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A Case of Diffuse Alveolar Hemorrhage Associated with Tegafur Plus Uracil and Warfarin Therapy

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Abstract: A 72-year-old man who received warfarin for myocardial infarction (prothrombin time-international normalized ratio [PT-INR] controlled between 2.2 and 2.5) for 2 years. He developed lung cancer, underwent surgery, and received tegafur plus uracil (UFT) after 1 month. After 2 months, he was admitted for hemoptysis and dyspnea. Chest radiography and computed tomography showed bilateral alveolar infiltration (PT-INR, 8.9). Bronchoalveolar lavage fluid (BALF) disclosed hemorrhagic features in sequential samples. And he was diagnosed with diffuse alveolar hemorrhage (DAH). A known interaction exists between fluoropyrimidines and warfarin. So, they were discontinued, and vitamin K was intravenously administered. One day later, the PT-INR returned to 1.14. The symptoms improved and, alveolar infiltration resolved after 2 weeks. Alveolar hemorrhage may be due to an interaction between UFT and warfarin. When fluoropyrimidines and warfarin are prescribed simultaneously, we recommend that PT-INR should be closely monitored.

Keywords: diffuse alveolar hemorrhage, Tegafur Plus Uracil, warfarin

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Introduction

DAH can occur as a manifestation of various diseases.¹ Anticoagulant therapy is one of the causes of DAH. Elderly individuals may have many coexisting illnesses and are typically prescribed different types of drugs. Therefore, drug interactions are a problem associated with medication.

Fluoropyrimidines (eg, 5-FU, UFT, TS-1, and capecitabine) are used as anticancer agents. A known interaction exists between fluoropyrimidines and warfarin.² Warfarin is an oral anticoagulant, which is often used to prevent thromboembolic complications in cardiovascular diseases. They are well-known to contribute to a large amount of inter-patient variability in warfarin metabolism, which appears to be related to genetic polymorphisms in cytochrome P-450 enzyme 2C9 (CYP2C9) and/or vitamin K epoxide reductase complex 1 (VKORC1).³⁻⁵ Therefore, we examined polymorphisms of CYP2C9 and VKORC1 in this patient.

There are only a few reports discussing DAH association with warfarin therapy.^{6,7} We report a case of DAH related to combination therapy using UFT and warfarin.

Case Report

The patient was a 72-year-old man who presented with hemoptysis and dyspnea. He had been taking 200 mg aspirin daily, 200 mg ticlopidine hydrochloride daily and 2 mg warfarin daily for 2 years for myocardial infarction after percutaneous coronary intervention. The PT-INR was controlled at 2.2 to 2.5. He then developed lung adenocarcinoma (pT1N0M0 stage IA), and a right lower lobectomy was performed. The tumor was 2.5 cm in diameter. UFT generally improves the survival rate among patients with tumors 2 to 3 cm in diameter.⁸ Thus, one month after operation, he began taking 2 capsules of UFT (200 mg tegafur and 448 mg uracil) twice daily as an adjuvant therapy. After the operation, he did not consult a cardiovascular physician but continued the same doses of medicines.

Two months later, he was admitted to our hospital with hemoptysis, cough, and dyspnea. Before his symptoms were evaluated, no antibiotics or other drugs, such as those that affect the metabolism of vitamin K, were prescribed. On the other hand, he did

not have diarrhea, so we speculated that his colonic flora and vitamin K absorption was normal.

The patient had previously been a smoker (smoking exposure, 100 pack-years) and he had chronic obstructive pulmonary disease (GOLD guideline stage II). Physical examination showed that he had many large purpuras on his limbs; his respiratory rate was 30 breaths/min; blood pressure, 109/58 mmHg; heart rate, 76 beats/min; and body temperature, 37.0 °C. Results of laboratory investigations were as follows: hemoglobin level, 7.5 g/dL; WBC count, 8,100 cells/ μ L; platelet count, 213,000 cells/ μ L; PT-INR, 8.9. Basic biochemical profiles were normal. Myeloperoxidase antineutrophil cytoplasmic auto-antibody (MPO-ANCA), proteinase 3-ANCA (PR3-ANCA), antiglomerular basement membrane antibody, antinuclear antibody, and anti-double-stranded DNA antibody were all negative. The results of urinalysis were within a normal range. Chest radiograph showed bilateral alveolar infiltration (Fig. 1). Chest computed tomography (CT) scan showed bilateral ground-glass opacities and multiple low attenuation areas (Fig. 2). Pulse oximetry showed 84% percutaneous O₂ saturation, and oxygen therapy was begun. Fiberoptic bronchoscopy was performed.



Figure 1. Chest radiograph showed bilateral alveolar infiltration.

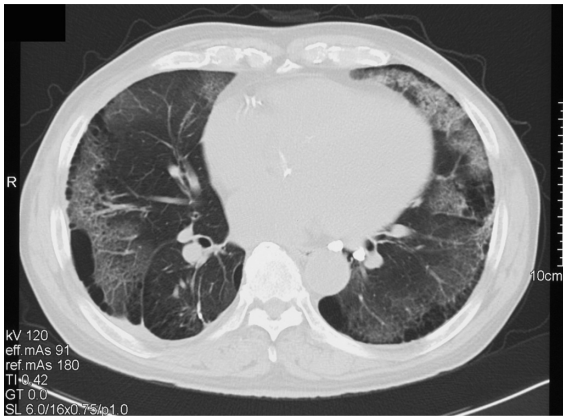


Figure 2. Chest CT scan showed bilateral ground-glass opacities and multiple low attenuation areas.

Airways with blood were observed, but abnormality of bronchial mucosa was not found. BALF disclosed hemorrhagic features in sequential samples. Histopathological analysis of bloody BALF showed hemosiderin-filled macrophages (>20% of total alveolar macrophages), thereby confirming alveolar hemorrhage (Fig. 3). Because of the presence of tarry stools, gastrointestinal fiberopticoscopy was conducted, and no abnormalities were found. UFT, warfarin, aspirin, and ticlopidine hydrochloride were discontinued, and 10 mg vitamin K was administered intravenously. One day later, the PT-INR returned to 1.14. His symptoms gradually improved, and bilateral alveolar infiltration resolved after about 2 weeks (Fig. 4).

We examined genetic polymorphisms of cytochrome P-450 enzyme 2C9 (CYP2C9) and vitamin K epoxide reductase complex 1 (VKORC1), which can

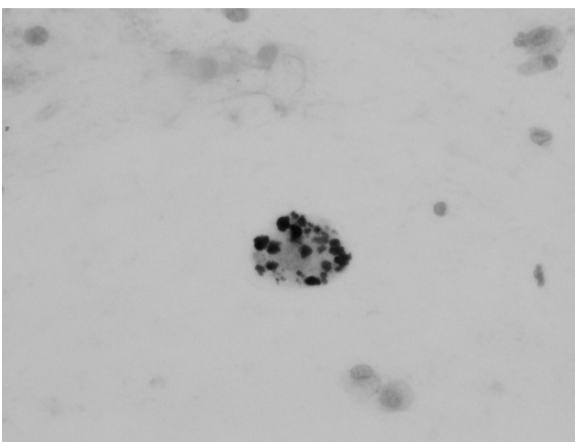


Figure 3. Histopathological analysis of bloody bronchoalveolar lavage fluid showed hemosiderin-filled macrophages.

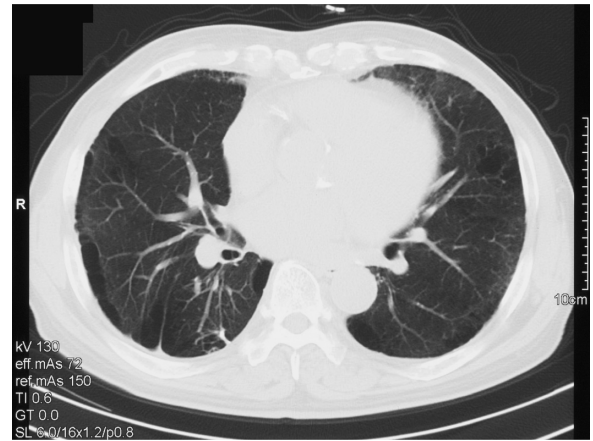


Figure 4. Chest CT scan showed bilateral alveolar infiltration resolved.

influence the management of warfarin therapy. The patient had no polymorphisms of CYP2C9 but a homozygous mutation was found in VKORC1. After prescribing warfarin, aspirin, and ticlopidine hydrochloride (with no UFT), the PT-INR was controlled at 2.2 (INR target range, 2.0–2.5). At follow-up visits, the patient remained asymptomatic.

Discussion

We report the case of a patient with DAH related to combination therapy of UFT and warfarin. The patient was prescribed 2 mg warfarin daily for 2 years; he had no bleeding episodes and PT-INR had been well-controlled, in the range of 2 to 2.5. However, after UFT was started, PT-INR markedly increased to 8.9. After DAH resolved, anticoagulant therapy was restarted, and PT-INR was controlled at 2.2. Thus, it is possible that an interaction exists between UFT and warfarin.

DAH can occur as a manifestation of various diseases such as Wegener's granulomatosis, Henochschönlein purpura, microscopic polyangiitis, antiphospholipid antibody syndrome, and Goodpasture's syndrome.¹ In this case, MPO-ANCA, PR3-ANCA, antiglomerular basement membrane antibody, antinuclear antibody, and anti-double-stranded DNA antibody were all negative. However, a renal function test and urinalysis were normal. Therefore, we diagnosed this patient with drug-induced DAH.

DAH can occur as a rare complication of warfarin therapy.^{6,7} To our knowledge, this is the first case of DAH associated with UFT and warfarin.



Recently, Saif reported that patients receiving concomitant capecitabine or fluorouracil (5-FU) and warfarin had altered coagulation parameters and consequent bleeding, thus causing shock in some cases.²

Warfarin is an oral anticoagulant, which is often used to prevent thromboembolic complications in cardiovascular diseases. They are well-known to contribute to a large amount of inter-patient variability in warfarin metabolism, which appears to be related to genetic polymorphisms in CYP2C9 and/or VKORC1.^{3–5} CYP2C9 is a key enzyme in the hepatic metabolism of warfarin, whereas VKORC1 works to maintain sufficient vitamin K levels when dietary vitamin K is limited. The VKORC1 homozygous mutation affects the high response to warfarin.

UFT is an orally available drug whose activity is comparable to that of intravenously administered 5-FU combined with folinic acid. Derivatives based on fluoropyrimidines (eg, 5-FU, UFT, TS-1, and capecitabine) are used for the management of several malignancies such as lung, pancreatic, upper gastrointestinal, and breast cancers. Kato et al reported that UFT as a postoperative adjuvant treatment, which can be used to improve the prognosis of patients with completely resected adenocarcinoma (stage IB).⁸ UFT was administered in this case and such an effect of UFT was expected. Recently, results of an enzymatic study suggested that 5-FU has inhibitory effects against the activities of microsomal enzymes, including CYP2C.⁹

On the basis of results of recent studies, we speculated that genetic polymorphisms of CYP2C9 and/or VKORC1 are mechanisms of interaction between fluoropyrimidines and warfarin in our patient. Therefore, we examined polymorphisms of CYP2C9 and VKORC1 in this patient. The patient's genotype was CYP2C9 *1/*1; thus, he did not have the polymorphisms of CYP2C9, but did have a homozygous mutation of VKORC1 A/A.

The patient responded well to warfarin treatment. Additionally, PT-INR was well-controlled using a small amount of warfarin for therapy. In addition to the inhibitory effects of UFT on the activities of CYP2C9, DAH may be induced by a smaller dose of warfarin.

Our patient was also prescribed aspirin and ticlopidine hydrochloride. However, it is well known that there are no correlations between the metabolism

of these drugs and CYP2C9 or VKORC1. Moreover, after re-administration of anticoagulants, PT-INR was controlled (2.2), and the patient remained asymptomatic. Thus, the interaction between warfarin and another anticoagulant may not be the cause of DAH.

Recently, a report described polymorphisms of CYP2C9 associated with metabolism of 5-FU.¹⁰ The clearance of 5-FU observed in patients with 2 variant alleles was significantly lower than that in patients with wild type alleles. We did not assess for this mutation, but it is possible that our patient has the mutation.

The exact mechanism of these interactions remains unclear, and further investigation is necessary. When fluoropyrimidines and warfarin are prescribed simultaneously, we recommend that PT-INR should be closely monitored.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References

1. Schwarz MI, Cherniack RM, King TE Jr. Diffuse alveolar Hemorrhage and other rare infiltrative disorders. In: Murray, Nadel, editors, *Textbook of Respiratory Medicine*, 3rd ed, WB Saunders Company. 2000:1733–51.
2. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. *Clin Colorectal Cancer*. 2005;5:175–80.
3. Takahashi H, Wilkinson GR, Caraco Y, et al. Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. *Clin Pharmacol Ther*. 2003;73:253–63.
4. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med*. 2005;352:2285–93.
5. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009;360:753–64.
6. Erdogan D, Kocaman O, Oflaz H, Goren T. Alveolar hemorrhage associated with warfarin therapy: a case report and literature review. *Int J Cardiovasc Imaging*. 2004;20:155–9.



7. Barnett VT, Bergmann F, Humphrey H, Chediak J. Diffuse alveolar hemorrhage secondary to superwarfarin ingestion. *Chest*. 1992;102:1301–2.
8. Kato H, Ichinose Y, Ohta M, et al. Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med*. 2004;350:1713–21.
9. Konishi H, Yoshimoto T, Morita K, Minouchi T, Sato T, Yamaji A. Depression of phenytoin metabolic capacity by 5-fluorouracil and doxifluridine in rats. *J Pharm Pharmacol*. 2003;55:143–9.
10. Fujita K, Yamamoto W, Endo S, et al. CYP6 and the plasma level of 5-chloro-2,4-dihydropyridine are determinants of the pharmacokinetic variability of tegafur and 5-fluorouracil, respectively, in Japanese patients with cancer given S-1. *Cancer Sci*. 2008;99:1049–54.

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