CASE REPORT

A rare complication in a patient taking rivaroxaban: Alveolar hemorrhage

Rivaroksabana bağlı nadir bir komplikasyon: Alveolar hemoraji

Salih Kılıç, M.D.,[1] Erhan Saraçoğlu, M.D.,[2] Gülin Alkan, M.D.[3]

[1]Department of Cardiology, Nizip State Hospital, Gaziantep, Turkey
[2]Department of Cardiology, Doctor Ersin Aslan Training and Research Hospital, Gaziantep, Turkey
[3]Department of Internal Medicine, Nizip State Hospital, Gaziantep, Turkey

Summary– Alveolar hemorrhage (AH) is a heterogeneous clinical syndrome with a high mortality rate that is characterized by extensive bleeding into the alveolar spaces. AH usually develops secondary to immunological disease and, less frequently, to drug use. Presently described is the case of an 86-year-old woman with AH who had been using rivaroxaban for 6 months.

Özet– Alveolar hemoraji (AH), alveol boşluklarının içine yaygın kanama ile karakterize mortalitesi yüksek heterojen bir klinik tablodur. Alveolar hemoraji genellikle immün kökenli hastalılıklara daha az oranda ise ilaçlara ikincil olarak gelişir. Bu yazıda, altı aydır rivaroksaban kullanan ve AH gelişen 86 yaşındaki bir olgu sunuldu.

Alveolar Hemorrhage (AH) is a heterogeneous clinical syndrome with a high mortality rate that is characterized by extensive bleeding into the alveolar spaces. AH usually develops secondary to immunological disease and, less frequently, to drug use. It has a wide spectrum, ranging from alveolar septal damage to massive hemorrhage. Presently reported is a case of AH developing due to rivaroxaban use.

Abbreviations:

AH	*Alveolar hemorrhage*
INR	*International normalized ratio*
NIMV	*Non-invasive mechanical ventilation*

CASE REPORT

Rivaroxaban treatment at 20 mg/day had been initiated 6 months earlier for an 89-year-old woman with a history of diabetes, hypertension, heart failure, and atrial fibrillation, but the patient failed to attend follow-up examinations. She was admitted to the hospital with sudden onset dyspnea, cough, and hemoptysis. On physical examination, her temperature was 37°C, respiration rate was 25/minute, blood pressure was 137/77 mmHg, and heart rate was 114 beats/minute. Inspiratory crackles were detected in the middle and lower lobes of the right lung and in the lower lobe of the left lung. The laboratory parameters included a hemoglobin level of 7.9 mg/dL (6 months prior: 12.4 mg/dL), platelet count of $315x10^3/mm^3$, leukocyte count of $10450/mm^3$, international normalized ratio (INR) of 1.3, prothrombin time of 14 seconds, creatinine level of 2.3 mg/dL (6 months prior: 0.9 mg/dL) and creatine clearance (Cockcroft-Gault formula) of 28 mL/minute (6 months prior: 71 mL/minute). Arterial blood gas analysis revealed a pH of 7.39, partial pressure of carbon dioxide of 31 mmHg, partial pressure of oxygen of 47 mmHg, and oxygen saturation (SaO2) of 78%. A chest X-ray showed diffuse, increased density, which was more pronounced in the right lung (Fig. 1). In order to maintain SaO_2 >90% non-invasive mechanical ventilation (NIMV) was initiated and parenteral ceftriaxone was administered empirically with a preliminary diagnosis of pneumonia. The rivaroxaban treatment was interrupted, and fluid replacement was performed at an appropriate dose. The clinical and laboratory findings of the patient did not support pneumonia at 24-hour follow-up. A thoracic computed tomography image taken with a preliminary diagnosis of AH re-

Received: May 16, 2017 *Accepted:* July 06, 2017
Correspondence: Dr. Salih Kılıç. Nizip Devlet Hastanesi, Kardiyoloji Poliklinigi, 27100 Gaziantep, Turkey.
Tel: +90 342 - 517 54 00 e-mail: kilicsalihhh@gmail.com

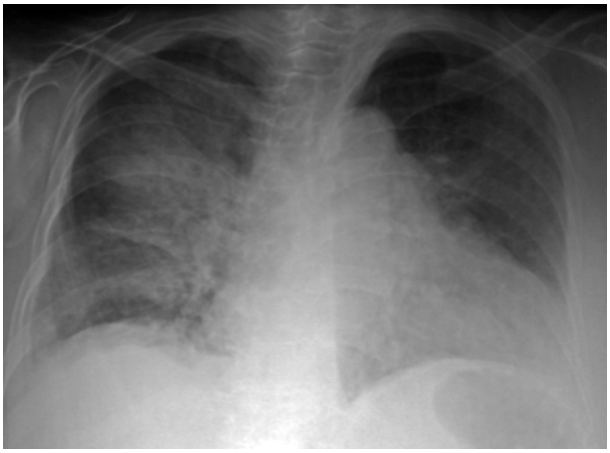

Figure 1. Chest X-ray upon hospitalization showing opacity in the lung fields, particularly on the right.

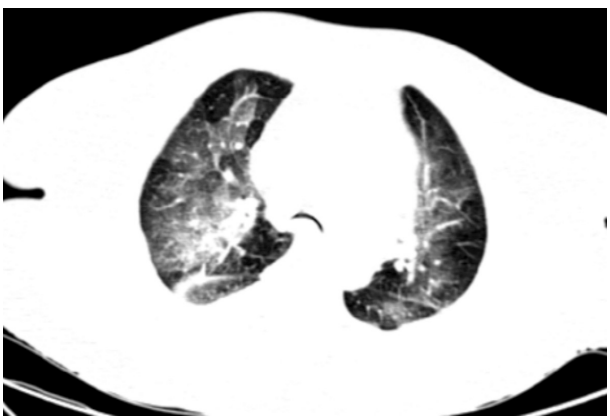

Figure 2. Chest computed tomography on second day of hospitalization revealing pulmonary alveolar haemorrhage in both lungs.

vealed focal ground-glass opacities on both sides of the lungs, supporting the diagnosis of AH (Fig. 2). The patient had no rheumatological disease or drug use that would ordinarily cause AH. Rheumatological parameters were also normal. The patient did have a history of very frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) recently. She developed acute renal failure, and was considered to have rivaroxaban-induced AH. Two units of erythrocyte suspension together with the appropriate dose of fluid were given for 48 hours. On the fifth day of follow-up, NIMV was no longer needed. Renal functions returned to normal in control laboratory tests, and the hemoglobin level remained stable at 10.2 mg/dL. On the 10th day of follow-up, a chest X-ray revealed significant improvement (Fig. 3). Warfarin was initiated to maintain the INR between 2.0 and 3.0. She was

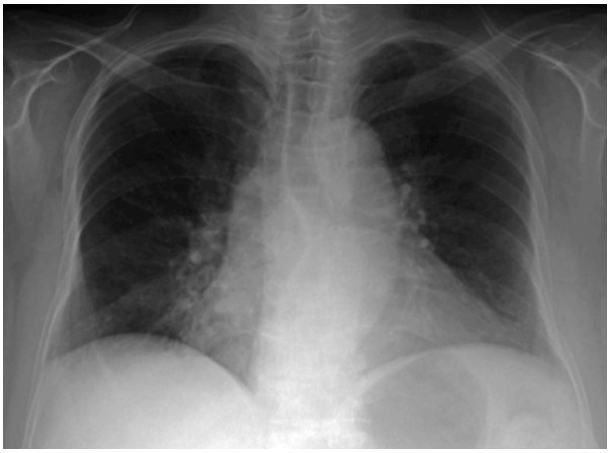

Figure 3. Chest X-ray on 10th day of hospitalization indicating the regression of opacity in the lung fields.

discharged with a recommendation for strict control.

DISCUSSION

AH is a clinical syndrome characterized by dyspnea, anemia, and hemoptysis that is caused by pulmonary alveolocapillary membrane damage that may have various etiologies. Although the most important step in the diagnosis of AH is clinical suspicion, imaging methods and detection of hemosiderin-laden macrophages in a bronchoalveolar lavage are important in diagnosis. Immune system diseases are the most common cause. Rarely, it can develop due to medication use. Although the mortality rate varies according to the etiology, it has been reported to be 25% to 50%.[1,2] It has been reported that AH developed as a rare complication of the use of anticoagulants (warfarin, dabigatran, apixaban and edoxaban).[3-7] Rivaroxaban is a new oral anticoagulant agent that acts as a direct factor Xa inhibitor and reduces the risk of bleeding and stroke compared with warfarin.[8] The most common types of rivaroxaban-related major bleeding are gastrointestinal tract and intracranial hemorrhages.[8] Rivaroxaban is not recommended for use in patients with renal insufficiency (estimated glomerular filtration rate <30 mL/minute). In addition, it is recommended that kidney functions be assessed at regular intervals in patients using the drug.[9] Our patient had AH associated with rivaroxaban after acute renal failure, which occurred during follow-up. According to our knowledge, a case of AH associated with rivaroxaban has not been previously reported. Supportive care and antidote administration are rec-

ommended for rivaroxaban-induced hemorrhage, as with other new oral anticoagulants.[9] Similarly, immunosuppressive agents (especially those that are secondary to immunological disease) in combination with supportive therapy are recommended in the treatment of AH associated with drug use. Our patient was stabilized with supportive treatment and did not require additional treatment.

Many individual comorbid medical conditions have been associated with elevated risks for bleeding in anticoagulant treatment. These include a history of congestive heart failure, cerebrovascular disease, hepatic or renal disease, diabetes mellitus, history of bleeding (especially in the gastrointestinal tract), and anemia.[9,10] Although, new oral anticoagulants have generally been associated with lower rates of fatal bleeding, individual comorbid medical conditions associated with elevated risks for bleeding should be considered before starting a new oral anticoagulant.[9,11] In addition, there are several bleeding risk scores to estimate the risk of bleeding in anticoagulated patients. Bleeding risk assessment can be performed using the well-validated HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (65 years), drugs/alcohol concomitantly] score. A high bleeding risk score should generally not result in withholding the anticoagulant.[9] Rather, bleeding risk factors and treatable factors (i.e., hypertension, NSAID use, anemia, impaired renal or liver function) should be identified. Accurate assessment of renal function is a prerequisite for the correct management of people at risk of developing chronic kidney disease. Serum creatine, the most widely used surrogate marker of glomerular filtration rate, is inaccurate with increasing age, particularly in sick and/or malnourished elderly people.[11] Current guidelines recommend that the 2 most commonly used equations to estimate glomerular filtration rate - the Modification of Diet in Renal Disease Study method and the Cockcroft-Gault formula - be used to estimate glomerular filtration rate in the clinical setting.[11] It is of vital importance that patients taking new oral anticoagulants are monitored at certain intervals for renal and liver function, and are informed about drugs that affect renal functions.

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None declared.

Authorship contributions: Concept – S.K.; Design – S.K.; Supervision – E.S.; Materials – S.K., G.A.; Data collection – S.K., E.S.; Analysis and/orinterpretation – S.K., E.S.; Literature search – S.K., G.A.; Writing – S.K.

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Keywords: Acute renal failure; alveolar hemorrhage; rivaroxaban.

Anahtar sözcükler: Akut böbrek yetersizliği; alveolar hemoraji; rivaroksaban.