

A case of lupus anticoagulant induced by bevacizumab targeted therapy after lung cancer surgery

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Case Report

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Abstract

Background: Lupus anticoagulant (LA) testing is a key component of laboratory detection for antiphospholipid antibodies, primarily used for diagnosing antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) ^[1,2], assessing venous thromboembolism (VTE) risk ^[3], and investigating unexplained prolonged activated partial thromboplastin time (APTT). Bevacizumab, a recombinant humanized monoclonal IgG1 antibody targeting vascular endothelial growth factor (VEGF), is widely used in various cancers, including non-small cell lung cancer (NSCLC) ^[4,5]. To date, no report has described bevacizumab-induced LA in lung cancer patients.

Case presentation: A 54-year-old male received cisplatin/pemetrexed chemotherapy combined with bevacizumab targeted therapy (every 21 days) for one year after lung cancer surgery. APTT remained normal throughout treatment and early post-operative period. In July 2025, during hospitalization for thyroid nodules, marked APTT prolongation was incidentally found. APTT mixing studies indicated the presence of an inhibitor. LA testing was positive (LA ratio 1.62, rising to 1.82 ten days later), while coagulation factors VIII, IX, XI, XII activities, factor VIII antibody, antinuclear antibody profile, anticardiolipin antibodies, and anti-β₂-glycoprotein I antibodies were all negative. After withholding one dose of bevacizumab, APTT and LA levels decreased significantly (LA ratio 1.39). The patient underwent uneventful thyroid surgery. Upon resuming bevacizumab, APTT prolonged again and LA increased (LA ratio 1.75). The patient had a 20-year history of clozapine use, but APTT was normal before lung cancer surgery, ruling out clozapine as the cause.

Conclusion: This is the first report of bevacizumab targeted therapy potentially inducing LA production in a lung cancer patient. The mechanism may involve VEGF inhibition leading to vascular endothelial injury, exposure of subendothelial phospholipids, and subsequent immune activation producing antiphospholipid antibodies. Clinicians should consider LA testing when encountering unexplained APTT prolongation in patients receiving bevacizumab, to accurately assess thrombotic risk and avoid misdiagnosis.

1 Introduction

Lupus anticoagulant (LA) testing is a cornerstone in the laboratory detection of antiphospholipid antibodies. It is primarily employed for diagnosing and monitoring antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) ^[1, 2], as well as for risk assessment of venous thromboembolism (VTE) ^[3] and evaluation of unexplained prolonged activated partial thromboplastin time (APTT). The “anticoagulant” effect of LA is confined to prolonging phospholipid-dependent coagulation tests in vitro; paradoxically, persistent LA in vivo is associated with an increased risk of thrombosis ^[3].

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody that inhibits angiogenesis by targeting vascular endothelial growth factor (VEGF), thereby slowing tumor growth and metastasis. It is approved for multiple cancer types, including certain subtypes of non-small cell lung

cancer (NSCLC) [4, 5]. When combined with standard platinum-based chemotherapy as first-line treatment for NSCLC, bevacizumab improves clinical outcomes without increasing the incidence of adverse reactions, underscoring its clinical value [4, 5].

Common adverse effects of bevacizumab include hypertension, proteinuria, and bleeding. However, reports of bevacizumab inducing LA are exceedingly rare, and no such case has been documented in lung cancer patients. Here, we present a case of LA development in a patient receiving adjuvant bevacizumab after lung cancer surgery, and we explore the potential underlying mechanisms and clinical implications.

2 Case Presentation

A 54-year-old man underwent video-assisted thoracoscopic left upper lobectomy with mediastinal lymph node dissection for peripheral lung adenocarcinoma (stage p-T1N0M0, IA2) in June 2024. From July 2024 to June 2025, he received adjuvant chemotherapy with cisplatin and pemetrexed disodium (every 21 days) combined with bevacizumab targeted therapy (every 21 days for a total of 16 cycles). Throughout this period and during the early postoperative phase, his APTT remained within normal range (Fig. 1).

On July 16, 2025, the patient was admitted for elective thyroid nodule surgery. Preoperative laboratory tests unexpectedly revealed significant APTT prolongation: 54.6 seconds (reference 25–37 s) on SYSMEX CS-1500 analyzer and 83 seconds (reference 26–40 s) on STAGO STAR MAX analyzer. He had a 25-year history of mental illness and regularly took clozapine tablets (4 tablets/day). On July 17, other laboratory parameters showed no remarkable abnormalities.

To investigate the APTT prolongation, a mixing study was performed on July 18. Both immediate and incubated mixing failed to correct the prolonged APTT, indicating the presence of a time-dependent inhibitor. Subsequent LA testing yielded a ratio of 1.62 (reference < 1.2); a repeat test 10 days later showed an increase to 1.82. Coagulation factor activities (VIII, IX, XI, XII) were within normal limits, and factor VIII antibody quantification was normal. Antinuclear antibody profile, anticardiolipin antibodies, and anti- β 2-glycoprotein I antibodies were all negative.

To identify the cause of LA production, the thyroid surgery was temporarily postponed. The patient consulted hematology, rheumatology, and oncology departments. The oncologist recommended withholding one dose of bevacizumab. On August 24, 2025 (three weeks after the last bevacizumab dose), APTT was rechecked: 40.3 seconds (SYSMEX) and 61 seconds (STAGO); LA ratio decreased to 1.39. On August 25, the patient underwent uneventful thyroid nodule resection and was discharged on August 28.

On September 7, 2025, bevacizumab therapy was resumed. Three weeks later (October 1), APTT was again prolonged: 47.8 seconds (SYSMEX) and 74 seconds (STAGO); LA ratio rose to 1.75. Throughout this period, the patient experienced no bleeding or thrombotic events.

3 Discussion

LA is not only detected in SLE but may also appear transiently in patients with infections, malignancies, or those taking certain drugs. The etiology of LA in our patient warrants detailed analysis.

First, the patient's APTT was normal at the time of lung cancer surgery and in the two months postoperatively, essentially ruling out LA induced by the tumor itself. Second, although clozapine, an antipsychotic agent, has been reported to induce LA ^[6], our patient had taken clozapine for 20 years with consistently normal APTT prior to lung cancer surgery; thus, clozapine is unlikely to be the cause. Third, no anticoagulant medications were used, excluding direct drug-induced coagulation factor inhibition.

The critical clue in this case is the temporal relationship between LA positivity and bevacizumab administration: LA levels decreased markedly after bevacizumab withdrawal and increased again upon rechallenge. This "on-off-on" pattern strongly implicates bevacizumab as the trigger for LA production. To our knowledge, this is the first report of bevacizumab-associated LA in a lung cancer patient.

Mechanistic considerations: The exact mechanism by which bevacizumab induces LA remains unclear, but several hypotheses can be proposed. Bevacizumab inhibits VEGF, thereby disrupting survival signals in vascular endothelial cells and leading to microvascular damage and endothelial apoptosis ^[7]. Endothelial injury can expose subendothelial phospholipids (e.g., phosphatidylserine), which are normally immunologically privileged. This exposure may trigger an immune response, activating B cells to produce antiphospholipid antibodies, including LA ^[8]. Moreover, VEGF itself possesses immunomodulatory properties; its inhibition might tilt the immune balance toward autoantibody production ^[9]. We therefore hypothesize a sequence: bevacizumab → VEGF inhibition → endothelial injury → exposure of subendothelial phospholipids → immune activation → generation of antiphospholipid antibodies (including LA).

Interestingly, our patient was positive for LA but negative for anticardiolipin and anti-β₂-glycoprotein I antibodies. This suggests that bevacizumab may preferentially induce the LA subtype of antiphospholipid antibodies rather than other subtypes. It also implies that LA testing might be more sensitive than conventional antiphospholipid antibody assays in detecting bevacizumab-related coagulation abnormalities.

Clinical implications

This case carries several messages for clinicians. First, when unexplained APTT prolongation occurs in patients receiving bevacizumab, LA should be included in the differential diagnosis, rather than simply attributing it to factor deficiency or liver disease. Second, LA positivity does not signify bleeding risk; on the contrary, persistent LA is associated with an increased risk of thrombosis ^[3]. Therefore, perioperative thromboprophylaxis should be considered on an individual basis. Finally, this case highlights the importance of multidisciplinary collaboration involving oncology, hematology, rheumatology, and laboratory medicine to comprehensively evaluate and manage such patients.

4 Conclusion

This is the first reported case of bevacizumab targeted therapy potentially inducing LA production in a lung cancer patient, demonstrating a clear “on-off-on” relationship. The mechanism may involve VEGF inhibition-mediated endothelial injury, exposure of subendothelial phospholipids, and subsequent immune activation leading to antiphospholipid antibody formation. Clinicians should be vigilant for this potential coagulation abnormality in patients treated with bevacizumab. When unexplained APTT prolongation is encountered, LA testing should be performed to accurately assess thrombotic risk and avoid misdiagnosis and inappropriate management.

Declarations

Conflict of Interest: The authors declare no conflict of interest.

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Ethics Approval and Consent to Participate: Ethics Approval and Consent to Participate: This study was approved by the Ethics Committee of Qingdao Municipal Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for Publication: The patient provided written consent for the publication of this case report.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article.

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References

1. Branch DW, Kim MY, Guerra MM, Worden J, Laskin CA, DeSancho MT, et al. Certolizumab pegol to prevent adverse pregnancy outcomes in patients with antiphospholipid syndrome and lupus anticoagulant (IMPACT): results of a prospective, single-arm, open-label, phase 2 trial. *Ann Rheum Dis.* 2025;84(6):1011–22.
2. Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. *Arthritis Rheumatol.* 2023;75(10):1687–702.

3. Diz-Küçükkaya R. Lupus anticoagulant, thrombosis, and death. *Blood*. 2015;125(22):3371–2.
4. Orillard E, Adhikari A, Malouf RS, Calais F, Marchal C, Westeel V. Immune checkpoint inhibitors plus platinum-based chemotherapy compared to platinum-based chemotherapy with or without bevacizumab for first-line treatment of older people with advanced non-small cell lung cancer. *Cochrane Database Syst Rev*. 2024;8(8):CD015495.
5. Shiraishi Y, Kishimoto J, Sugawara S, Mizutani H, Daga H, Azuma K, et al. Atezolizumab and Platinum Plus Pemetrexed With or Without Bevacizumab for Metastatic Nonsquamous Non-Small Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2024;10(3):315–24.
6. Kanjolia A, Valigorsky JM, Joson-Pasion ML. Clozaril-induced lupus anticoagulant. *Am J Hematol*. 1997;54(4):345–6.
7. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer*. 2007;96(12):1788–95.
8. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med*. 2002;346(10):752–63.
9. Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. *Nat Med*. 1996;2(10):1096–103.

Figures

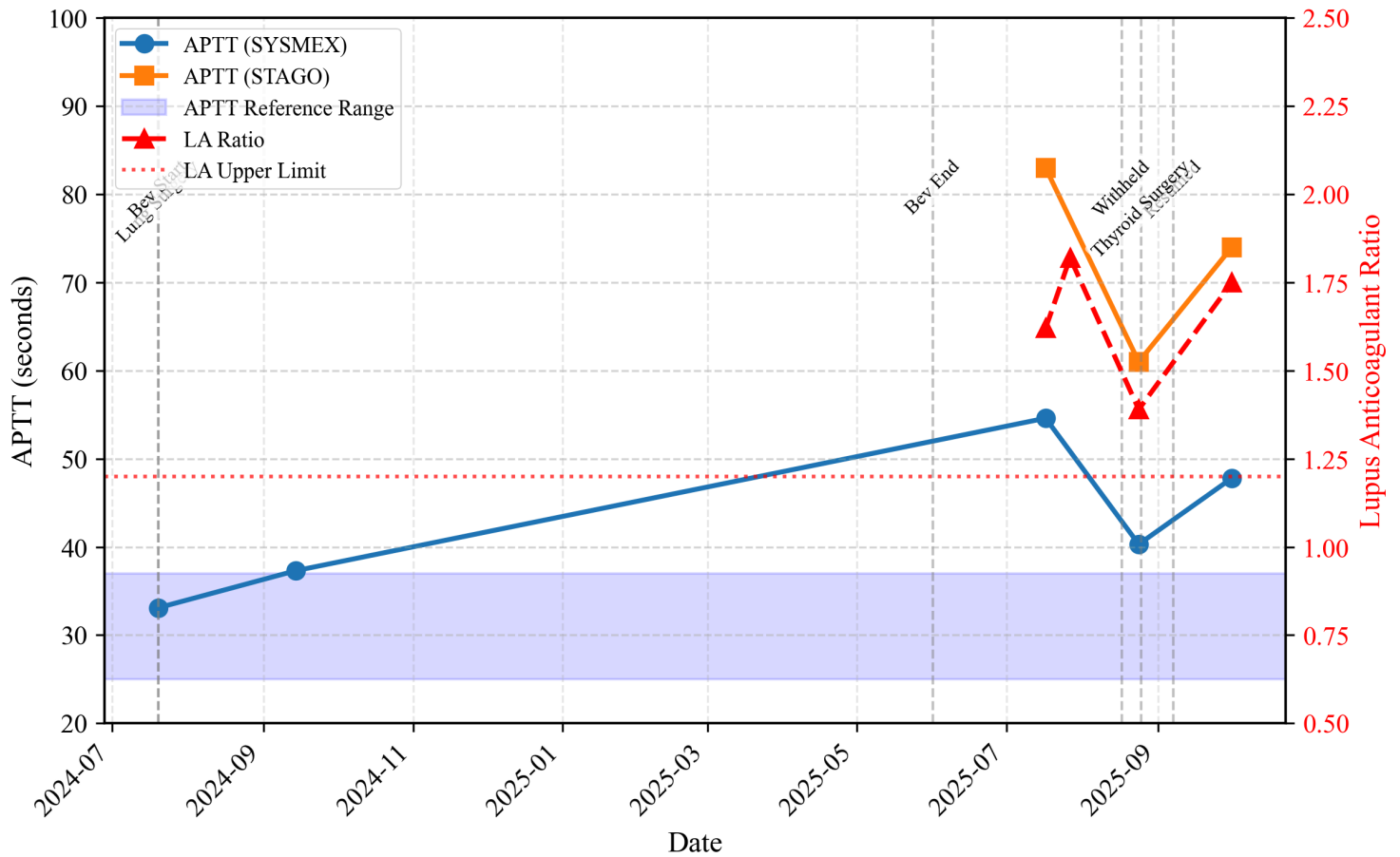


Figure 1

Trends of APTT and lupus anticoagulant ratio.

Fig. 1 *Left Y-axis (blue): APTT (seconds). Right Y-axis (red): LA ratio. Blue circles with solid line: APTT (SYSMEX CS-1500). Orange squares with solid line: APTT (STAGO STAR MAX). Red triangles with dashed line: LA ratio. Light blue band: APTT reference range (25–37 s, SYSMEX). Horizontal red dotted line: LA upper limit (1.2). Vertical dashed gray lines: key events (lung surgery, bevacizumab start/end, withholding, thyroid surgery, resumption). Data points without measurements are omitted.*