Thromboembolic complications in autoimmune hemolytic anemia: Retrospective study

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Abstract

Introduction: A small number of retrospective studies suggest AIHA to be associated with an increased risk to suffer from thromboembolic events. However, based on these studies it remains unclear whether the complement activation per is a risk factor to develop thromboembolic events in AIHA patients. The aim of this retrospective study is to investigate the incidence of thromboembolic events and the relation to complement activation in a cohort of AIHA patients.

Patients and Methods: We included 77 patients in this study with a positive DAT and hemolytic parameters or with AIHA diagnosis based on the medical report. The included patients were screened for thromboembolic events (TEE) and have been stratified in groups with and without complement activation based on the positivity for complement in the DAT.

Results: Of the 77 included patients, 51 (66%) had warm AIHA, 13 (17%) cold-AIHA, 5 (7%) mixed AIHA, and 8 (10%) atypical AIHA, respectively. Primary and secondary AIHA was diagnosed in 44% and 56%, respectively. Twenty patients (26%) suffered from TEE. The majority (80%) of these patients suffered from warm AIHA and 10% from cold-AIHA. Hemolysis parameters did not differ in patients with and without TEE. There was no correlation with complement activation as evidenced by a positivity for complement in the monospecific DAT with the occurrence of TEE.

Conclusion: AIHA is associated with an increased risk of TEE. Based on these results prophylactic anticoagulation might be considered as soon as the diagnosis of AIHA is confirmed.

KEYWORDS
AIHA, complement, Hemolysis, Thromboembolism, Thrombosis

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disease characterized by autoantibodies directed to surface antigens of erythrocytes inducing hemolysis.1,2 The estimated incidence of AIHA is 1 to 3 per 10^5/year.1,2 AIHA may occur in the absence of an obvious underlying disease (primary AIHA) or in association with an underlying disease (secondary AIHA).1,2

The classification of AIHA is based on the optimal binding temperature at which the autoantibody reacts with the red blood cell.
Complement regulators resulting in intravascular hemolysis with alternate pathway of complement due to a lack of GPI-anchored (PNH), a disease characterized by uncontrolled activation of the phagocytes as well as the efficacy to activate complement. IgM is a very effective activator of the classical pathway of complement, to a lesser extent IgG1 and IgG3 do activate complement as well. The other subtypes of IgG as well as other isotypes (eg, IgA) only weakly or do not activate complement at all. Interestingly, in AIHA patients a DAT positivity for C3d is mostly caused by autoantibodies of iso-type IgM. This also holds for situation where the DAT is positive for both, IgG and C3d, respectively. In most of these cases, the IgM responsible for complement activation escapes detection in the DAT. Complement activation as reflected by DAT positivity for C3d seems to be associated with a more severe anemia, high morbidity, and a significantly lower chance to respond to therapy.5

Complement-induced hemolysis is associated with thrombophilia. This is evident in paroxysmal nocturnal hemoglobinuria (PNH), a disease characterized by uncontrolled activation of the alternate pathway of complement due to a lack of GPI-anchored complement regulators resulting in intravascular hemolysis with subsequent arterial and/or venous thrombosis.6,7 In PNH, up to 67% of deaths are caused by thromboembolic complications, nearly half of the patients with PNH do suffer at least from one thromboembolic event.7 Based on a small number of studies, there is evidence that AIHA is associated with thromboembolic events as well. In 1967, Allgood and Chaplin reported a mortality of 28% in a cohort of AIHA patients.8 More than half of the fatalities in this cohort have been caused by pulmonary embolism. According to the literature, 11% up to 27% of patients with AIHA suffer from thromboembolic events.9,10 In a collective of patients with cold agglutinin disease, 7.2% suffered from thromboembolic complications as compared with 1.9% in healthy controls after one year and 11.5% versus 7.8% after 5 years, respectively.11 In a systematic review and meta-analysis, patients with AIHA showed a 2.6-fold higher risk of VTE compared with non-AIHA patients, the risk being highest in the first year after diagnosis.12 Risk factors for TEE in AIHA patients are active hemolysis and splenectomy.5,12-14 In a large AIHA patient cohort, 11% of the patients had thrombotic complications, mainly venous thrombosis, and to a lesser extent arterial thrombosis.5 In addition, the same authors report that in 80% of the AIHA patients presenting with Hb < 8 g/dL the incidence of thromboembolic events (TEE) reaches 15%.5 The few retrospective studies on this subject suggest that AIHA is associated with an increased risk for thromboembolic events. However, based on these studies it remains unclear whether complement activation significantly contributed to the development of thromboembolic events in AIHA patients. The aim of this retrospective study is to investigate the incidence of thromboembolic events and the relationship to complement activation in a cohort of AIHA patients diagnosed and treated at the department of hematology at the Inselspital since the beginning of case registration in 1993.

2 | PATIENTS AND METHODS

We included patients with the diagnosis of AIHA who have been diagnosed and/or followed in the outpatient clinic since the beginning of registration at the Inselspital University hospital in Bern, Switzerland. This covers a period of 26 years from 1993 to 2019. The screened patients had specific internal diagnostic codes for AIHA, lymphoproliferative disease, and acute or chronic leukemia, respectively. In total, we have screened 2020 patients according to our inclusion criteria. The study has been approved by the medical ethical committee of the University of Bern.

Electronic files including discharge letters and laboratory values have been screened. The inclusion criteria for AIHA based on available laboratory values applied were as follows: positive DAT and signs of hemolysis based on decreased hemoglobin (anemia), haptoglobin levels decreased, and increased LDH and/or bilirubin, respectively. In the absence of available hemolysis parameters or incomplete laboratory information extractable from the laboratory information system, patients with a diagnosis of AIHA as stated in the medical discharge report have been included. In these patients with no primary laboratory data available, the medical discharge report was screened for information on laboratory data indicating hemolysis, such as low hemoglobin, increased LDH and bilirubin, and decreased/not detectable haptoglobin, respectively.

Serological parameters, such as poly and monospecific DAT test and clinical parameters, such as age, gender, underlying disease, and applied treatment have been collected in the patients included in the study. Based on the recent recommendations, the patients were classified according to the DAT results in WA-AIHA (IgG ± C3c/d, CA-AIHA (C3c/d ± IgM), mixed AIHA (IgG ± IgM + C3c/d), or atypical AIHA (IgA a/o C3c/d a/o warm IgM a/o DAT negativity).1 According to the absence or presence of an underlying disease, diagnosis of primary vs secondary AIHA has been made. The records of the patients included in the study have been screened for the occurrence of arterial and venous thromboembolic events, ie, deep venous thromboses, pulmonary embolisms, and strokes, based on imaging studies (CT, echo-Doppler, scintigraphy), and/or documentation in the discharge report. Further, the presence of hemolysis at the time period between AIHA diagnosis and occurrence of thromboembolic complications as well as the presence of hereditary and other acquired thrombophilia, such as factor V Leiden mutation, prothrombin 20 210 mutation, protein C, S, and antithrombin deficiency have been documented. Data on anticoagulant prophylaxis and therapy have been extracted from the patient files.
3 | RESULTS

3.1 | Demographic, clinical, and laboratory characteristics of AIHA patients at diagnosis

Following strictly the study inclusion criteria, 82 patients have been identified. Due to refusal of general informed consent, five patients had to be excluded from the study. Finally, 77 patients have been included in our study (Figure 1). From these 77 patients in six patients, primary laboratory parameters have been available in the laboratory information system for AIHA diagnosis. Due to the absence of primary laboratory data, in 71 of the included patients, the diagnosis of AIHA is based on the medical discharge report only. From these patients, the medical discharge report revealed laboratory data on hemolysis in 86% (n = 61) of the patients. In 15% (n = 11) of the patients, no laboratory data on hemolysis have been mentioned in the discharge report (for details see Table S1). There were 45 men and 32 women, with a median age of 72 years (range 26-91 years). At the time of data analysis, 13 patients have died, three because of a malignancy (pancreatic carcinoma, chronic lymphocytic leukemia (CLL), hepatocellular carcinoma (HCC)), three because of an infection and seven without a documented cause of death. Primary and secondary AIHA was diagnosed in 44% and 56% of the patients, respectively. Lymphoproliferative disease (42%), autoimmune disease (33%), and infection (19%) were the most frequent diseases associated with secondary AIHA. In the case of autoimmune diseases, 29% suffered from systemic lupus erythematosus (SLE), 14% from autoimmune hepatitis, 7% from immune thrombocytopenia (ITP), 7% from common variable immunodeficiency (CVID), and 7% from ulcerative colitis. Evans syndrome, the concomitant presence of ITP and AIHA, has been found in 36% of the patients. Lymphoproliferative diseases included CLL (50%), M. Waldenström (33%), follicular lymphoma (6%), non-CLL-like MBL (6%), and non-specified mature B-cell-non-Hodgkin lymphoma (6%). Infections related to AIHA were viral infections (38%), pneumonia due to influenza (12%), Mycoplasma pneumoniae (12%), and bacteremia (25%, S. aureus/K. oxytoca). In 12% of the patients, vaccination against pneumococci (pneumovax®) was identified as cause of secondary AIHA. Acute myeloid leukemia and drugs were found as additional causes of AIHA (5% and 2%, respectively). The serological and laboratory characteristics of all included patients are indicated in Table 1.

3.2 | Applied therapies

The number of therapy lines and the specific treatments applied in the different AHIA types are indicated in Table 2. The vast majority of patients suffering from WA-AIHA have been treated with steroids in first line (78%). Two patients underwent splenectomy as first-line therapy. Due to lack of responsiveness or relapse, about half of the
patients with WA-AIHA required a second-line therapy. In 46% of the CA-AIHA, “watch and wait” was the initial therapy. Interestingly, in 30% of the patients, steroids only and 24% of the patients received a rituximab-containing regimen (single agents or combinations) as first-line therapy. Corticosteroid was the first treatment of choice in most cases of mixed and atypical AIHA.

### 3.3 Thromboembolic events and AIHA

Of the 77 included patients, 20 (26%) suffered from TEE (Table 3). The occurrence of TEE in primary AIHA (n = 34; 11 with TEE) as compared with secondary AIHA (n = 43, 9 with TEE) was comparable (odds ratio 1.8, CI 0.65-5.04). Eighty percent of the TEE occurred in WA-AIHA patients 10% in CA-AIHA and the remainder of cases equally distributed in mixed and atypical AIHA patients, respectively. There was no difference in the occurrence of TEE in patients with primary (n = 21) and secondary (n = 30) WA-AIHA (odds ratio 1.6, CI 0.35-3.86). Looking to the subgroups of secondary WA-AIHA, there was also no difference regarding TEE between primary WA-AHIA and secondary WA-AHIA due to underlying neoplasm or autoimmune disease (data not shown). In primary CA-AIHA, two out of six patients suffered from TEE (30%) whereas none of the patients with secondary CA-AIHA experienced TEE. The median time from AIHA diagnosis to the TEE event was 17.5 months (range 0-144 months). Seven of the 20 TEE (35%) have been diagnosed at the time point of AIHA diagnosis (±2 months). Three of the cases of TEE

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**Table 1 Clinical and laboratory characteristics of different AIHA serological type**

|                      | WA-AIHA | CA-AIHA | mixed AIHA | atypical AIHA |
|----------------------|---------|---------|------------|---------------|
| n (%)                | 51 (66) | 13 (17) | 5 (7)      | 8 (10)        |
| Age                  | 71 (26-91) | 71 (36-89) | 63 (50-80) | 71 (28-85)   |
| Gender               | 31 (61) | 7 (54)  | 1 (20)     | 6 (75)        |
| Etiology             | 21 (41) | 6 (46)  | 4 (80)     | 3 (37)        |
| Hb (g/L)             | 70 (38-123) | 85 (61-122) | 94 (20-71) | 72 (55-106)  |
| LDH (U/L)            | 932 (446-3040) | 578 (379-2548) | 673 (220-1536) | 1385 (650-3563) |
| Total Bilirubin (µmol/L) | 40 (9-192) | 46 (31-62) | 51 (20-71) | 45 (18-90)    |

**Table 2 Applied treatments in AIHA patients**

|                      | WA-AIHA | CA-AIHA | mixed AIHA | atypical AIHA |
|----------------------|---------|---------|------------|---------------|
| Watch and wait, n (%)| 4 (8)   | 6 (46)  | 1 (20)     | 3 (38)        |
| First-line therapy   |         |         |            |               |
| Corticosteroids, n (%)| 40 (78) | 4 (30)  | 4 (80)     | 5 (62)        |
| + Rituximab           | 2 (4)   | 1 (8)   |            |               |
| + Rituximab & Other   | 1 (2)   |         |            |               |
| + Rituximab & Chemotherapy | 1 (8) |         |            |               |
| + Chemotherapy        | 1 (2)   |         |            |               |
| Rituximab, n (%)      | 1 (2)   | 1 (8)   | 0 (0)      | 0 (0)         |
| Chemotherapy, n (%)   | 0 (0)   | 0 (0)   | 0 (0)      | 0 (0)         |
| Other, n (%)          | 2 (4)   | 0 (0)   | 0 (0)      | 0 (0)         |
| Therapy lines, n (%)  |         |         |            |               |
| 1                     | 24 (47) | 6 (46)  | 2 (40)     | 3 (38)        |
| 2                     | 14 (27) | 1 (8)   | 2 (40)     | 1 (12)        |
| 3                     | 8 (16)  |         | 1 (12)     |               |
| 4                     | 1 (2)   |         |            |               |
| Splenectomy, n (%)    |         |         |            |               |
| First line            | 2 (4)   |         |            |               |
| Second line           | 2 (4)   |         | 1 (20)     |               |
occurred more than 10 years after the diagnosis, one of them during a relapse. In 50% of the patients, active hemolysis was present at the time point of TEE. No sufficient data to diagnose ongoing hemolysis at the time point of the TEE was available in 40% of the patients. Thrombophilia screening performed in 9 (45%) of the patients with TEE, revealed APS in two cases. However, in 55% of the patients, no thrombophilia screening has been performed. Eighty percent of the patients with TEE had concomitant corticosteroid therapy at the time of TEE. Forty percent of patients have been treated with DOACs, 35% with VKA, 10% with LMWH, and 5% with UMWH, respectively.

Of the 13 patients who died, nine suffered from a TEE. Although this is statistically significant (odds ratio: 10.8, CI: 2.8-41.5; Table S1), none of the deaths could be clearly associated with the TEE. Of these nine patients, two died because of a malignancy (HCC and pancreatic carcinoma), three died due to an infection and in four patients the cause of death has not been documented in the patient history. At the time point of TEE, three of these nine patients had evidence of ongoing hemolysis.

Ten patients had therapeutic anticoagulants for atrial fibrillation, two patients under therapeutic anticoagulants suffered from TEE. According to the reports, none of the remained 67 included patients received thrombosis prophylaxis.

We compared the hemolysis laboratory parameters in patients with and without TEE, respectively (Table 4). There was no significant difference in hemolysis parameters in patients with and without TEE. The individual patients with AIHA complicated by TEE are represented in supplementary data Table S3. Further information on the anticoagulation after the TEE is represented in supplementary data in Table S4.

3.4 | Complement and thromboembolic events

Based on the monospecific DAT for complement, 44 (64%) of 69 patients had evidence of complement activation. In eight patients, no information about the monospecific DAT was available. These patients have been excluded from the statistics. Twelve of the 44 patients with positive DAT for complement suffered from TEE (27%), whereas 73% did not suffer from TEE. Interestingly, 71% of the patients with a TEE had complement deposition in the DAT, whereas 62% without TEE had evidence of complement deposition (OR 1.5; confidence interval 0.5-4.9). In WA-AIHA, 69% of the patients with a TEE had a positive DAT for complement, whereas 53% of the patients without TEE had complement deposition (OR 1.97; confidence interval: 0.5-7.8).

4 | DISCUSSION

The serological characteristics of the AIHA patients included in the present study are comparable with other studies. WA-AIHA was the most prominent form accounting for 80% of the cases, followed by CA-AIHA. The majority (78%) of the patients suffering from WA-AIHA have been treated with steroids in first line, which is in accordance with the recently published recommendations. Less than half of the patients received at least a second-line therapy. In contrast, "watch and wait" strategy has been applied in nearly half of the patients with CA-AHIA. Interestingly, steroids have been chosen in 30% of the patients with CA-AIHA, and only 1 patient received combined immunotherapy including rituximab. Immunochemotherapy (rituximab with either fludarabine or bendamustine) in patients with cold agglutinin disease has been shown to result in response rates up to 76% and is now considered the standard first-line therapy in symptomatic patients. The value of steroids in that situation is debatable and the evidence for its...
efficacy is low. However, patients in our study have been treated before the publication on the efficacy of immunotherapy in CA-WHA which may explain this discrepancy.

In the present study, we identified 26% of the included patients with primary or secondary AIHA to suffer from thromboembolic complication. This incidence of TEE is in line with the data from the literature reporting an incidence between 11% and 27%. TEE are better studied in WA-AIHA as compared with other forms of AIHA. Accordingly, in the current study, most TEE were found in warm AIHA. In the literature, primary and secondary AIHA are associated with a similar risk of TEE, which is in line with our data. Although one might consider underlying malignancy, such as lymphoproliferative disorders, additionally increases the thrombophilia risk. We did not find a difference in the occurrence of TEE in patients with primary and secondary WA-AIHA, respectively. In addition, 2 out of 6 suffering from primary CAD suffered from TEE, whereas no patient out of 7 with secondary CAD suffered from TEE. Together, our data are not in line with this hypothesis. However, due to the low number of patients in the different subgroups, statistical evaluation remains difficult, and these results should be interpreted with care. In the literature, primary and secondary AIHA are associated with a similar risk of TEE. We did not find any correlation with complement activation as evidenced by positivity for complement in the monospecific DAT (Table S4). In the literature, the relationship between hemolysis parameters (Hb, bilirubin, LDH), and the TE risk is controversially discussed. In a large AIHA patient cohort, an association between TEE, low Hb (<8g/dL) at onset and higher median LDH level could be shown. This was also confirmed in a case-control study in which patients with a TEE had a significant lower Hb level during follow-up in contrast to the patients without a TEE. In contrast, no association between Hb levels and TEE could be found in another study. In the present study, the data suggested that there was no correlation between hemolysis parameters and TEE. However, we have to point out that active hemolysis was confirmed in only 50% of the AIHA patients suffering from TEE, whereas in the other 50% hemolysis data were incomplete. This is in part due to the fact that for a considerable number of patients AIHA diagnosis was extracted from the patients’ discharge report since no laboratory values have been available anymore.

There is a body of literature describing the relationship between complement activation and thrombosis. Uncontrolled complement activation due to inadequate regulation of the alternate pathway of complement with subsequent (intravascular) hemolysis as seen in PNH is considered to be the most thrombophilic condition. A considerable percentage of AIHA is characterized by complement activation as evidenced by a positive monospecific DAT for C3c and/or C3d, respectively. A possible relationship between complement activation and thrombophilia in CAD is illustrated by a study reporting 1 and 5 years after diagnosis TEE in 7.2% and 11.5% of the CAD patients as compared with 1.9% and 7.8% in matched controls, respectively. A recent retrospective study even reported an occurrence of TEE in 29.6% of CAD patients as compared with 17.6% in control patients over a time period of 10 years. Besides complement, especially intravascular hemolysis may lead to the release of cell-free hemoglobin, heme, and iron, which upon release exert strong procoagulant effects on endothelial cells, neutrophils, and platelets and may compromise the function of anticoagulants.

One has to appreciate that the majority of patients included in this study suffered from WA-AIHA and not CA-AIHA. However, 70% of the patients in the current study with WA-AIHA had evidence of complement activation based on positivity for monospecific DAT for C3d that could suggest a probable role of complement in the development of TEE. However, we could not demonstrate this relationship in our patients. We have to point out that DAT positivity for complement indicate local complement activation with subsequent complement deposition on erythrocytes, but does not necessarily indicates systemic complement activation. In none of the patients, data on systemic complement consumption as reflected by decreased C4 antigen levels or complement activation as reflected by complement activation products, eg, C4b/c, have been available. In addition, a negative DAT in the presence of hemolysis does not definitively rule out AIHA. DAT negativity in these cases could be due to low-affinity antibodies and/or the amount of autoantibodies bound is beyond the threshold of the applied test.

Since we screened our patients on

|            | TEE n = 20 | No TEE n = 57 | p-Value |
|------------|------------|---------------|---------|
| Hb (g/L)   |            |               |         |
| Median (range) | 70 (40-123)| 75.5 (38-123)| .910    |
| Missing data, n (%) | 5 (25)   | 11 (19)       |         |
| LDH (U/L)  |            |               |         |
| Median (range) | 1442 (446-3563) | 934.5 (220-2950) | .137    |
| Missing data, n (%) | 9 (45)    | 19 (33)       |         |
| Total Bilirubin (µmol/L) |       |               |         |
| Median (range) | 46 (9-132) | 41 (14-192) | .914    |
| Missing data, n (%) | 9 (45)    | 22 (39)       |         |

Abbreviations: AIHA, autoimmune hemolytic anemia; Hb, hemoglobin; LDH, lactate dehydrogenase; TEE, thromboembolic event.

Groups have been compared using Mann–Whitney rank-sum test, p < .05 considered statistically significant.
DAT positivity, patients with DAT negative AIHA are not included in the current analysis. Based on these findings, we cannot provide evidence that complement activation in our study clearly contributes to the development of TEE.

The current study has another important limitation. It is a retrospective study including patients over the last 26 years. Inherent to this design, there is a considerable risk that the data set is incomplete. Indeed, we could not rely on the primary laboratory data extractable from the laboratory information system of most patients included in our retrospective study. We were mainly dependent on the AIHA diagnosis and on the laboratory values documented in the medical discharge report in 92% of the patients included in this study. From these patients, in 15%, no laboratory data have been available in the medical discharge report at all. At least one up to four laboratory parameters needed for diagnosis of hemolytic anemia could be extracted in 85% of these patients (see Table S1). However, in many cases, one could not trace back on whether these reported laboratory analyses have been made at diagnosis or in the course of the disease. This also impressively illustrates indirectly the shortcoming in clinical practice to properly diagnose immune-mediated hemolysis by the assessment of DAT together with biochemical parameters indicative for hemolysis, such as increased LDH, increased total bilirubin, decreased or not detectable haptoglobin, and finally also reticulocyte count. In addition, there was also scarce information on supportive medication and the transfusion history.

In summary, the results of this current retrospective study are in accordance with other studies where the risk of a TEE is increased in patients with the diagnosis of AIHA. Due to the high incidence of TEE in patients with AIHA, prophylactic anticoagulation might be considered as soon as the diagnosis of AIHA is confirmed.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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