CASE REPORT

Diffuse Large Cell Lymphoma Presenting as a Sacral Mass and Lupus Anticoagulant

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A 67-year-old gentleman presented to Yale-New Haven Hospital (YNHH\textsuperscript{†}) for assessment of a supratherapeutic INR and sacral lesion. Hematologic workup revealed elevated ESR, PT, INR, PTT, and CRP, mixing studies that failed to correct, and a positive Russell Viper Venom Test (RVVT), which confirmed the presence of lupus anticoagulant (LA), a subtype of antiphospholipid syndrome (APA). Pathology of the patient’s sacral lesion revealed diffuse large B-cell lymphoma. This case provides insight into the association between APA and lymphoid neoplasm. The patient’s unique presentation is in marked contrast to other reports of APA and lymphoid malignancy, which are typically associated with elevated PTT, normal PT, minimal extranodal disease, and potential thrombotic complications. Further, treatment with Rituximab-CHOP chemotherapy led to excellent clinical response with tumor remission and normalization of PT and PTT.

INTRODUCTION

While antiphospholipid syndrome (APA) exhibits a strong association with several autoimmune disorders, it is relatively uncommon to find individuals with both APA and lymphoid-derived neoplasm. Clinically, APA and associated thrombotic events are typically correlated with solid tumor malignancies. However, there have been several case reports positing a relationship between antiphospholipid antibodies and lymphoproliferative diseases, which may be due to APA production by malignant B cells or by B cells that are activated via cytokine secretion by malignant T cells [1].

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\textsuperscript{†}Abbreviations: YNHH, Yale-New Haven Hospital; PT, prothrombin; PTT, partial thromboplastin time; LA, lupus anticoagulant; APA, antiphospholipid syndrome; R-CHOP, rituximab-cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone/prednisolone; NHL, non-Hodgkin lymphoma; RVVT, Russell Viper Venom Time.

Keywords: coagulopathy, diffuse large cell lymphoma, lupus anticoagulant, antiphospholipid syndrome, sacral lesion, R-CHOP, supratherapeutic INR
CASE PRESENTATION

A 67-year-old gentleman was seen at Yale-New Haven Hospital (YNHH) for assessment of a supratherapeutic INR and sacral lesion. The patient had been well until approximately 6 months prior, when he developed right leg pain following an episode of intermittent fevers and a sledding injury. The patient was subsequently worked up for sciatica, which led to the discovery of a sacral lesion on imaging. Pre-operative assessment prior to biopsy led to an incidental discovery of a supratherapeutic INR of 8.41, in addition to elevated ESR, PT, INR, PTT, and CRP (see Table 1). At YNHH, the physical examination was notable for mild hepatosplenomegaly, decreased right plantar-flexion (tibial nerve, S1-S2), pain with right knee flexion (sciatic nerve, L5-S2), and a 1+ right patellar reflex (L4). The patient also presented with a smooth sacral target-like lesion, 7.5 cm in diameter with blurry outlines, over the area of biopsy for which he was subsequently treated with doxycycline and hydrocortisone given a recent history of multiple tick bites.

Of note, the patient reported lethargy, intermittent low grade fevers, and a 12- to 15-pound weight loss over the past 6 months. He claimed to bruise and bleed easily while on aspirin. The patient denied Coumadin use, night sweats, back pain, chills, headaches, swollen lymph nodes or joints, dark or bloody urine, black tarry stools, jaundice, or recent changes in diet. Recent medication use included coenzyme Q10, and current medications included Losartan, HCTZ, and Centrum silver multi-vitamin. He has no known drug allergies.

DISCUSSION

Differential Diagnosis

The patient presented with a supratherapeutic INR, as well as significantly elevated PT and PTT levels. The patient noticed increased bruising and bleeding in the past several years, which coincided with the use of aspirin and coenzyme Q10. Importantly, salicylic acid inhibits prostaglandin and thromboxane synthesis, which deters platelet aggregation. Furthermore, coenzyme Q10 is a lipid soluble antioxidant, which has been proposed to increase bleeding time and decrease blood pressure [2]. The patient also recently took doxycycline for a target-like lesion due to Lyme disease. Antibiotics can change gut flora and decrease Vitamin K synthesis, potentially affecting the rate of gamma carboxylation of Factors II, V, VII, and X of the clotting cascade.

Overall, when assessing coagulopathies, it is helpful to consider inherited versus acquired etiologies as explored in Table 2. Our patient had late-onset, acute elevations of PT and PTT, making inherited disorders less likely. Possible etiologies on initial assessment include DIC, liver disease, or inhibitors of fibrinogen, factor II, V or X. The patient did not exhibit any signs of active bleeding and had a normal platelet count, making DIC less likely. Further, the patient did not manifest symptoms

Table 1. Serum Analysis

| Variable               | Reference Range | Patient’s Value |
|------------------------|-----------------|-----------------|
| WBC (per mm3)          | 4,500-11,000    | 8,600           |
| Platelets (per mm3)    | 150,000-350,000 | 260,000         |
| AST (U/L)              | 8-20            | 19              |
| ALT (U/L)              | 8-20            | 12              |
| Bilirubin (mg/dL)      | 0.1-1.0         | 0.47            |
| Albumin (g/dL)         | 3.5-5           | 3.5             |
| ESR (mm/hr)            | 1-14 (males)    | 22              |
| PT (sec)               | 10.3-13.2       | 86.2            |
| INR                    | 0.8-1.2         | 8.41            |
| PTT (sec)              | 22.1-34.0       | 66.3            |
| CRP (mg/L)             | <10             | 58.6            |
of infection or shock. Liver disease is similarly unlikely since the patient had normal LFTs, alkaline phosphatase, bilirubin, and albumin levels. Consequently, the most likely etiology is either a factor inhibitor or antiphospholipid antibody, the latter of which typically presents with only elevated PTT levels [3].

Pathological Discussion

Diagnostic workup consisted of mixing studies, Russell Viper Venom Time (RVVT) and serum analysis of factor levels, von Willebrand factor antigen, and Ristocetin Cofactor antigen. The results of each test are reported in Tables 3 and 4. While the workup for von Willebrand disease and Hemophilia A were noncontributory, the mixing studies and RVVT were particularly helpful.

A mixing study helps to differentiate between factor deficiency and inhibition. Our patient’s plasma was mixed at a 1:1 ratio with normal plasma. However, the PT and PTT values failed to normalize and remained elevated, indicating the role of a factor inhibitor. Inhibitors are commonly associated with hemophilia, lymphoproliferative disorders and other malignancies, autoimmune disease, and the post-partum state.

The RVVT utilizes the clotting cascade; specifically, venom coagulant activates factor X, which facilitates the formation of thrombin from prothrombin in the presence of factor V and phospholipid. In the RVVT, the concentration of viper venom and phospholipid are rate-limiting. Lupus anticoagulant interferes with the clotting cascade by interacting with in vitro phospholipids, and thereby prolongs the clotting time. With the confirmatory RVVT test, excessive phospholipid is added to the assay and the clot-

| Table 2. Inherited vs. Aquired Coagulopathies |
|-----------------|--------------|
| PT  | PTT  | Inherited                   | Acquired                                           |
| ↑  | ↔   | Factor VII deficiency       | Vitamin K deficiency, liver disease, and factor VII inhibitor |
| ↔  | ↑   | Hemophilias, von Willebrand disease | Factor inhibitors, antiphospholipid antibody |
| ↑  | ↑   | Fibrinogen, Factor II, or V deficiency | Disseminated intravascular coagulation, liver disease, and fibrinogen, Factor II, V, or X inhibitor |

| Table 3. Serum Factor Analysis |
|-----------------------------|
| Factor | Patient’s Level | Normal Range |
| II    | 118%            | 50-150%      |
| V     | 120%            | 50-150%      |
| VII   | 43%             | 50-150%      |
| X     | 60%             | 50-150%      |

| Table 4. Coagulopathy Diagnostic Results |
|-----------------|----------------|
| Test             | Time           | Normal        |
| PTT Mixing Study 0’ | 51.0 seconds   | -             |
| PTT Mixing Study 60’ | 60.7 seconds   | -             |
| PT Mixing Study 0’  | 50.5 seconds   | -             |
| PT Mixing Study 60’  | 48.0 seconds   | -             |
| Russell Viper Venom Time | 2.52         | 0-1.2         |
| von Willebrand Factor Antigen | 159%       | 50-150%      |
| Ristocetin Cofactor     | 187%          | 50-150%      |
| Factor VIII           | 99%           | 50-200%      |
ting time is measured. After normalizing the assay and confirmatory test, it is then possible to determine a ratio of clotting time without phospholipid excess to with phospholipid excess. Our patient’s ratio was significantly greater than the normal range of 0-1.2, indicating the presence of lupus anticoagulant (LA) [4].

**Lupus Anticoagulant**

Lupus anticoagulant, as stated, is detected based upon prolonged clotting times on assay. However, LA causes thromboembolism *in vivo*. The current understanding is that while LA interferes with both coagulation and anticoagulation, cell membranes *in vivo* are postulated to create an environment of net inhibition of anticoagulant pathways to consequently promote thrombosis. The three prevailing hypotheses for the mechanism of action include activation of endothelial cells, oxidant-mediated injury of the vascular endothelium via oxidized LDLs, and interference of the regulatory functions of prothrombin, protein C, tissue factor, and other regulators of coagulation. Typically, diagnosis of LA requires meeting one of two vascular criteria, including vascular thrombosis or obstetrics complication, and at least one of two laboratory criteria of either antiphospholipid antibodies or lupus anticoagulant antibodies. The differential diagnosis for thrombotic disorders, in general, includes but is not limited to heparin-induced thrombocytopenia, homocysteinemia, myeloproliferative disorders, and hyperviscosity. Patients with APA who have concomitant risk factors, including venous or arterial bed stasis or injury, atherosclerosis risk factors, and oral contraceptive use, exhibit an increased risk of thromboses. In rare cases, patients may present with multiple vascular occlusions that result in death or a pulmonary embolism following a venous thrombosis [5].

**Diagnosis and Treatment**

Biopsy and pathological assessment of the patient’s sacral lesion revealed diffuse large B-cell lymphoma. Standard therapy consisting of Rituximab-CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone) led to complete response, as well as normalization of PT and PTT.

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen found on the surface of both normal and malignant B lymphocytes. CD20 is expressed on more than 90 percent of B cell non-Hodgkin lymphomas (NHL) and is thought to interact with rituximab to promote complement and antibody-dependent cytotoxicity, as well as apoptosis. A critical trial revealed the strengths of treating patients with rituximab with CHOP versus CHOP alone with event-free survival at 2 years at 57 percent versus 38 percent (*p* < 0.001), overall survival after 2 years at 70 percent versus 57 percent (*p* < 0.01), and a complete response rate at 76 percent versus 63 percent (*p* < 0.01). R-CHOP, therefore, is an important treatment modality for B-cell malignancies, further supported by a decrease in reported adverse effects such as neutropenia and infections [6]. Rituximab also has been shown to be efficacious in treating a patient with APA and SLE who presented with significant thrombo-embolic events. Interestingly, long-term clinical remission was associated with the concomitant disappearance of lupus anticoagulant after 2 months of treatment with rituximab. Fewer consistent changes were noted for serum levels of anticardiolipin and B2GP1 [7].

**Antiphospholipid Syndrome and non-Hodgkin Lymphoma**

While antiphospholipid syndrome exhibits a strong association with several autoimmune disorders such as systemic lupus erythematosus (SLE), it is relatively uncommon to find individuals with both APA and lymphoid-derived neoplasm. Clinically, APA and associated thrombotic events are typically correlated with solid tumor malignancies. However, there have been several case reports positing a relationship between antiphospholipid antibodies and lymphoproliferative diseases, which may be due to APA production by malignant B cells or by B cells that are activated via cytokine secretion by malignant T cells [1]. Several studies
have explored the relationship between APA and non-Hodgkin lymphoma. In one study of 90 NHL patients, 24 (26.6 percent) were identified to have elevated serum APA. Interestingly, lymphoma-induced vessel compression was the most common cause of clot formation in these NHL patients. Moreover, APA positive patients with elevated antiphospholipid antibodies and anti-β2-glycoprotein-I antibodies were followed for 14 months without a single occurrence of thromboembolism. Elevated APA was detected more frequently in women and the elderly and was not correlated with the histology or stage of the lymphoma. Twelve of 24 patients (50 percent) had diffuse large B-cell lymphoma, as diagnosed in our patient [8].

However, a case report from Italy describes a patient with an APA positive peripheral T cell lymphoma that presented with deep venous thrombosis (DVT) [1]. Another Italian group reports a statistically significant association between antiphospholipid antibodies and lymphomas after correcting for age, sex, type, and stage of lymphoma, as well as supports the use of APA to identify lymphoma patients who are at increased risk to develop thrombotic complications. The study reveals that 5.1 percent of sampled APA-positive patients develop thromboses annually, compared to 0.75 percent of APA-negative patients. The Italian group did not find APA to be a useful predictor of treatment outcome or overall prognosis [9].

Yet a more recent study claims that APA may play a role as a prognostic marker in NHL. In 2006, the study revealed 41 percent of NHL patients (35/86 patients) to have elevated APA at diagnosis. The patients had a statistically significant, shorter 2-year survival time at 63 +/- 11 percent, compared to 90 +/- 5 percent for patients without APA at diagnosis. The study did not find a correlation between APA and age, sex, disease state, grade, progression, performance status, treatment choice, or response to treatment [10].

Another analysis consisting of 22 NHL patients, of whom nine (40.9 percent) were positive for elevated APA, were assessed for response to treatment. Interestingly, all patients who responded to treatment exhibited normalization of their APA titers, while non-responders retained elevated APA levels [11]. Though various treatment modalities have been attempted, the use of R-CHOP has been shown to be effective in treating several patients with APA-positive large B-cell lymphoma via published case reports [12-13]. Further, one case report describes the development of systemic thromboses despite radiologically proven resolution of a lymphoma upon treatment with only CHOP chemotherapy without rituximab [14].

CONCLUSION

This report describes the presentation of large-cell lymphoma and acquired lupus anticoagulant as a lower extremity pain following a recent sledding injury and provides insight into the association between APA and lymphoid neoplasm. The patient in this vignette presented with a sacral mass and elevated PT and PTT levels and was ultimately diagnosed with diffuse large B-cell lymphoma. Interestingly, the patient’s tumor was early stage with extranodal disease. The patient did not sustain any thrombotic events and underwent a sacral biopsy and porta-catheter placement without bleeding. This unique presentation is in marked contrast to other reports of APA and lymphoid malignancy, which are typically associated with elevated PTT, normal PT, minimal extranodal disease, and potential thrombotic complications [1,3,5,9,10]. Further, treatment with R-CHOP led to excellent clinical response with tumor remission and normalization of PT and PTT. A PET scan confirmed complete response to R-CHOP prior to consolidation with radiation therapy at a time point corresponding with the disappearance of APA levels, thereby indicating a correlation between APA and lymphoid neoplasm. Overall, it would be interesting to further explore the role of rituximab in treating APA as it is unclear whether the drug acts directly on APA, elicits an indirect response by treating an underlying malignancy, or promotes a combination of both mechanisms.
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