA patients with or without thrombosis.

Methods

AIHA patients followed from January 2019 until September 2022 at a tertiary hematologic center in Milan, have been systematically tested for Factor V Leiden (FVL) and prothrombin (FII) G20210A mutation, protein C (PC), protein S (PS), antithrombin (AT) levels, and the presence of antiphospholipid antibodies (APLA, i.e., lupus anticoagulant, LAC, anti-cardiolipin and anti-b2-glycoprotein-1). Patients' hematological characteristics, additional thrombotic risk factors, history of venous/arterial thrombosis before and after AIHA diagnosis, and anticoagulant and/or antiplatelet therapies were retrospectively recorded.

Results

As shown in table 1, 59% of 92 enrolled patients were female with a median age at diagnosis of 70.5 years (range 24-89), and were classified as warm AIHA (50%), cold agglutinin disease (31.5%), mixed/atypical AIHA (9.8%), and Evans syndrome (association of AIHA and other immune cytopenia, 8.7%). Thrombophilia screening resulted positive in 19 patients (20.7%) including FVL (1.1%), F II (1.1%), APLA (10.8%), PC deficiency (1.1%), PS deficiency (2.2%), AT deficiency (2.2%), and more than one abnormality (2.2%). Additional risk factors considered were thrombosis prior to AIHA diagnosis, reported in 6 patients (7%, 3 venous and 3 arterial), and associated conditions (29%), including autoimmune disease (N=17), lymphoproliferative disease (N=7), myeloproliferative neoplasm (N=1), and paroxysmal nocturnal hemoglobinuria (N=1). Furthermore, 97% of subjects presented at least one risk factor (i.e., diabetes, obesity, bed rest, etc.) in addition to AIHA. Twenty-seven patients (28%) received anticoagulant prophylaxis after AIHA diagnosis, mainly short-term for hemolysis (42%) or surgery of lower limb fractures (37%), and long-term for atrial fibrillation in 24%; 22% of patients were on antiplatelet prophylaxis, and 4 patients had been splenectomized. Since AIHA diagnosis, 26 patients (28%) experienced thrombosis (77% venous, 23% arterial), with 33 total events (3 patients had > 1 event). Median hemoglobin and LDH at thrombosis were 8.6 g/dL (2-11.7), and 374 U/L (129-1873) respectively, indicating active hemolysis. No relationship was found with inherited thrombophilia abnormalities (3 patients, 8% experienced thrombosis vs 7, 10.5% who did not), whilst a significant association was noted with APLA positivity ($p < 0.05$). Two patients with APLA experienced more than 1 event, one had 1 venous and 1 arterial event.

Conclusions

Along with disease activity and Evans syndrome, positivity for APLA appears the main predictor of thrombosis in AIHA and is therefore worth of testing, whilst extensive thrombophilia screening encompassing inherited abnormalities appears less useful.

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Table 1. Clinical and laboratory features according to thrombosis occurrence at/after AIHA diagnosis

	All patients N=92 (%)	Thrombosis N=26 (%)	No Thrombosis N=66 (%)
AIHA features at diagnosis			
Sex (M/F)	38 (41) / 54 (59)	8 (31) / 18 (69)	30 (45) / 36 (55)
Age, median (range)	70.5 (24-89)	75 (36-87)	69.5 (24-89)
AIHA Type			
Warm	46 (50)	10 (38.5)	36 (54.5)
Cold	29 (31.5)	6 (23.1)	23 (34.8)
Mixed/atypical	9 (9.8)	5 (19.2)	4 (6.1)
Evans Syndrome	8 (8.7)	5 (19.2)	3 (4.6)**
Thrombotic complications at/after AIHA diagnosis			
Venous thrombosis		20 (77)	
At AIHA diagnosis	-	8 (40)	-
After AIHA diagnosis	-	12 (60)	-
Arterial thrombosis		6 (23)	
At AIHA diagnosis	-	3 (50)	-
After AIHA diagnosis	-	3 (50)	-
Thrombophilia screening			
Thrombophilia abnormalities	19 (20.7)	7 (26.9)	12 (18.2)
Factor V Leiden	1 (1.1)	1 (3.8)	-
prothrombin G20210A mutation	1 (1.1)	-	1 (1.5)
APLA	10 (10.8)	5 (19.2)	5 (7.6)**
Protein C deficit	1 (1.1)	-	1 (1.5)
Protein S deficit	2 (2.2)	-	2 (3)
Antithrombin deficit	2 (2.2)	1 (3.8)	1 (1.5)
Combined abnormalities	2 (2.2)		2 (3)*

*1 patient had PC and AT qualitative deficit; 1 patient had FVL and PS qualitative deficit

**p<0.05

AIHA autoimmune hemolytic anemia; APLA anti-phospholipid antibodies

Figure 1

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