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ORIGINAL ARTICLE

Acquired Hemophilia A In Adults: A Multicenter Study from Turkey

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Abstract Acquired hemophilia A (AHA) is a rare disease caused by autoantibodies inhibiting factor VIII (FVIII) activity. Although the conditionis usually idiopathic, there may be other underlying diseases. Treatment consists of two steps: treatment of acute bleeding and immunosuppression. In this multicenter study, we aimed to demonstrate the clinical characteristics, management details, and survival of AHA patients in Turkey. Data was collected from eleven centers in Turkey. aPTT, FVIII, FVIII inhibitor, and hemoglobin (HB) levels, mixing test results, and demographics at diagnosis, treatment information, adverse events, bleeding episodes during follow-up, relapses, and outcome were analyzed. Twenty-nine patients were analyzed (58.6% female). No underlying disorder could be detected in 14 patients. The most prevalent etiologies were pregnancy, malignancy and infections. The median FVIII activity and FVIII inhibitor titer at diagnosis were 0.7% (0.0–29.4%) and 32.6 BU (0.6–135.6 BU) respectively. Bleeding was severe in 44.8% of patients. The HB value was significantly lower in patients with severe bleeding. Most of the patients (n = 25, 86.2%) had only one bleeding episode without relapse, three patients (10.3%) had two bleeding episodes, and one patient had more than three bleedings. 21 (75%) patients received hemostatic therapy. The use of recombinant FVIIa was

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slightly higher than activated prothrombin complex concentrate (15 versus 10 patients). Immunosuppressive treatment was initiated in 26 (93%) patients. Regimens containing steroid, cyclophosphamide, and rituximab in different combinations were the most preferred. The median follow-up period was 13 months (2–156 months). Median overall survival was 154.97 months. Four and six-year survival were 90.9 ± 0.8% and 77.9 ± 14.1% respectively. This is a unique study that investigated the demographic characteristics, treatment approaches, and patient survival of AHA in Turkey.

Keywords Acquired coagulation disorders · Hemophilia and other bleeding disorders · Other coagulation inhibitors

Introduction

Acquired hemophilia A (AHA) is an autoimmune disease that causes hemorrhages in patients without a prior history of bleeding disorders [1]. It is caused by autoantibodies that inhibit factor VIII (FVIII) activity which is the result of a dysregulated immune system [2]. AHA is generally idiopathic [3] but the most prevalent detectable causes are collagen vascular disorders, malignancy, pregnancy, and drugs. The most common collagen vascular diseases are systemic lupus erythematosus (SLE), rheumatoid arthritis, myastenia gravis, multiple sclerosis, Graves' disease, and hemolytic anemia. The etiologic role of malignancies is more prominent in lymphoproliferative disorders. Although less apparent, some solid tumors may be associated with AHA regardless of their stage or grade [2]. Estimated incidence has been reported to be 1.48/million/year [4]. Mortality rates are variable, but are low and range from 9 to 22% [4, 5].

The clinical manifestation is usually acute bleeding in patients without known bleeding diathesis. Unlike congenital hemophilia where joint and muscle bleeding is common, patients present mucocutaneous, gastrointestinal, and soft tissue bleeding.

Activated partial thromboplastin time (aPTT) is prolonged in typical basic laboratory results and mixing tests indicate a positive inhibitor screen. FVIII level (%) and inhibitor titer (Bethesda Unit, BU) can be quantified if factor inhibitor is suspected [2].

The treatment of AHA has two major objectives: bleeding control in the early stage and antibody eradication in the long term [6]. Bleeding control can be achieved by replacement products such as desmopressin, recombinant FVIII products, activated prothrombin complex concentrates (aPCC), or recombinant factor VIIa (rFVIIa). The aim of antibody eradication is to provide immunomodulation in order to prevent recurrent bleeding. Eradication treatment starts with corticosteroids alone or in combination with cyclophosphamide. Switching to other immunosuppressive agents, intravenous immunoglobulin, and rituximab is possible in the case of refractoriness.

Materials and Methods

This study is a multicenter retrospective registry developed to collect data on adult AHA patients. Patients older than 18 years and diagnosed with AHA between January 2009 and December 2019 were included in the study. The diagnosis of AHA was made in the presence of the following findings: prolonged aPTT, low FVIII level, normal thrombin time, normal prothrombin time, normal platelet count, and positive antibodies against FVIII (in Bethesda units) [7]. If performed, mixing study results were also recorded to demonstrate the presence of a time-dependent inhibitor of FVIII. Data was collected on the patients' current age, gender, age at diagnosis, clinical manifestations, referring department, presence of severe bleeding at diagnosis, time of delay in diagnosis, laboratory results, approach for hemorrhage and immunosuppressive treatment, response to hemostatic and immunosuppressive therapy, adverse events, bleeding episodes during follow-up, relapses, and outcome of the patient. Any trigger factors were also recorded.

aPTT level, mixing test result, FVIII, FVIII inhibitor, and hemoglobin (HB) levels at diagnosis, aPTT level, FVIII and FVIII inhibitor levels during follow-up were recorded.

Severe bleeding episodes were defined as HB level less than 8 g/dl or a 2 g/dl drop from baseline, and/or life or

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organ threatening (central nervous system, limb, deep muscle, retroperitoneal) bleeding.

Since all the factor and inhibitor tests were performed in local laboratories, it was accepted that there might be minor differences between the results.

Data was reported as frequency (percentage) or median for categorical and continuous variables. Survival analyses were performed using the Kaplan–Meier method. Overall survival (OS) was calculated from the date of presentation to the date of death due to any cause. The Mann-Whitney U test was used to evaluate the significance of the difference between two arithmetic averages. IBM SPSS Statistics 25 for Windows was used for statistical analyses. A p value less than 0.05 ($p < 0.05$) was considered to be statistically significant.

Informed Consent was obtained from all individual participants included in the study (for deceased patients, consent was obtained from their relatives).

Results

A total of 29 patients with AHA were diagnosed in eleven different centers in Turkey. Baseline patient characteristics, information regarding bleeding, treatment, complications, and outcome have been summarized for each patient in Table 1. The patient group comprised 17 female (58.6%) and 12 male (41.4%) patients. The median age at diagnosis was 52 years (range 18–84 years). Nine of the patients (31%) had been referred to the hematology clinic from other departments including obstetrics and gynecology (n = 3), internal medicine (n = 2), orthopedics and traumatology (n = 2), dermatology (n = 1), and ear-nose-throat (n = 1).

In all cases (100%), AHA was diagnosed with the complaint of bleeding. The distribution of predominant bleeding locations is presented in Table 2.

The median duration from the onset of complaints to diagnosis was found to be 14 days (range 2-120 days) in 27 patients whose data on this parameter were available. No underlying disorder that could be associated with the development of AHA was detected in 14 patients (48.3%). The distribution of the patients with an underlying disorder according to etiologies is presented in Table 3. Bleeding was severe in 13 patients (44.8%).

The aPTT level was prolonged at the time of diagnosis in all of the patients. The mixing test could be demonstrated in 24 patients (82.7%) and in these cases there was no recovery in aPTT with incubation that suggested the presence of an inhibitor. The diagnosis for the remaining five patients who could not perform the mixing test was made with factor VIII and factor VIII inhibitor tests. The median FVIII activity at diagnosis was 0.7% (range 0.0-29.4%). The median FVIII inhibitor titer for 28 patients was 32.6 BU at the time of diagnosis (range 0.6-135.6 BU). The result of the remaining patient was 'positive'. Due to the multicenter nature of the study, it was impossible to avoid differences between laboratories. This issue should also be considered, especially when evaluating the FVIII inhibitor titer.

The distribution of patients according to FVIII, FVIII inhibitor, and HB level at diagnosis is presented in Table 4. While the HB value was significantly lower in patients with severe bleeding (median HB 10.2 mg/dl versus 8.5 mg/dl, p 0.045), there were insignificant differences in FVIII and FVIII inhibitor levels between the two groups (p 0.812 and 0.880 respectively).

Of the 29 patients with bleeding events at presentation, 25 patients (86.2%) had only one bleeding episode without relapse after receiving successful initial therapy. Two bleeding episodes occurred in 3 patients (10,3%). Only one patient had more than three bleedings (exact number is unknown).

One patient refused to be treated after the diagnosis and discontinued the follow-up. All patients received blood product transfusions and other supportive treatments as required. Hemostatic therapy was provided to 21 (75%) patients. There was only one patient who did not receive hemostatic treatment despite suffering severe bleeding. The drugs selected for the treatment of acute bleeding have been summarized in Table 5. Doses of rFVIIa and aPCC administered throughout the study were similar to congenital hemophilia patients with inhibitors. rFVIIa doses started from 90 mcg/kg, every 2 to 3 h until bleeding was controlled after which the interval between administrations increased. aPCC was used in 50–100 units/kg every 6 to 12 h, but not exceeding 100 units/kg/dose or 200 units/kg/day.

Immunosuppressive treatment was started on 26 (93%) patients. Methylprednisolone was the preferred steroid agent in all cases and a dose of $0{,}5-1$ mg/kg was used on all patients. Cyclophosphamide was given orally except for one patient who received the drug intravenously. Cyclophosphamide dose varied between 50 and 150 mg/day. One third (33.3%) of the patients who received immunosuppressive drugs used rituximab (375 mg/m^2, 4 weeks) in their treatment regimen. Azathioprine was used for two patients after the failure of steroid + cyclophosphamide + rituximab and steroid + cyclophosphamide regimens respectively. Both patients are in remission. Intravenous immunoglobulin (IVIG) was administered at a dose of 1 mg/kg in two patients, one alone and the other with steroids. Both of the patients were breastfeeding women who were diagnosed with AHA in the postpartum period, so other immunosuppressive treatments could not be used. The treatment strategies for immunosuppression have been presented in Table 5.

Relapse was reported in four (14%) patients. The first patient relapsed 18 months after steroid + cyclophosphamide regimen and achieved remission after steroid treatment alone. The second and third patients relapsed after

Table 1 Patient characteristics, information about bleeding, treatment, complications, and outcome

Patient No	Age	Gender	Aetiology	Localisation of bleeding	Severe bleeding	Time to diagnosis (days)	APTT at diagnosis (min)	FVIII at diagnosis (%)	FVIII inhibitor at diagnosis (BU)	HB level at diagnosis (g/dL)	Hemostatic agent	IS agent	Follow-up time (months)	Relaps	Treatment for relapse	Status
1	74	F	None	Soft tissue	No	7	48.7	0,90	46,80	8,70	None	Steroid + Cyc	8	Once (after 18 months)	Only steroid	Alive
2	28	F	Pregnancy	Intraabdominal	Yes	14	57.6	1,00	30,2	8,50	rFVIIa (90 mcg/kg, 5 days)	Steroid + Cyc + Rituximab	49	No		Alive
3	73	F	None	Rectal	Yes	30	108.5	0,00	117,7	9,70	High dose FVIII (40 u/kg, 3 days), rFVIIa (90 mcg/kg, 2 days)	Steroid	2	No		Exitus
4	83	M	None	Soft tissue	Yes	30	60.1	1,20	53,7	6,30	None	Steroid + Rituximab	6	Once (after 2 months)	Only rituximab	Alive
5	24	F	Pregnancy	Soft tissue	No	20	99.5	0,10	positive	11,00	None	Steroid	56	No		Alive
6	43	F	Pregnancy	Hematuria	No	30	68	2,20	4,6	11,70	None	Steroid + Cyc	7	No		Alive
7	77	M	Bullous pemphigoid	Soft tissue	Yes	?	121	0,6	60	8,20	rFVIIa (90-120mcg/kg, 30 days intermittently) + aPCC (100U/kg 2 × 1, 30 days intermittently)	Cyc	15	No		Exitus
8	51	F	Infections	Soft tissue	Yes	30	90	0,67	9,6	6,30	rFVIIa (90 mcg/kg, ? days), aPCC (50U/kg 2 × 1, ? days)	Steroid + Cyc + Rituximab	156	Yes, several times	Steroid + cyc + Rituximab	Exitus
9	30	M	Pregnancy	Soft tissue	No	30	115	0,1	73,2	14,70	None	Steroid	40	No		Alive
10	55	F	None	Intraoperatively excess bleeding	Yes	30	96	0,4	78,4	13,50	rFVIIa (90 mcg/kg, 6 days), aPCC (75U/kg 2 × 1, 20 days)	Steroid + Cyc	56	No		Alive

Table 1 (continued)

Patient No	Age	Gender	Aetiology	Localisation of bleeding	Severe bleeding	Time to diagnosis (days)	APTT at diagnosis (min)	FVIII at diagnosis (%)	FVIII inhibitor at diagnosis (BU)	HB level at diagnosis (g/dL)	Hemostatic agent	IS agent	Follow-up time (months)	Relaps	Treatment for relapse	Status
11	26	M	Pregnancy	Hemartrosis	No	120	> 120	0,4	32	10,20	aPCC (50U/kg 2×1, 5 days)	Steroid + Rituximab	2	No		Alive
12	67	F	Infections	Soft tissue	No	30	62,2	0,8	11	7,20	High dose FVIII (2000 U/day, 1 day), rFVIIa (90 mcg/kg, 1 day)	Steroid + Cyc + Rituximab + Aza	2	No		Alive
13	33	F	None	Intraabdominal	No	60	44.5	0,2	30,6	8,70	rFVIIa (90 mcg/kg, 5 days), plasmapheresis (4 days)	Steroid + Cyc	6	No		Alive
14	36	F	Pregnancy	Vaginal	Yes	?	42	1	7	10,90	rFVIIa (90 mcg/kg, 2 days)	Steroid + IVIG	8	No		Alive
15	74	M	None	Soft tissue	Yes	7	59	2	44,1	11,30	rFVIIa (90 mcg/kg, 5 days)	Steroid + Cyc	3	No		Alive
16	79	M	None	Soft tissue	Yes	7	70	0,5	28	5,20	High dose FVIII (2000 U/day, 2 days)	Steroid + Cyc	60	No		Alive
17	72	M	None	Soft tissue	Yes	21	79,4	0,4	41,4	9,70	aPCC (100U/kg 2×1, 5 days)	Steroid	30	No		Alive
18	47	M	None	Soft tissue	No	13	96,4	0,7	10,20	12,70	rFVIIa (40 mcg/kg, 3 days)	Steroid + Cyc + Aza	120	No		Alive
19	72	M	None	Soft tissue	No	7	54,79	29,4	0,6	10,20	None	None	?	No		Unknown
20	18	M	None	Hemartrosis	No	7	94,29	0,1	120	8,60	aPCC (100 U/kg 2×1, 3 days)	Steroid	6	No		Alive
21	62	M	None	Soft tissue	Yes	7	69	2	17	6,90	rFVIIa (90 mcg/kg, 3 days), aPCC (50U/kg 2×1, 10 days)	Steroid + Cyc	13	No		Alive
22	53	M	None	Soft tissue	Yes	7	83	1	45	7,70	rFVIIa (90 mcg/kg, 3 days)	Steroid + Cyc + Rituximab	19	No		Alive
23	27	F	Pregnancy	Hemartrosis	No	7	77.8	0.3	365	10,20	aPCC (50U/kg 2×1, 10 days)	None	20	No		Alive

Table 1 (continued)

Patient No	Age	Gender	Aetiology	Localisation of bleeding	Severe bleeding	Time to diagnosis (days)	APTT at diagnosis (min)	FVIII at diagnosis (%)	FVIII inhibitor at diagnosis (BU)	HB level at diagnosis (g/dL)	Hemostatic agent	IS agent	Follow-up time (months)	Relaps	Treatment for relapse	Status
24	22	F	Pregnancy	Postoperatively excessive bleeding from scar	No	14	55	1,77	33,2	10,10	aPCC (50U/kg 4 × 1, 15 days)	None	21	No		Alive
25	83	M	None	Soft tissue	No	14	46,8	0,7	53,7	12,4	aPCC (50U/kg 2 × 1, 2 days)	Steroid	24	Once (after 2 months)	Only steroid	Alive
26	20	F	Pregnancy	Vaginal	Yes	21	68,4	0,55	2,5	9	rFVIIa (90 mcg/kg, 2 days)	IVIG	24	No		Alive
27	74	F	CLL	Soft tissue	No	21	80,4	0,2	135,6	7,8	rFVIIa (90 mcg/kg, 2 days)	Steroid + Cyc	24	No		Alive
28	42	F	Other	Hemartrosis	No	2	53	4,9	2,8	10,7	Desmporessin (1 month) + rFVIIa (90 mcg/kg, 5 days)	Steroid + Cyc + Rituximab	9	No		Alive
29	84	M	CLL	Soft tissue	No	12	83	2	2,80	9,80	No	Steroid + Rituximab (+ obinutuzumab for CLL and AHA)	6	No		Alive

F female, *M* male, *CLL* chronic lymphocytic leukemia, *APTT* activated partial thromboplastin time, *HB* hemoglobin, *rFVIIa* recombinant factor VIIa, *aPCC* activated prothrombin complex concentrate, *IS* immonosupressive, *Cyc* cyclophosphamide, *IVIG* intravenous immunoglobulin, *Aza* azathiopurin, *AHA* acquirred hemophilia A

Table 2 Predominant location of bleeding

Soft tissue/skin	17 (58.6%)
Hemarthrosis	4 (13.8%)
Vaginal	2 (6.9%)
Intrabdominal	2 (6.9%)
Hematuria	1 (3.4%)
Intraoperatively excessive bleeding	1 (3.4%)
Rectal	1 (3.4%)
Postoperatively excessive bleeding from scar	1 (3.4%)

Table 3 Underlying disorders

Pregnancy	9 (60%)
Malignancy (Chronic lymphocytic leukemia)	2 (13.3%)
Infections	2 (13.3%)
Bullous pemphigoid	1 (6.6%)
Other	1 (6.6%)

steroid treatment (2 and 3 months respectively) and achieved remission with single agent rituximab and steroid treatments respectively. Patient 4 is a patient who has used steroid, cyclophosphamide and rituximab treatments intermittently during the 13-year follow-up period and has invariably remained resistant. This patient died due to bleeding.

One diabetic patient had grade 2 hyperglycemia (serum glucose level up to 250 mg/dl) while on steroid treatment. The complication was solved by temporarily increasing the dose of the patient's oral antidiabetic drugs. Two patients had grade 2 leucopenia without fever (leukocyte levels of 2030 and 2100/mm3 respectively) while on oral cyclophosphamide treatment. The drug doses of both patients were reduced, and they did not present leucopenia again during their follow-up.

Table 4 FVIII, FVIII inhibitor, and HB levels at diagnosis

FVIII activity	n, %
Less than 1%	18 patients, 62%
1–5%	10 patients, 34.5%
More than 5%	1 patient, 3.5%
FVIII inhibitor level (BU)	n, %
0–10	7, 25%
11–100	17, 60.7%
More than 100	4, 14.3%
HB level (median) (g/dl)	9,7 (range 5.2–13.5)

Follow-up data was available in 27 cases (93.1%). Three of these patients died during the study period. One of the patients was the one who had never achieved remission and died from post-trauma retroperitoneal bleeding. One patient died because of intestinal perforation when while in remission. The third patient died of an unknown reason while in remission at her last visit. The median follow-up period was 13 months (range 2-156 months). Median overall survival was 154.97 months. Four- and six-year survival were $90.9 \pm 0.8\%$ and $77.9 \pm 14.1\%$ respectively. The OS of all patients have been presented in Fig. 1.

Discussion

This is the only multicenter study conducted on AHA in Turkey. Given how rare the disease is [4], a total of 29 patients from the 11 centers in country of 83.6 million [8] seems to be a sufficient group for evaluation.

Compared to other large AHA studies with a median age of 73.9 [3] and 64 years [9], our patient group was younger with a median age of 52. Gender distribution shows female dominance in our study (58.6%). Similar to other data, the most common underlying condition in our group was idiopathic [3, 4, 9]. However, in our study, pregnancy-related causes constituted 60% of patients with an underlying disease for bleeding, and the most common etiological reasons encountered in other patient groups lagged behind pregnancy in our group. The reasons for this may be the relatively small size of our sample, the high rate of reproductive women in our country, and the fact that admission to the hospital due to childbirth facilitates the diagnosis of AHA in a shorter time. In accordance with the literature, our all pregnancy-related AHA cases occurred in the postpartum period [10–12]. Both of AHA patients associated with malignancy were diagnosed with chronic lymphocytic leukemia (CLL). AHA has been found to be associated with various malignancies in the literature, and CLL is one of the most common hematologic malignancy [13]. One of these patients was simultaneously diagnosed with AHA and CLL. This patient did not need treatment for leukemia because she had RAI stage 1 CLL. AHA bleeding symptoms were treated with rFVIIa and the patient received steroid + cyclophosphamide for immunosupression. The patient is still in remission for AHA and did not present CLL progression. The other patient was diagnosed with RAI stage 1 CLL ten years before being diagnosed with AHA. The progression of CLL coincided with the diagnosis of acquired hemophilia. Bleeding treatment was not given as there were no AHA related severe bleeding symptoms. Steroid and rituximab were preferred for both AHA and CLL, considering the patient's age, concomitant CLL disease, and unwillingness towards other immunosuppressive treatments. The treatment was switched

Table 5 Hemostatic and immunosuppressive therapy

Hemostatic therapy	Number of patients
Desmopressin + rFVIIa	1
High dose FVIII + rFVIIa	2
rFVIIa only	7
rFVIIa + aPCC	4
rFVIIa + plasmapheresis	1
aPCC only	6
Immunosuppressive therapy	
Steroid only (methylprednisolone)	6
Cyclophosphamide only	1
Steroid + cyclophosphamide	8
Steroid + Rituximab	3
Steroid + cyclophosphamide + Rituximab	4
Steroid + cyclophosphamide + Rituximab + Azathiopurin	1
Steroid + cyclophosphamide + Azathiopurin	1
IVIG only	1
Steroid + IVIG	1

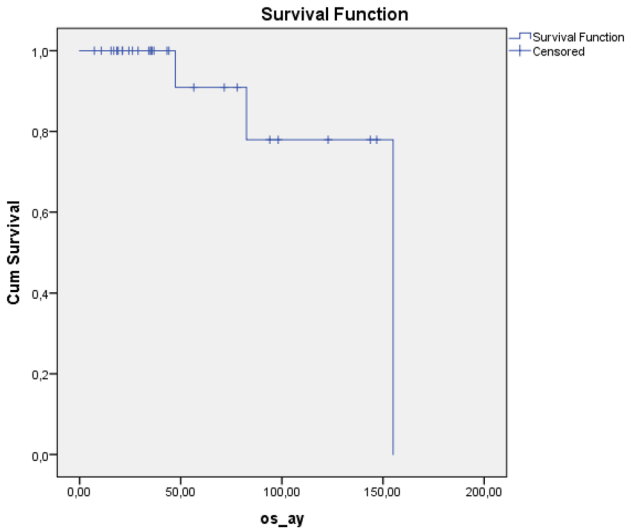

Fig. 1 Overall survival of the patients

to obinutuzumab after a partial response was obtained with this treatment for both CLL and AHA. Complete remission was achieved for both diseases at the end of six cycles.

All of our patients were diagnosed with AHA while being examined for bleeding complaints. None of them had a history of an underlying diagnosis at the time of the examination for the incidentally detected prolonged aPTT. Our diagnostic delay (median time to diagnosis is 14 days) is longer than the EACH2 group (three days) [3]. The most likely reasons for delayed diagnosis is thought to be the delay in patient referral to a tertiary healthcare center and the long time required to receive the FVIII and FVIII inhibitor test results.

The median FVIII activity is approximately two to three times lower and the median FVIII inhibitor level is three times higher in our group compared to the AHA patient group of other studies [3, 4, 9]. Although this is the numerical data, making comparisons may be misleading as the results of these two tests may differ between laboratories.

By-passing agents were used alone or in combination in all patients receiving bleeding therapy. In terms of the preference of by-passing agents in Turkey, the use of rFVIIa was slightly higher (15 patients) than aPCC (10 patients). A similar result was reported in the EACH2 study [14] and in another prospective AHA study [15]. Although it is known that thrombotic events observed with by-passing agents are more common in AHA than congenital hemophilia [16], such adverse events were not reported in our group.

Although there were 3 deaths in total among our patients, there was only one patient who died from an AHA-related cause. The mortality rate in our study is lower than in other research groups. We think that the reason for this is the relatively small number of patients.

The most commonly employed initial immunosuppressive treatments in our group were similar to the EACH2 study [17]. Comparing treatment groups was impossible due to the small number of patients and the inhomogeneous distribution of each group. Although the role of IVIG treatment has been reported to be limited [6], our experience with two breastfeeding women is positive and both patients are in remission after the first episode.

The main limitations of the study are that it is retrospective and related to a rare disease. Due to its retrospective nature, some data may be less detailed or incomplete. For example, detailed definition on bleeding locations and treatment complications of some patients diagnosed earlier may be unclear and also the referring clinic is unknown. Most of the patients were out of follow-up after a recovery period, therefore the actual follow-up times are short. These patients applied before an invasive procedure or surgery or in case of any hematological complaint. Patient numbers are relatively low due to the rarity of the AHA disease. This numerical inadequacy prevents making comparisons with patients divided according to factor, inhibitor, etiology, treatment groups, etc.

To the best of our knowledge, our study is the only multicenter AHA study conducted in Turkey. In our opinion, the study is important in terms of demonstrating the characteristics and the survival of patients, revealing the approach to this rare disease in Turkey. It is important to share this and similar studies in the literature in order to increase awareness on AHA, since the duration between admission and diagnosis, and that between diagnosis and

the initiation of treatment are factors that directly affect mortality.

Declarations

Ethical Aproval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Ege University Medical Faculty ethics committee (No 19-7T/71).

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