Oncology Advances **2024** vol. 2(1) | 55–57
DOI: 10.14218/OnA.2023.00046

Research Letter

Acquired Factor V Inhibitor Developed after Radio-chemotherapy for Non-small Cell Lung Carcinoma

Yuki Takahashi[1], Yutaka Shimazu[2,3], Keisuke Shindo[2], Mototaka Fukui[1], Yusuke Chihara[1], Takashi Miyoshi[2] and Shinsaku Imashuku[2,4*]

[1]*Division of Respiratory Medicine, Uji-Tokushukai Medical Center, Uji, Japan;* [2]*Division of Hematology, Uji-Tokushukai Medical Center, Uji, Japan;* [3]*Kyoto Innovation Center for Next Generation Clinical Trials and iPS Cell Therapy, Kyoto University Hospital, Kyoto, Japan;* [4]*Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Japan*

Received: November 27, 2023 | **Revised:** January 27, 2024 | **Accepted:** March 07, 2024 | **Published online:** March 25, 2024

Bleeding and coagulopathy are important issues in oncology. As one of the rare causes, acquired coagulation factor V deficiency (AFVD), which is caused by coagulation factor V (FV) inhibition and characterized by simultaneous prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), must be considered.[1] FV is an essential component of the prothrombinase complex activating the zymogen prothrombin to thrombin. The FV inhibitor (anti-FV autoantibody) neutralizes the procoagulant activity of activated coagulation factor V (FVa) by disrupting the formation of the prothrombinase complex.[2] According to a 2020 review,[3] approximately 200 cases of AFVD were recorded globally, with an estimated incidence ranging from 0.023 to 0.09 per million persons per year. Various factors, including the use of bovine thrombin in surgical procedures, antibiotics, autoimmune diseases, malignancies, and others have been described as triggers for developing FV inhibitors.[1–4] Among 105 cases treated with FV inhibitors, the malignancy was present in 16% of the patients.[1] A survey in Japan reported 201 cases of AFVD in the 2022 report, of which 39 cases (19.4%) were solid cancer, higher than antibiotics (34 cases; 16.9%), and autoimmune disease (23 cases; 11.4%).[4] Clinical symptoms associated with AFVD range from asymptomatic to life-threatening bleeding. We report here a case of AFVD that developed during radio-chemotherapy for non-small cell lung carcinoma (NSCLC).

A 67-year-old male, a smoker, was found to have a mass (4.1cm-size, 12.9 maximum standardized uptake value) shown by ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography in the left lower lobe of the lung in April 2023. The pathology confirmed NSCLC at stage III A. The patient had type 2 diabetes mellitus, treated with oral glimepiride and epalrestat, and took pregabalin for diabetic neuropathy. He had no autoimmune diseases, recent administration of antibiotics, or immune checkpoint inhibitors for the treatment of NSCLC. Laboratory data included a white blood cell count 10,500/μL, Hb of 10.8 g/dL, platelet count of 357 K/μL, CRP of 1.94 mg/dL (reference; <014), lactate dehydrogenase of 153 U/L (124–222), blood glucose of 196mg/dL (73–109), and HbA1c of 7.6% (4.9–6.0). He had normal hepatic and renal function. The serum tumor markers were: carcinoembryonic antigen 2.41 ng/mL (reference <5.0), cytokeratin 19 fragment (CYFRA) 2.6 ng/mL - 3.0 ng/mL (<2.2), and pro-gastrin-releasing peptide (PROGRP) 50.6 pg/mL (<81.0). He was negative for herpes simplex virus and hepatitis c virus. The patient was treated with a regimen of CBDCA (carboplatin) + PAC (paclitaxel) + RT (radiotherapy), with intensity-modulated radiotherapy; 2 Gy/day × 5 days/week for 6 weeks, for a total of 60 Gy. RT was planned from May 8 to June 19. From May 9, he received 5 weekly doses of CBDCA+PAC (carboplatin 90 mg/m^2 + paclitaxel 40 mg/m^2), which ended on June 8. Regarding radiotherapy, 54 Gy was administered until June 14. No antibiotics were administered during this period. Before the radio chemotherapy, his coagulation was normal. In April, the prothrombin time-international normalized ratio (PT-INR) was 1.04 (reference; 0.9–1.1), the APTT was 28.8 sec (26.0–38.0), and the APTT ratio was 1.02 (0.9–1.1). On June 15, one week after the fifth dose of CBDCA+PAC, the patient showed abruptly abnormal coagulation data (PT-INR 4.94 and APTT 98.8 sec, APTT ratio 3.53), with intraoral hemorrhages noted. The remaining radiotherapy was continued as planned, and 60 Gy was administered on June 19 despite coagulation abnormalities (Fig. 1). Differential diagnostic studies revealed a convex curve in the cross-mixing study after 2 hours of incubation, suggesting the presence of an inhibitor affecting coagulation factor(s). The coagulation activity data showed that coagulation factor II (FII) was 74.1%, coagulation factor V (FV) was <1.0%, and coagulation factor X (FX) was 71.7%. The FV inhibitor was detected as 3.0 Bethesda units (reference; 0 unit). Anti-nuclear antigen and lupus anticoagulant/antibodies for anti-phospholipid syndrome were negative. Following the diagnosis of AFVD, no severe hemorrhage occurred, and without treatment, the coagulation data spontaneously normalized within 2 weeks. In this case, no oral antidia-

Abbreviations: AFVD, acquired coagulation factor V deficiency; APTT, activated partial thromboplastin time; CBDCA, carboplatin; FV, coagulation factor V; NSCLC, non-small cell lung carcinoma; PAC, paclitaxel; PROGRP, pro-gastrin-releasing peptide; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; RT, radiotherapy.

***Correspondence to:** Shinsaku Imashuku, Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, 611-0042, Japan. ORCID: https://orcid.org/0000-0001-9795-0819. Tel.: +81-774-20-1111, Fax: +81-774-20-2336, E-mail: shinim95@mbox.kyoto-inet.or.jp

How to cite this article: Takahashi Y, Shimazu Y, Shindo K, Fukui M, Chihara Y, Miyoshi T, *et al.* Acquired factor V inhibitor developed after radio-chemotherapy for non-small cell lung carcinoma. *Oncol Adv* 2024;2(1):55–57. doi: 10.14218/OnA.2023.00046.

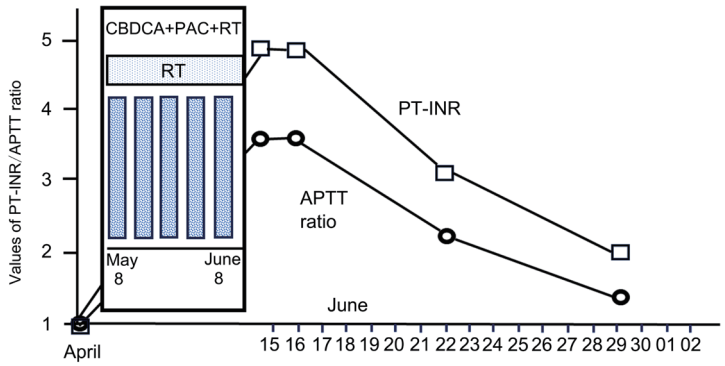

Fig. 1. PT and APTT prolongation after treatment with a CBDCA+PAC+RT regimen in a case of non-small cell lung carcinoma. The vertical axis shows values of PT-INR and APTT ratio while the horizontal axis duration (days) from April to June 2023. The APTT ratio was calculated with the patient's APTT (sec) divided by the control (sec). The remaining radiotherapy was given and a total of 60 Gy of radiotherapy was completed on June 19 (data not shown in Figure). APTT, activated partial thromboplastin time; CBDCA, carboplatin; PAC, paclitaxel; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; RT, radiotherapy.

betic drugs were responsible for AFVD. Thus, malignant disease (NSCLC) itself was thought to be the main cause of AFVD, rather than anticancer drugs or irradiation, because no previous reports (evidence) linking cytotoxic drugs or irradiation directly to the development of AFVD.

In the PubMed survey, AFVD associated with hematological neoplasms was reported in malignant lymphoma, myeloma, myeloproliferative neoplasms, and chronic myeloid leukemia.[5–8] On the other hand, cases of an acquired FV inhibitor in solid cancers have been reported in esophageal small cell carcinoma,[9] stomach carcinoma,[10] pancreatic carcinomas,[11] double cancer (squamous cell carcinoma of the lung and hepatocellular carcinoma),[12] double cancer (buccal epidermoid carcinoma and prostatic adenocarcinoma),[13] and hypopharyngeal cancer.[14] In lung carcinomas, unlike the previously reported AFVD with a well-differentiated squamous cell carcinoma,[12] our case of NSCLC-triggered AFVD, although small cell carcinoma was initially suspected from mildly increased CYFRA values, was pathologically diagnosed as NSCLC, not otherwise specific. Generally, in malignancies, aberrant hemostasis is a common manifestation.[15] In addition, in patients with malignancies, autoimmunity can occur due to the generation of autoantibodies against a wide range of autoantigens from the breakdown of the immune control system. However, the precise mechanism remains unknown.[16] We suspect in our case that NSCLC cells killed by radio-chemotherapy might have exacerbated aberrant hemostasis and stimulated autoantibody production against FV. In AFVD patients, hemorrhagic phenotypes vary from asymptomatic to severe bleeding. In terms of the treatment of AFVD, timely initiation of hemostatic and antibody-eradication/ reduction therapies is required to stop the bleeding and eliminate anti-FV inhibitors. Malignancy-triggered AFVD treatment is various depending on the severity of hemorrhages, including observation alone, plasmapheresis, corticosteroids, corticosteroids/ cyclophosphamide, and rituximab, in addition to the cytotoxic therapy for the underlying malignancy. In our case, no treatment was given because the bleeding episode did not worsen and the hemorrhagic data spontaneously improved within two weeks. Similar to our case, approximately 6% of patients with bleeding and 34% of patients without bleeding due to AFVD received no treatment.[4] The limitation of this study is that it is a single case report. We may need to accumulate and analyze more data on cases of malignancy-triggered AFVD. In summary, whenever patients with cancer develop sudden PT and APTT prolongation with or without hemorrhagic symptoms, AFVD must be suspected, and patients should receive appropriate management.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Drafting of the manuscript (YT, YS, SI), patient treatment (YT, YS, KS, MF, YC), abnormal coagulation data analysis (YS, TM, and SI). All authors approved the final version of the manuscript.

Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

References

[1] Knöbl P, Lechner K. Acquired factor V inhibitors. Baillieres Clin Haematol 1998;11(2):305–318. doi:10.1016/s0950-3536(98)80050-4, PMID:10097809.

[2] Ortel TL, Quinn-Allen MA, Charles LA, Devore-Carter D, Kane WH. Characterization of an acquired inhibitor to coagulation factor V. Antibody binding to the second C-type domain of factor V inhibits the binding of factor V to phosphatidylserine and neutralizes procoagulant activity. J Clin Invest 1992;90(6):2340–2347. doi:10.1172/JCI116123, PMID:1281831.

[3] Yamada S, Asakura H. [Acquired factor V inhibitor]. Rinsho Ketsueki

2020;61(7):791–798. doi:10.11406/rinketsu.61.791, PMID:32759567.
[4] Ichinose A, Osaki T, Souri M. A Review of Coagulation Abnormalities of Autoimmune Acquired Factor V Deficiency with a Focus on Japan. Semin Thromb Hemost 2022;48(2):206–218. doi:10.1055/s-0041-1740149, PMID:34942668.
[5] Aljohani NI, Matthews JH. Acquired factor V inhibitor in a patient with mantle cell lymphoma presenting with hematuria followed by thrombosis: a case report. Int Med Case Rep J 2014;7:27–30. doi:10.2147/IMCRJ.S59236, PMID:24591851.
[6] Quek JKS, Wong WH, Tan CW, Tha MH, Nagarajan C, Lee LH, *et al*. Acquired factor V deficiency in a patient with myeloma and amyloidosis. Thromb Res 2018;164:1–3. doi:10.1016/j.thromres.2018.01.045, PMID:29427868.
[7] Ashrani AA, Tefferi A, Pruthi RK, Pardanani A. Acquired factor V deficiency in myeloproliferative neoplasms: a Mayo Clinic series of 33 patients. Br J Haematol 2015;171(5):875–879. doi:10.1111/bjh.13438, PMID:25854415.
[8] To AQ, Ciurea SO, Kongtim P. Acquired Factor V Deficiency: A New Cause of Bleeding in Patients with Chronic Myeloid Leukemia and Extreme Leukocytosis. Acta Haematol 2023;146(6):543–546. doi:10.1159/000524630, PMID:35500558.
[9] Ahmadinejad M, Roushan N. Acquired factor V inhibitor developing in a patient with esophageal squamous cell carcinoma. Blood Coagul Fibrinolysis 2013;24(1):97–99. doi:10.1097/MBC.0b013e328359bc59, PMID:23080366.
[10] Ma ES, Liang RH, Chu KM, Lau GK. Complete response of acquired FV inhibitor to rituximab. Int J Hematol 2015;101(4):421–422. doi:10.1007/s12185-015-1742-z, PMID:25616916.
[11] Kuto M, Izuchi Y, Deguchi K, Morito T, Lee C, Wada H. An inhibitor against factor V occurring postoperatively in a case of pancreatic cancer. Nihon Ketsueki Gakkai Zasshi 1981;44(4):938–950. PMID:7331712.
[12] Endo H, Kawauchi K, Tomimatsu M, Iga D, Ogasawara T, Yasuyama M, *et al*. Acquired factor V inhibitor responsive to corticosteroids in a patient with double cancers. Intern Med 2007;46(9):621–625. doi:10.2169/internalmedicine.46.6390, PMID:17473502.
[13] Bayani N, Rugina M, Haddad-Vergnes L, Lelong F. High-titer acquired factor V inhibitor responsive to corticosteroids and cyclophosphamide in a patient with two malignant tumors. Am J Hematol 2002;71(1):33–36. doi:10.1002/ajh.10172, PMID:12221671.
[14] Kida W, Nakaya M, Ito A, Kozai Y, Bingo M. A Case of Acquired Factor V Inhibitor Following Nivolumab Administration. Cureus 2022;14(1):e21670. doi:10.7759/cureus.21670, PMID:35242461.
[15] Rondon AMR, Kroone C, Kapteijn MY, Versteeg HH, Buijs JT. Role of Tissue Factor in Tumor Progression and Cancer-Associated Thrombosis. Semin Thromb Hemost 2019;45(4):396–412. doi:10.1055/s-0039-1687895, PMID:31096312.
[16] Abu-Shakra M, Buskila D, Ehrenfeld M, Conrad K, Shoenfeld Y. Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies. Ann Rheum Dis 2001;60(5):433–441. doi:10.1136/ard.60.5.433, PMID:11302861.