

Preoperative Coagulopathy as a Diagnostic Clue to Lupus Anticoagulant Associated with Hidden Marginal Zone Lymphoma: A Case Report

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Case Report

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Abstract

Marginal Zone Lymphoma encompasses a heterogeneous clinical and histopathological entity that originates from B cells in the marginal zones of lymphoid tissues. This article presents an initial, unexpected case of Mantle Zone Lymphoma, characterized by prolonged prothrombin time (PT) and partial thromboplastin time (PTT) before elective cataract surgery rather than the typical lymphoproliferative signs and symptoms. The patient was diagnosed with Marginal Zone Lymphoma associated with lupus anticoagulant antibodies and received R-CVP (rituximab, vincristine, and cyclophosphamide) chemotherapy protocol. As such, this article highlights the association between malignancies and coagulation abnormalities that clinicians should be aware of in order to tailor anticoagulation therapy. This case underscores the importance of a structured diagnostic approach to prolonged coagulation studies, particularly the use of mixing studies and lupus anticoagulant testing to differentiate clotting factor deficiencies from the presence of an inhibitor.

Key Clinical Message

Occult lymphoma may present as an unexplained coagulopathy rather than with the typical lymphoproliferative symptoms and a comprehensive and structured coagulation studies assessment may reveal clinically silent but significant clinical conditions.

Introduction

Marginal zone lymphoma (MZL) is an indolent B-cell tumor that is typically diagnosed in the seventh decade of life. It encompasses a heterogeneous group of neoplasms (extranodal MALT, splenic, and nodal subtypes) that develops in the marginal zone of lymphoid tissues. MZL represents approximately 7% of all Non-Hodgkin lymphomas and usually have an indolent course and favorable prognosis as its five-year survival exceeds 80–90% [1]. Autoantibodies, such as antiphospholipid (aPL), including lupus anticoagulant (LA), anticardiolipin, and anti- β 2-glycoprotein I antibodies, target phospholipid-binding proteins and can cause prolonged clotting times in laboratory tests in vitro, such as the activated partial thromboplastin time (aPTT), due to interference with the coagulation assay's phospholipid reagents [2]. The simultaneous occurrence of MZL with aPL (especially LA) is uncommon [2]. Patients in such circumstances may initially report abnormal coagulation tests rather than typical lymphoproliferative symptoms. This underscores the significance of recognizing the possible link between unexplained coagulation irregularities and an underlying undiagnosed malignancy. Herein, we report the case of a patient who was initially planned for cataract surgery which was then cancelled due to abnormal coagulation studies. An extensive workup ultimately led to the diagnosis of MZL associated with lupus anticoagulant antibodies. A review of the available literature on the possible mechanisms and clinical implications of this unusual presentation of this rare disease is discussed.

Case presentation

A 63-year-old female patient (G2P2A0), non-smoker, non-alcohol drinker, presented to our clinic after being referred from the ophthalmology department. Initially, she was planned for right eye cataract surgery. However, her surgery was cancelled, as disturbed laboratory tests after the routine blood tests needed for pre-operation clearance, were found. Notably, her Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) were found to be at 12,8 seconds and 102 seconds respectively. Further laboratory results showed that she had a hemoglobin level of 10 mg/dl, a white blood count of 27k along with lymphocytes of 80% in addition to platelets of 139k. Her past medical history is unremarkable for hypertension and diabetes mellitus type 2 both of which were adequately controlled with appropriate medical treatment. Her vital signs were within normal range upon presentation, however she looked pale and fatigued. Her past surgical history is relevant for a C-section and cholecystectomy both of which were done without any complicated post-operative course, a dozen of years ago. Upon further questioning, she mentioned profuse night sweats that began 1 year ago, associated with anorexia and significant weight loss (more than 10% of her weight within 6 months). On physical exam, her sclera were pale. Auscultation revealed a regular heart rate without murmurs, with clear lung fields. Her abdominal wall was lax but a massive splenomegaly was to be noted. A Positron Emission Tomography–Computed Tomography (PET/CT) scan confirmed the enlarged spleen (16*11*26,7 cm). However, no extranodal sites had an abnormal uptake which was only limited to the bone marrow. Concerning the laboratory results, as PTT was markedly elevated without any anticoagulant use, and laboratory artefact was unlikely, and a 1:1 mixing study was therefore performed (Table 1). The mixing test fails to normalize the PTT, and the Rosner index of 36 confirms no correction after mixing. This strongly supports the presence of a circulating inhibitor, not a factor deficiency. Given the patient's lack of bleeding symptoms and the clinical context, a lupus anticoagulant was suspected (as LA is known to prolong clotting tests but typically does not cause bleeding). Furthermore, as Von Willebrand factor and Factor VIII levels were normal to high, Von Willebrand disease or factor deficiency as causes of prolonged PTT were excluded. What supported the presence of an inhibitor rather than a mere clotting factor deficiency was the incomplete correction of the PTT. The markedly elevated LA1/LA2 ratio (2.43) confirms a strongly positive lupus anticoagulant, indicating the presence of antiphospholipid antibodies that interfere with phospholipid-dependent coagulation assays (Fig. 1.). Indeed, the prolonged PTT was the initial hematologic manifestation of an underlying lymphoid neoplasm, unmasking the presence of an acquired antiphospholipid antibody.

Latterly, a Bone Marrow biopsy was performed. The cellularity was marked, formed predominantly by small cell proliferation masking the hematopoietic cells, corresponding to small lymphocytes slightly larger than normal with round nucleus, clumped chromatin. On immunohistochemistry, the neoplastic lymphoid cells were positive for CD20, CD79a, and BCL2, and negative for CD5, CD10, and Cyclin D1. Flow cytometric analysis confirmed a monoclonal B-cell population, and thereafter the diagnosis of MZL was established. Thereafter, the R-CVP chemotherapy protocol that consisted of MabThera (rituximab), vincristine, and Endoxan (cyclophosphamide) was initiated. Treatment led to remission and normalization of the coagulation parameters after 3 cycles of chemotherapy. No complications were noted after several months of follow-up and patient was in complete remission.

Table 1
Patient's Hematology and mixing studies results.

Test	Result	Unit	Reference Range
PTT - Patient	57.8	sec	[25.9–36.6]
PTT - Control	31.4	sec	[27–36]
Lupus Anticoagulant - LA1 screening reagent	85.2	sec	[31–52]
Lupus Anticoagulant - LA2 confirmation reagent	35	sec	[30–38]
Lupus Anticoagulant - Ratio LA1/LA2	2.43		Normal: 0.8–1.3; LA weakly positive: 1.3–1.5; LA moderately positive: 1.5–2; LA strongly positive: >2
Factor VIII	155	%	[70–150]
Von Willebrand Factor, Antigen	98.1	%	[50–160]
Von Willebrand Activity	150	%	Blood Group O: 40–200; Non-O blood group: 60–200
Mixing Studies for Prolonged PTT - PTT of patient plasma	57.8	sec	[25.9–36.6]
Mixing Studies for Prolonged PTT - PTT of normal plasma control	28	sec	[27–36]
Mixing Studies for Prolonged PTT - Immediate 1:1 mix	49	sec	[25.9–36.6]
Mixing Studies for Prolonged PTT - Incubated 2 h, 37°C 1:1 mix	44.1	sec	[25.9–36.6]
Mixing Studies for Prolonged PTT - Rosner index	36		< 12: Correction (factor deficiency); 12–15: Suspicious (re-test); >15: No correction (lupus anticoagulant or inhibitor)

Discussion

MZL patients usually present with symptoms related to the organ affected. For example, gastric MALT lymphoma could cause gastrointestinal symptoms as dyspepsia, nausea, vomiting, or epigastric pain [4]. Splenic MZL may be discovered due to splenomegaly on physical exam or imaging, or incidentally through lab findings as lymphocytosis or cytopenias. Some patients present with symptoms of hypersplenism or autoimmune phenomena, but many can even be asymptomatic at diagnosis [5]. Nodal MZL usually presents with painless lymphadenopathy, often disseminated, and may be found incidentally on imaging or lymph node examination. B symptoms (fever, night sweats, weight loss) are uncommon at presentation [6]. MZL cases, especially extranodal types, are sometimes discovered incidentally during procedures for unrelated conditions such as endoscopy, surgery, or imaging [7, 8]. Although prolonged PT and PTT due to the presence of lupus anticoagulant antibodies are not typical features of MZL, yet some case reports exist on such rare clinical presentation and even reports highlight rare presentations with MZL initially manifesting as SLE or vice versa [2, 9, 10, 11]. MZL in SLE can present as nodal, splenic, or extranodal (including MALT) lymphoma, sometimes mimicking or coexisting with SLE flare-ups, further complicating the diagnosis [10]. Indeed, a growing body of evidence suggests a strong association between MZL and chronic autoimmune diseases, particularly systemic lupus erythematosus (SLE). Patients with SLE have an increased risk of developing MZL, likely due to chronic immune activation and continuous B-cell stimulation, which may contribute to malignant transformation. However, up to this day, no extensive epidemiological studies have been conducted. Studies have shown a strong link between SLE and MZL, with studies indicating that SLE patients are 7.5 times more likely to develop MZL than the general population. This increased risk is believed to stem from prolonged immune activation and sustained B-cell stimulation, which are key features of autoimmune diseases. Persistent antigenic exposure may cause genetic changes, eventually leading to the malignant transformation of B-cells and lymphoma. A hypothesis can be suggested is that the mechanism of provoking the production of anti-antibody can be the malignant B-cells or the dysregulated immune environment in lymphoma (a form of paraneoplastic phenomenon). Indeed, an association between malignancy and aPL has been described and mentioned in the literature, with some studies reporting increased prevalence of aPL in cancer patients. In such cases, treating the cancer often leads to the disappearance of the autoantibodies, reinforcing the notion that the neoplasm may drive autoantibody generation [2].

Among the autoimmune markers commonly found in SLE, antiphospholipid antibodies (aPL), including lupus anticoagulant (LA), anti-cardiolipin, and anti-β2-glycoprotein antibodies, have been linked to an elevated risk of cerebrovascular disease and chronic kidney disease. The clinical significance of aPL in MZL patients remains unclear, and its impact on disease progression or treatment outcomes has not been well defined. The exact mechanism connecting MZL with the production of aPL remains uncertain. One possibility among other is that the chronic antigenic stimulation seen in lymphoproliferative disorders may promote the generation of autoantibodies.

A well-known risk factor for thrombosis is aPL (antiphospholipid syndrome); from a clinical point of view, they are also associated with complications like renal failure and stroke [3]. In general, clinicians should be mindful that lupus anticoagulant is a frequent cause of isolated aPTT prolongation; however, it can sometimes prolong the PT as well (depending on reagent sensitivity) [12]. In such cases, as this report illustrates, a stepwise laboratory evaluation with mixing studies and phospholipid-dependent clotting assays is indispensable. The coexistence of LA and MZL has contrasting implications as LA is pro-

thrombotic, whereas MZL therapy more typically causes cytopenias, infections, and infusion reactions rather than coagulopathy, and the actual risk of thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, stroke) in MZL patients with aPL remains uncertain [3]. As a result, despite the lack of standardized criteria, patients with high-titer or multiple aPL positive may benefit from increased monitoring and individualized thromboprophylaxis. In our case, no thrombosis was observed despite a positive LA, and the patient's abnormal PT/aPTT normalized after three cycles of a chemotherapy protocol—an outcome consistent with reports in which controlling the underlying lymphoproliferative disease leads to resolution of abnormal PT/aPTT.

Immunotherapy such as the anti-CD20 monoclonal antibody rituximab in combination with chemotherapy agents is one of the standard therapies for symptomatic or advanced MZL. These treatment responses rates are high and provide prolonged remissions in MZL. In our patient, treatment with a based chemotherapy not only induced lymphoma remission but also normalized the coagulation parameters after several cycles, paralleling findings from similar reports. This successful treatment of the underlying malignancy can lead to resolution of antiphospholipid antibodies and correction of coagulopathy and point to a causality rather than a simple correlation. However, how concomitant antiphospholipid antibodies (aPL), particularly lupus anticoagulant (LA), influence treatment responses or laboratory coagulation parameters (PT/aPTT) is not well documented.

Conclusion

Despite the rare coexistence of MZL and aPL, clinicians need to recognize this relationship because of their increased risk of thromboembolic complications, and consequently the tailored anticoagulant therapy needed to prevent them. Treating the lymphoma not only induced remission but also resulted in the resolution of the lupus anticoagulant. Being aware of this paraneoplastic phenomenon is particularly important; a meticulous workup of abnormal coagulation tests can unmask underlying malignancy. Further studies or case accumulations are needed to characterize better the frequency and pathophysiology of antiphospholipid antibodies in MZL. In the meantime, a high index of suspicion and a proactive multidisciplinary approach will help ensure that patients with unusual presentations receive prompt and appropriate care, improving their patient's outcomes.

Declarations

Conflict of interest

The authors declare no conflict of interest in publishing this article.

Ethical Approval:

The patient provided a written informed consent for her case to be published.

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Author Contribution

J.A, J.T., A.E.K., and W.H. contributed to the conceptualization and investigation of the case. J.A, J.T., A.E.K., and W.H. contributed to writing the original manuscript and to its review and editing. All authors contributed to validation of the work. W.H. supervised the study. All authors reviewed and approved the final manuscript.

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Data availability:

Not applicable as no new data were generated

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Figures

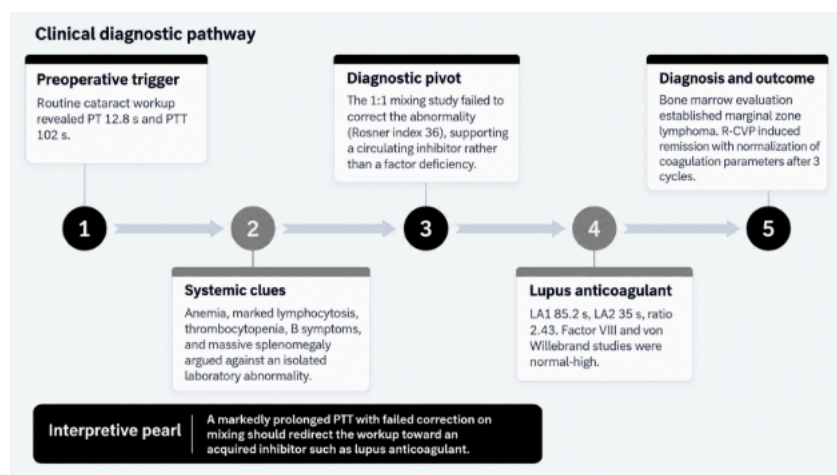


Figure 1

Diagnostic pathway of unexpected preoperative coagulopathy leading to the diagnosis of lupus anticoagulant-associated marginal zone lymphoma

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; LA, lupus anticoagulant; LA1/LA2, lupus anticoagulant screening and confirmatory assays; MZL, marginal zone lymphoma; PET/CT, positron emission tomography/computed tomography; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; Hb, hemoglobin; WBC, white blood cell count; vWF, von Willebrand factor.