

Case
Report

Perioperative Bypassing Agent Therapy for Pulmonary Pleomorphic Carcinoma with Acquired Hemophilia

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A 74-year-old man was admitted with lung cancer, and preoperative blood test showed abnormal activated partial thromboplastin time (APTT). Coagulation factor screening and APTT mixing test achieved a diagnosis of acquired hemophilia A (AHA). Bypassing agent therapy was indicated and lobectomy was successfully performed without bleeding complications. APTT returned to normal after the operation without any additional treatment for AHA. The pathogenesis of AHA is still unknown and there is no evidence for hemostatic strategy for AHA patients requiring surgery. This study supports the importance of hemostatic therapy and suggests that malignancy might cause AHA.

Keywords: acquired hemophilia, lung cancer, surgery

Introduction

Acquired hemophilia A (AHA) is a rare autoimmune disease, and has a high risk of bleeding.^{1–3} Most cases of AHA are idiopathic, while some are associated with various diseases including malignancy.³ However, understandings of its pathophysiology and of its management approach are still insufficient. Although abnormal coagulation is a risk factor for perioperative bleeding

complications, there is little evidence of hemostatic methods for patients with AHA who require surgery.^{4,5} Herein, we report a patient with pulmonary pleomorphic carcinoma and AHA who underwent lobectomy safely using a bypassing agent.

Case Report

A 74-year-old man was referred to our hospital with a left hilar pulmonary mass (**Fig. 1A** and **1B**). He had many comorbidities, which included diabetes mellitus, chronic obstructive pulmonary disease, and vascular problems; brain ischemic stroke due to occlusion of the carotid artery, ischemic heart disease treated with percutaneous coronary intervention, and bilateral arteriosclerosis obliterans. Upon admission, transbronchial biopsy revealed non-small-cell lung carcinoma, and a left upper lobectomy was indicated. However, preoperative blood screening test revealed an abnormal activated partial thromboplastin time (APTT) of 55.2–58.9 seconds (normal range: 24.0–39.0 seconds). He had no history of bleeding, and his APTT was 47.4 seconds 6 months ago (**Fig. 1C**). His platelet count, prothrombin time, and bleeding time were within normal range. Specific blood

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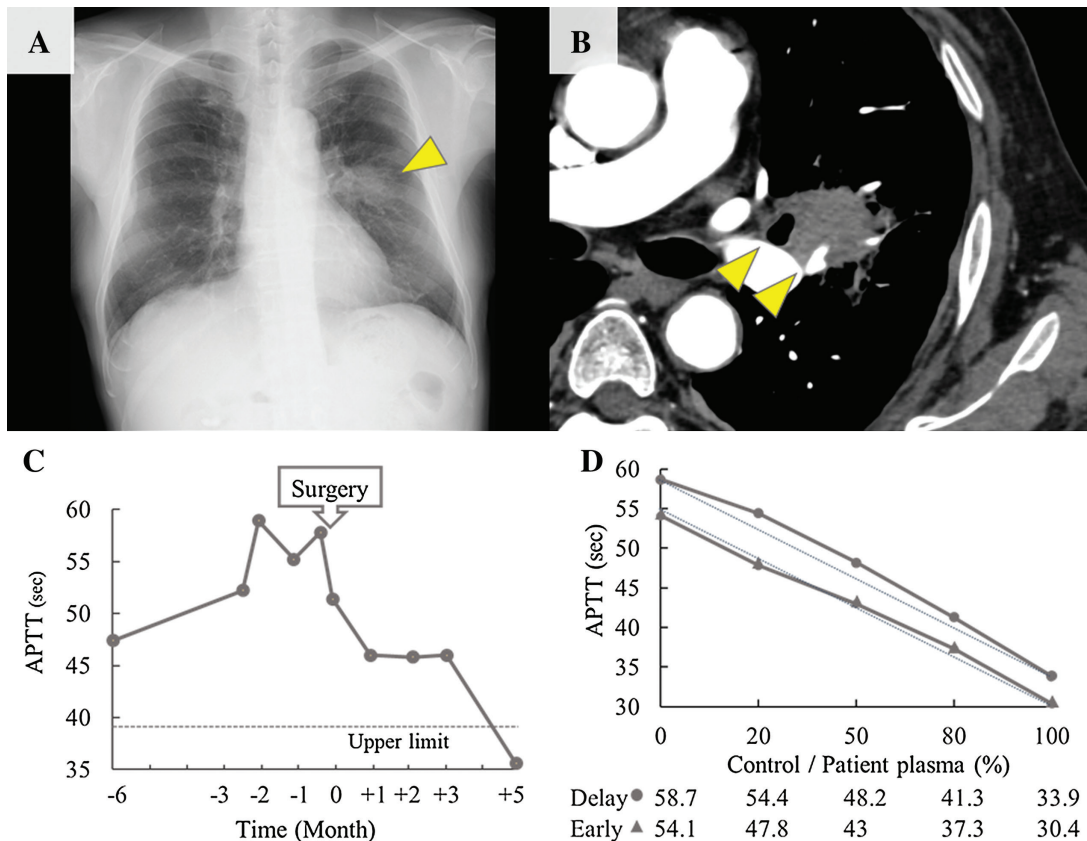


Fig. 1 (A) Chest X-ray and (B) computed tomography scan revealed that mass is located in the hilum and closed to the left main pulmonary artery. (C) APTT prolonged with cancer progression and improved after tumor resection. (D) APTT mixing test of the patient. A convex or linear decreasing pattern is generally observed in the presence of the inhibitor. A convex pattern was observed in the delayed response of the patient, suggesting the existence of inhibitor for coagulation factor VIII. APTT: activated partial thromboplastin time

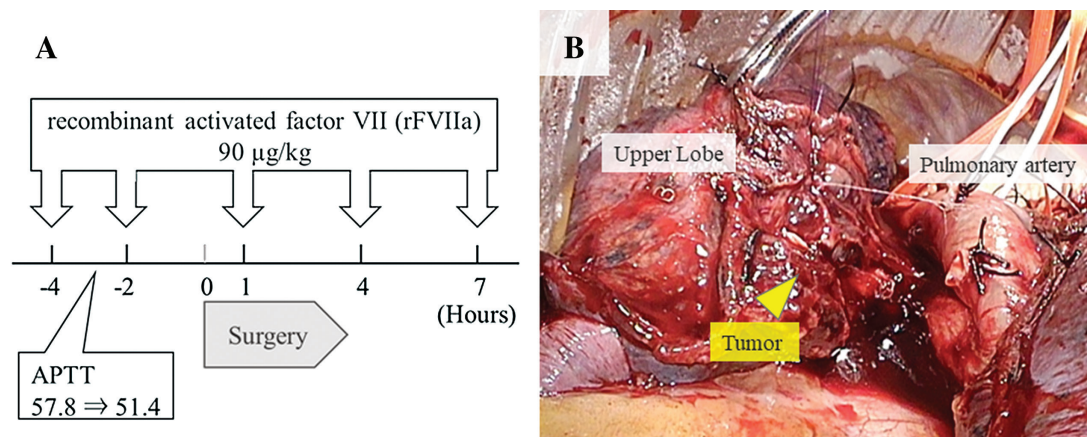


Fig. 2 (A) Time table of the day of surgery. Perioperative bypass hemostatic therapy with recombinant activated factor VII was performed with its dose of 90 µg/kg. (B) The tumor was approximated to the pulmonary artery, however, not infiltrated and could be resected completely.

tests were thus performed. Based on the coagulation factor and inhibitor tests, factor VIII coagulant activity was decreased at 39% (normal range: 60–150%),

activity of von Willebrand factor was normal, and detection of lupus anticoagulant and cardiolipin-IgG were negative. The APTT mixing test suggested the presence

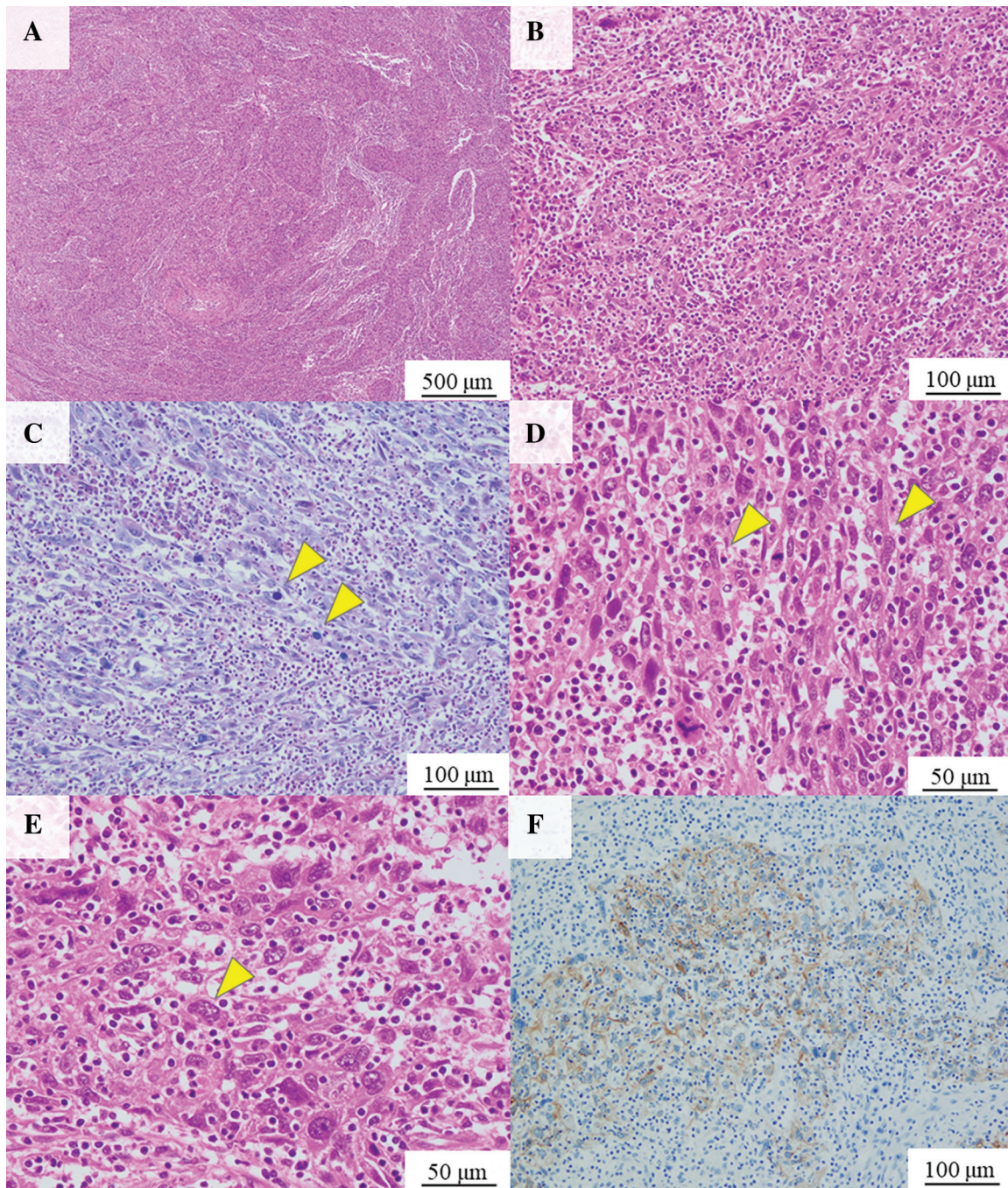


Fig. 3 Histological findings of the carcinoma (A) at lower magnification (hematoxylin and eosin method, $\times 40$) and (B) at higher magnification (hematoxylin and eosin method, $\times 200$). Tumor cells proliferated with infiltration of various inflammatory cells. (C) Some tumor cells showed mucin production (Alcian blue stain, $\times 200$), and (D) spindle cells ($\times 400$) and (E) giant cells ($\times 400$) also proliferated at the rate of 30% in the tumor. (F) Tumor cells showed diffuse positive for cytokeratin AE1/AE3 immunohistochemically ($\times 200$); therefore, the pathological diagnosis was pulmonary pleomorphic carcinoma.

of inhibitors (Fig. 1D), a diagnosis of AHA was therefore achieved.

Considering the tumor location in the hilum which was in close proximity to the left main pulmonary artery, in addition to the diagnosis of AHA (Fig. 1B),

intraoperative bleeding risk was quite high. Thus, the clinical decision for preoperative hemostatic therapy was made. This involved the administration of recombinant activated factor VII every 2–3 hours at a dose of 90 $\mu\text{g}/\text{kg}$ (Fig. 2A). During surgery, thoracotomy with 15 cm

incision was performed, the main pulmonary artery was taped, the tumor was peeled off the pulmonary artery and each artery was carefully ligated (**Fig. 2B**). Although an abnormal APTT of 50.9–51.4 seconds and bleeding from the muscle and chest wall was observed, lobectomy was successfully performed without massive blood loss with its amount of 191 mL during the 4.5 hours of surgery. Chest drain could be removed 2 days post-surgery and the patient was discharged 10 days later without any bleeding or thromboembolic complications.

Histologically, tumor cells without distinctive morphological features were proliferated with extensive infiltration of inflammatory cells including neutrophil, lymphocyte, and macrophage, although there were no findings of post-obstructive pneumonia (**Fig. 3A** and **3B**). Tumor cells with severe nuclear atypia showed some mucin production (**Fig. 3C**) but no findings of keratinization. Spindle cells (**Fig. 3D**) and giant cells (**Fig. 3E**) were proliferated at a rate of 30% within the tumor. Immunohistochemically, tumor cells were diffusely positive for cytokeratin AE1/AE3 (**Fig. 3F**), partially positive for CK5/6, and negative for TTF-1, Napsin A, and p40. Therefore, a pathological diagnosis of pulmonary pleomorphic carcinoma was made.

During the 9-month follow-up, cancer recurrence was not observed and APTT improved to normal (34.6 seconds) without any treatment for AHA (**Fig. 1C**).

Discussion

AHA is an autoimmune disease in which antibodies against coagulation factor VIII are generated due to its breakdown by the immune system.⁶⁾ Most cases of AHA are idiopathic, but underlying disease such as malignancy may influence the immune system,⁷⁾ and the etiology of this is still unknown. Previous studies showed that about 6%–17% of patients with AHA had a malignancy^{8–11)} and 12%–22% of patients with AHA and malignant tumor had a lung cancer.^{11,12)} Previous studies showed that patients with AHA had various histological types including small and non-small-cell carcinoma^{12,13)}; however, no correlation could be found concerning the histology of lung cancer.^{12,14)} As far as we searched, this is the first report of pulmonary pleomorphic carcinoma with AHA.

In this case, APTT prolonged with tumor progression and improved after resection, suggesting that an abnormal autoimmune response toward the malignant tumor might have induced the formation of factor VIII inhibitors. Various lymphocytes extremely aggregated in the

tumor, which might relate to the autoimmune reaction. Our study was in line with previous reports on AHA improvement after treatment for malignancy,¹²⁾ although the outcome of surgery for malignancy has rarely reported.⁴⁾

Surgery is a significant risk factor for perioperative bleeding in patients with AHA. Previous studies have shown that surgery have caused initial bleeding events in 8.2% of AHA patients.⁶⁾ Specific preoperative screening for patients with abnormal APTT may lead to a diagnosis of AHA and prevent bleeding complications. Furthermore, due to rarity in reports on surgery for patients with AHA, perioperative hemostatic strategies for those who require surgery are hence not established.^{1,4)} Although further perspective studies are needed, our study suggests the importance of perioperative hemostatic therapy to improve surgical outcomes of patients with AHA.

Conclusion

This study suggests that malignancy might cause AHA which pathogenesis is still unknown. Although further studies are required, this study supports the importance of perioperative hemostatic therapy for AHA patients requiring surgery including lung resection.

Informed Consent

Written informed consent was obtained by the patient for publication of this report.

Disclosure Statement

None declared.

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