Hairy cell leukaemia and venous thromboembolism: a case report and review of the literature

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Introduction

The interplay between cancer and venous thromboembolism (VTE) has long been recognised[1]. VTE typically occurs in patients with active cancer but may also be the first sign of an underlying neoplasm[1]. In the last few years, there has been a particular focus on the risk of occult malignancy in patients with unprovoked VTE, and the clinical usefulness of cancer screening in these cases remains controversial[2]. Interestingly, there is evidence of increased long-term risk of cancer even in patients without prevalent malignancy[3,4].

Hairy-cell leukaemia (HCL) is an uncommon type of mature B-cell neoplasm with an indolent course. It is usually characterised by progressive anaemia and pancytopenia, marked splenomegaly, and rare circulating tumour cells with hairy-looking projections and unique immunophenotypic features[5]. HCL is generally diagnosed when there is heavy infiltration of bone marrow, spleen, and liver by leukaemic cells.[5] However, a few cases of HCL diagnosed at earlier stages have been reported, presenting with atypical findings such as leucocytosis[6].

Despite evidence of increased risk of VTE in lymphoid neoplasms, the association between HCL and VTE has been poorly defined, in part due to the rarity of the malignancy. In the present report, we discuss the case of a patient diagnosed with HCL 3 years following an episode of unprovoked VTE and presenting with unusual clinical features.

Case report

A 45-year old man presented with a 2-week history of worsening fatigue, palpitations, and mid-dorsal back pain. He had been well until 3 years before this evaluation, when he experienced a pulmonary embolism without apparent precipitating factors. He had no hypertension, diabetes mellitus, family or personal history of venous thrombosis and was not a smoker. On evaluation at that time, the physical examination was unremarkable; the findings of the complete blood count, biochemical profile, serum protein electrophoresis and erythrocyte sedimentation rate were normal. Measurement of protein C, protein S, and antithrombin levels, a coagulation assay for lupus anticoagulant, an immunological analysis for anticardiolipin and anti-β2-glycoprotein I antibodies, testing for activated protein C resistance and a genetic analysis for prothrombin G20210A mutation did not reveal any abnormalities. The plasma homocysteine level was 62.2 μmol/L (normal range, 0 to 15 μmol/L). Abdominal ultrasonography and contrast-enhanced computed tomography of the chest did not reveal evidence of an underlying neoplasm. The patient started treatment with warfarin and folic acid supplementation. After 12 months, warfarin was discontinued. During follow-up, repeated measurements of plasma homocysteine levels were normal.

One week before current presentation he reported an episode of self-limiting epistaxis. Laboratory tests revealed thrombocytopenia and an elevated alanine aminotransferase level and he was referred to our centre for further evaluation. On examination, he had a palpable liver edge at about 2 cm below the right costal margin and no enlarged spleen. Tests for antibodies against human immunodeficiency virus, hepatitis B and hepatitis C were negative; other test results are shown in Table I.

A peripheral blood smear revealed 40% abnormal lymphocytes with abundant pale-blue cytoplasm, oval or indented nuclei, fine chromatin, and circumferential cytoplasmic projections. Similar abnormal lymphocytes were also evident on microscopy examination of bone marrow aspirate. The bone marrow biopsy showed a diffuse (~90%) infiltrate of small lymphoid cells with the same morphology as those found in blood, with increased reticulin fibres. Immunophenotypic analysis revealed that tumour cells were κ surface Ig light-chain-restricted, sIgD+, CD19+, CD20+, CD22+, CD25+, FMC7+, CD103+, ANXA1+, CD5−, CD10−, CD23−, and CD38−. Cytochemical staining was positive for tartrate-resistant acid phosphatase.

Based on these findings, the patient was diagnosed with HCL. Computed tomography staging did not reveal abdominal lymphadenopathy. Conventional cytogenetics showed a normal karyotype; fluorescence *in situ* hybridisation revealed that 5.7% of analysed cells had aberrant rearrangements within the immunoglobulin heavy variable (IGHV) region gene.

Blood Transfus 2014; 12: 276-9 DOI 10.2450/2014.0248-13

Table I - Laboratory data.

Variable	Patient, HCL diagnosis	Reference range, male adults
Haematocrit (%)	47.4	40 - 51
Haemoglobin (g/dL)	16.5	13 - 17
Erythrocyte count (per mm^3)	5,100,000	4,4-6,3×10^6
White blood cell (per mm^3)	8,230	4,000-10,000
Differential count (%)		
Neutrophils	18	40-80
Lymphocytes	70	20 -40
Monocytes	2	2-10
Eosinophils	0	1.0-6.0
Basophils	0	0.3-1.0
Platelet count (per mm^3)	68,000	202,000
Immature platelet fraction (%)	8.7	0-1.7
Erythrocyte sedimentation rate (mm/h)	1.0	2-20
Lactate dehydrogenase (IU/L)	384	240-480
Uric acid (mg/dL)	7.4	2.4-7.0
Creatinine (mg/dL)	1.14	0.50-1.10
Homocyteine (µmol/L)	13.5	0-15
Serum protein electrophoresis	Normal pattern	
Lupus anticoagulant	Absent	
Anti-cardiolipin IgG (GPL/mL)	9.0	<20
Anti-cardiolipin IgM (MPL/mL)	12.0	<20
Anti-β2-glycoprotein I IgG (GPL/mL)	14.0	<20
Anti-β2-glycoprotein I IgM (MPL/mL)	8.3	<20

The patient was treated with pentostatin at a dose of 4 mg/m^2 every 2 weeks for six cycles, followed by two further consolidation doses. Prophylactic-dose low-molecular weight heparin (LMWH) was recommended for the duration of chemotherapy. After six cycles, he had a symptomatic recurrence of VTE (thrombosis of left superficial femoral and popliteal veins, and bilateral pulmonary embolism) and a therapeutic dose of LMWH dose was prescribed. The serum level of homocysteine was 13.1 µmol/L.

The peripheral blood count normalised early in the course of treatment, and bone marrow morphology confirmed complete remission after therapy, with minimal residual disease detected by immunohistochemistry. Long-term warfarin treatment was then resumed. Twenty-four months after diagnosis, the patient remains in complete remission without clinical evidence of relapse or recurrent VTE.

Discussion and review of literature

HCL is a rare disease that accounts for approximately 2% of lymphoid leukemias[5]. Most patients present with an enlarged spleen, pancytopenia, bone marrow fibrosis, and few neoplastic cells in the peripheral blood. Immune dysregulation may account for recurrent opportunistic infections, vasculitis and other autoimmune disorders[5,7]. Recently, the BRAF V600E mutation has been identified in nearly all patients with HCL, thus providing a novel diagnostic tool and therapeutic target[8].

Here we report a case of HCL with several distinctive features, including absence of anaemia and splenomegaly, a large number of circulating tumour cells, and association with recurrent VTE.

In the spleen, hairy cells infiltrate the red pulp cords diffusely; the liver may also show infiltrates of tumour cells, predominantly in the sinusoids[5]. Splenomegaly is present in about 80% of patients but is apparently less common in HCL variant[9]. Normal spleen volume, leucocytosis and a high number of circulating tumour cells have also been associated with early phases of the disease and may raise a diagnostic challenge[6,10]. Given the increasing indication of haematological screening in the course of peripheral cytopenia, it could be hypothesised that the classical presentation of HCL will be observed less frequently because of a higher number of patients diagnosed at earlier stages.

Pancytopenia is typically progressive and results from bone marrow failure caused by leukaemic infiltration, cytokines that suppress haematopoiesis and reticulin fibrosis, as well as a consequence of splenomegaly[11]. In addition, immune-mediated cytopenias have been reported[12]. We observed minimal residual haematopoietic marrow, a large immature platelet fraction and preserved haemoglobin level suggesting that thrombocytopenia may be related to enhanced peripheral destruction of platelets rather than bone marrow failure[13]. In accordance with this hypothesis, immune thrombocytopenia has been reported in HCL[14].

In the present case, HCL was diagnosed 3 years after an unprovoked pulmonary embolism, and a recurrent VTE was recorded during treatment of the malignancy. Even though this association might be coincidental, at least three points about this relationship should be discussed.

First, there is consistent evidence that VTE may be the first symptom of an occult neoplasm[1] and, among the haematological malignancies, lymphoma was reported to be associated with the highest rates of VTE[15]. Even though an extensive screening is not routinely recommended, during the initial 6 months after a thrombotic episode a new cancer is diagnosed in up to 10% of patients[16]. The pro-thrombotic state of malignancy is due to complex interactions between tumour cells and the haemostatic system, and may also precede the clinical detectability of cancer by months or years, especially in case of indolent disorders such as HCL[1]. Acquired immune-mediated thrombophilic states have been described in association with lymphoproliferative neoplasms, including five cases of HCL[17]. In one of these cases, HCL was diagnosed during long-term follow-up after an antiphospholipid antibody-related VTE, and both HCL and antiphospholipid activity responded to chemotherapy[18]. In our patient, the diagnostic

work-up performed after VTE was unrevealing and antiphospholipid antibodies were absent. However, given the low proliferation rate of hairy cells, we cannot exclude that a minimal disease burden had been present at the time of the pulmonary embolism.

Second, there is evidence indicating that VTE may be associated with a higher long-term incidence of cancer[3,19]. Though controversial, these data suggest that VTE and cancer might share common risk factors, such as lifestyle and dietary habits, and/or underlying disorders leading to persistent inflammation and immune dysregulation[19]. As regarding antithrombotic therapy, available evidence suggests that extended treatment with warfarin is not associated with a higher incidence of cancer, and may indeed be protective[20,21]. Although the net effect of homocysteine-lowering on vascular risk is uncertain[22], folic acid supplementation is often used in patients with hyperhomocysteinemia and previous thrombosis. Concerns about possible adverse effects of folic acid therapy on cancer incidence or prognosis have been raised[23]. However, a recent, large-scale meta-analysis showed that long-term folic acid supplementation does not substantially increase the incidence of site-specific cancer[24].

Third, prophylactic-dose LMWH is recommended in outpatients with cancer who have additional risk factors for VTE such as previous thrombosis, immobilisation, hormonal therapy, angiogenesis inhibitors and immunomodulators[25]. However, this recommendation is based on moderate-quality evidence, disease-specific guidelines are lacking and there is no consensus on the optimal duration of prophylaxis. Extended follow-up of HCL patients treated with purine analogues did not record a high thrombotic burden[26-28]. In addition to traditional cancer-related risk factors, additional elements may promote VTE in HCL, including antiphospholipid antibodies, portal hypertension, erythrocytosis, thrombotic microangiopathy, platelet dysfunction, splenectomy, infections, and persistent minimal residual disease[17,29-33]. However, the relationship between these alterations and VTE in patients with HCL has been mainly anecdotal[17,34,35].

In conclusion, we reported a case of HCL presenting without classical findings of pancytopenia and splenomegaly. We suppose that these unusual features may be related to an early stage of the disease and will be more frequently encountered as the diagnosis of this malignancy continues to improve. Although evidence of clinical and molecular connections between lymphoproliferative disorders and thrombosis has been increasing, data on HCL are limited. Further investigations are needed to explore the exact incidence, risk factors, clinical impact and appropriate prophylaxis and/or treatment of VTE in patients with this rare neoplasm.

Keywords: hairy cell leukaemia, deep vein thrombosis, pulmonary embolism.

The Authors declare no conflicts of interest.

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Arrived: 9 September 2013 - Revision accepted: 20 November 2013
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