IMPACT OF INTRAVASCULAR HEMOLYSIS AND MULTITREATMENT ON THROMBOSIS OCCURRENCE IN AUTOIMMUNE HEMOLYTIC ANEMIA

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Contributions

ABSTRACT

Abstract

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Background

Autoimmune hemolytic anemia (AIHA) is a clinically heterogeneous disease classified as warm (wAIHA) (direct antiglobulin test positive for IgG and IgG+C), cold (cAIHA, DAT+ for C), mixed (IgG+C with high titer cold agglutinins), and atypical (DAT-, IgA+, wIgM). An increased thrombotic risk has been described possibly due to the release of free Hb and nitric oxide depletion at endothelial surface, and to the proinflammatory autoimmune milieu. However, predictors of thrombosis in AIHA are still lacking and no guidelines for anticoagulant prophylaxis are available

Aims

to characterize the frequency and severity of thrombotic episodes and their relationships with AIHA features

Methods

we analyzed a large single-centre cohort of primary AIHA patients to evaluate the frequency, type, and severity of thrombotic episodes. We also evaluated the relationship with disease characteristics (AIHA type, blood counts, hemolytic markers) and therapies, with the Padua score for thrombotic risk (cancer/chemo-/radiotherapy in past 6 months, previous thrombosis, bedrest>3 days, known thrombophilia, surgery/trauma, age>70, cardiac/respiratory failure, myocardial infarction/stroke, obesity, ongoing hormonal treatment), and with the occurrence of AIHA-related complications and death

Results

Twenty-five out of 225 (11%) AIHA patients experienced a thrombosis during a median follow-up of 32 months (1-540), and 72% required hospitalization. Venous episodes were mainly pulmonary embolism (N=10), followed by deep venous thrombosis of lower limbs or splanchnic vessels (N=5 and N=2, respectively), thromboflebitis (N=3), and catheter-associated thrombosis (N=2); 2 myocardial infarction and 1 stroke were also registered. Of note, 5 patients had multiple thrombotic episodes (2 in 3, 3 in 1, and 5 in 1). Nine cases started low-molecular-weight heparin, 11 oral anticoagulants, 4 anti-platelets agents, and 1 died because of the event. Table 1 shows clinical data in patients with and without thrombosis: baseline LDH levels were significantly higher in patients experiencing thrombosis (p=0.02), whilst Hb, reticulocytes, and bilirubin levels were similarly distributed, indicating a prominent role for intravascular hemolysis in thrombosis. This is also strengthened by persistent LDH elevation at the time of thrombosis, whilst other AIHA parameters (Hb, reticulocytes, and bilirubin) were all significantly improved due to treatment. AIHA type, white blood cells and platelets were similar in the two groups. Regarding treatment, patients experiencing thrombosis had received more frequently 2, 3 or 4 lines. Considering specific treatments, the difference was particularly significant for rituximab and

patients experiencing thrombosis had received more frequently 2, 3 or 4 lines. Considering specific treatments, the difference was particularly significant for rituximab and immunosuppressors. As expected, thrombotic episodes were more common among splenectomized patients. Among complications, infections were associated with thrombosis occurrence. The Padua score highlighted age and bedrest as the most frequently associated factors (40% and 28%, respectively)

	Thrombosis (N=25)	No thrombosis (N=200)	p
Median follow up, days (range)	1584 (71-8915)	950 (28-16483)	ns
Males, N(%) / Females, N(%)	10 (40) / 15 (60)	74 (37) / 126 (63)	ns
Median age, years (range)	65 (24-82)	61(5-96)	ns
Type of AIHA, N(%)			
Warm IgG+	6 (24)	78 (39)	ns
Warm IgG+C	5 (20)	22 (11)	ns
Cold agglutinin disease	8 (32)	66 (33)	ns
Mixed AIHA	3 (12)	17 (8,5)	ns
Atypical AIHA	3 (12)	17 (8,5)	ns
Hematologic parameters at diagnosis			
Median Hb, g/dL(range)	7.1 (2-9.9)	7.3 (2.1-14.1)	ns
Median Ret, x 10e9/L(range)	155 (49-570)	161 (13-780)	ns
Median LDH, x ULN(range)	1.93 (1.18-14)	1.5 (0-18)	0,02
Median unconj bilirubin, mg/dL(range)	1.38 (0.28-6)	1.1 (0.11-6.7)	ns
Median WBC, x 10e9/L(range)	5.8 (3.3-14)	7.18 (3.4-28)	ns
Median PLT, x 10e9/L(range)	200 (48-414)	264 (2.66-464)	ns
Hematologic parameters at thrombosis			
Median Hb, g/dL(range)	9.1 (3.2-14)	-	
Median Ret, x 10e9/L(range)	116 (22-400)	-	
Median LDH, x ULN(range)	1.49 (0-19)	-	
Median unconj bilirubin, mg/dL(range)	1.25 (0.2-4.9)	-	
Median WBC, x 10e9/L(range)	6.9 (1.5-25)	-	
Median PLT, x 10e9/L(range)	204 (77-794)	-	
N. of therapy lines, median (range)	3 (1-5)	1 (0-5)	0.001
1st line, N(%)	22 (88)	166 (83)	ns
2nd line, N(%)	17 (68)	75 (37)	0.006
3rd line, N(%)	11 (44)	27 (13)	0.0004
4th or> line, N(%)	5 (20)	10 (5)	0.01
Steroids, N(%)	24 (94)	163 (82)	ns
Rituximab, N(%)	18 (72)	54 (27)	<.0001
Splenectomy, N(%)	6 (24)	18 (9)	0.05
Immunosoppressors, N(%)	14 (56)	38 (19)	0.0001
Erythropoietin, N(%)	4 (16)	8 (4)	0.04
Bortezomib, N(%)	3 (12)	4 (2)	0.03
Complications and outcome			
Acute renal failure, N(%)	2 (8)	6 (3)	ns
Evans' syndrome, N(%)	5 (20)	18 (9)	ns
Infections, N(%)	7(28)	21(10)	0.02
Death, N(%)	4(16)	46(23)	ns
Death AIHA-related, N(%)	3(12)	8(4)	ns

Conclusion

thrombotic episodes occurred in 11% of AIHA patients, were mostly severe, and required hospitalization in the great majority of cases. Intravascular hemolysis, multitreatment, and infections were the major associated risk factors, while age and bedrest are important cofactors. The presence of underlying clinical and biological prothrombotic conditions, and the efficacy of different prophylactic/therapeutic anticoagulants need to be explored in larger prospective studies

Session topic: 28. Enzymopathies, membranopathies and other anemias

Keyword(s): Autoimmune hemolytic anemia (AIHA), Hemolysis, Splenectomy, Thrombosis

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