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Review

Venous thromboembolism related to warm autoimmune hemolytic anemia: A case–control study

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ABSTRACT

Background: The risk of venous thromboembolism (VTE) during warm autoimmune hemolytic anemia (wAIHA) is apparent in several published series. Unlike proximate disorders (autoimmune thrombocytopenia, non-immune hemolytic diseases) little is known about the presentation and risk factors for VTE in this setting.
Objective: To determine the frequency, presentation and risk factors for VTE associated with wAIHA.
Methods: We performed a single center retrospective study of adult patients (>18 years) followed for wAIHA between 2009 and 2013. VTE risk factors were systematically assessed. The characteristics of patients with or without VTE were compared. VTE presentation and precipitating factors were analyzed. The Padua VTE risk score was calculated in each case.
Results: Forty patients were included. wAIHA was idiopathic in 24 patients (60%). Twelve patients (30%) had Evans syndrome. Mean lowest hemoglobin level was 6.6 g/dl [3.7–11.5]. Eight patients (20%) presented VTE after the appearance of wAIHA, at a mean age of 52.5 years. All patients had pulmonary embolus, associated with a deep venous thrombosis in 4 cases. At the time of VTE 7/8 patients had frank hemolysis (median hemoglobin level: 7 g/dL) and 6/8 were outpatients with a low Padua VTE risk score. The frequency of usual VTE risk factor was similar in cases and controls. By contrast, lowest hemoglobin level was significantly lower in patients that experienced VTE (5.3 vs 7.2 g/dL, $p = 0.016$). During the first episode of wAIHA, patients with concurrent VTE had a more pronounced anemia (5.3 vs 7.4 g/dL, $p = 0.026$). At the time of VTE, anemia was more severe when no other precipitating factor was present (6 vs 8.9 g.dL, $p = 0.04$).
Conclusion: In our cohort, 20% of patients with wAIHA presented VTE. The vast majority of VTE occurred during severe hemolytic flares and were not attributable to usual VTE risk factors. VTE prophylaxis is advisable in any patient admitted for wAIHA, irrespective of Padua VTE risk score. Prophylaxis also seems reasonable for outpatients with marked hemolysis.

Contents

Abbreviations: AIHA, autoimmune hemolytic anemia; APL, antiphospholipid antibodies; CLL, chronic lymphocytic leukemia; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; wAIHA, warm autoimmune hemolytic anemia.

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1. Introduction

Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disorder in which auto-antibodies directed against red blood cell surface antigens induce hemolysis. The estimated incidence in adults is 0.8–3 per 10^5/year [1]. Autoimmune hemolytic anemia due to warm antibodies (wAIHA) accounts for 75% of all AIHAs in adults [2]. wAIHA may be secondary to various conditions such as lymphoproliferative diseases, autoimmune disorders (mainly systemic lupus erythematosus), primary immunodeficiencies, chronic viral infections, solid tumors or drugs [2]. However, wAIHA is idiopathic in 50% of cases.

The increased risk of venous thromboembolism (VTE) associated with autoimmune diseases is an increasing matter of concern [3]. In AIHA, it has been suspected since the 1960s, when Allgood et al. found that pulmonary embolus (PE) was the main cause of death in their patients [4]. VTE risk has been well studied in proximate diseases such as non auto-immune hemolytic disorders [5–7] and idiopathic thrombocytopenic purpura (ITP) [8–10], in which several risk factors have been identified, such as splenectomy. By contrast, the incidence, presentation, pathogenesis and risk-factors for VTE in AIHA remains poorly delineated [11]. Interestingly, several veterinary studies performed in dogs suffering wAIHA also identified VTE as an important source of mortality and suggested a causal relationship [12–14]. The aim of our study is to analyze the frequency, presentation and risk factors for VTE in patients with wAIHA.

2. Methods

2.1. Study population

This single-center retrospective study was performed in Nantes University Hospital (France). It has been declared to the French data protection authority (Commission Nationale Informatique et Liberté) and was approved by our local ethic committee.

All patients that had a direct antiglobulin test performed at our institution between January 2009 and April 2013 were screened for inclusion in the study. The eligibility criteria were as follows: (1) diagnosis of AIHA defined by hemoglobin < 12 g/dl with features of hemolysis (low haptoglobin level) with no other cause (2) a positive IgG or IgG + C3d direct antiglobulin test (DAT) (3) age > 18 years at inclusion. Since they frequently exhibit hemorheologic abnormalities, a monoclonal IgM and a distinct clinical course, patients with cold agglutinin disease or C3d-type only positive DAT were excluded. Similarly, because of their intrinsic VTE risk and the multifactorial nature of anemia in these settings, cases presenting with solid malignancy, high-grade lymphoproliferative disease, myelodysplastic and/or myeloproliferative disorders were excluded. Patients with stage A chronic lymphocytic leukemia were not excluded.

2.2. Data collection

Eligibility criteria were verified by two investigators (JG and MLD). Chart review and anonymized data collection were performed using a standardized form (MLD). VTE presentation and risk factors were systematically recorded. The latter included personal or family history of VTE, smoking, combined oral contraceptive, menopausal hormone therapy, body mass index > 30 kg/m^2, respiratory or cardiac deficiency, venous insufficiency, splenectomy, active malignancy and antiphospholipid antibodies (APL). Biological features at diagnosis, lowest hemoglobin level during follow-up, treatment and number of relapses were recorded. Relapses were defined by the reappearance of hemolytic anemia <10 g/dL leading to a therapeutic intervention.

All patients and/or general practitioners were asked for history of VTE, including lower limb deep vein thrombosis (DVT) and pulmonary embolism (PE). Superficial vein thromboses and intra-abdominal venous thromboses (i.e. post-splenectomy portal vein thrombosis) were not studied. For patients with VTE, a triggering factor for thrombosis was searched and Padua Prediction Score Risk Assessment for VTE score was calculated, using the following baseline features: active cancer, previous VTE (with exclusion of superficial vein thrombosis), reduced mobility, already known thrombophilic condition, recent trauma or surgery, age > 70 years, heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity with BMI > 30 kg/m^2 and ongoing hormonal treatment [15].

2.3. Literature review

A Pubmed (NCBI) search was performed in order to identify case series that reported the frequency of VTE in patients with AIHA. Database search terms were “venous thromboembolism”, “pulmonary embolism”, “deep vein thrombosis”, “thrombosis”, “auto-immune hemolytic anemia” and “hemolysis”. References of all relevant articles were also checked.

2.4. Statistical analysis

Descriptive statistics included mean (95% confident interval) or median (range) as indicated for continuous variables and frequency (percentage) for categorical variables. Univariate analysis involved χ^2 or Fischer exact test as appropriate to compare categorical variables and the nonparametric Mann–Whitney test to compare continuous variables. Significant difference was considered as $P < 0.05$. Data analysis was performed using the open-source R software R (Package 2.37–4) [16].