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Diffusie Alveolar Hemorrhage-Complication of Warfarin Treatment

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Diffüz Alveolar Hemoraji-Varfarin Tedavi Komplikasyonu

ABSTRACT

Diffuse alveolar hemorrhage (DAH) is a medical emergency which can cause acute respiratory failure. The diagnosis and treatment of DAH should be carried out as soon as possible. DAH has various causes such as vasculitis, infections, pesticides intoxication, barotrauma, diffuse alveolar damage, pulmonary embolism and may be associated with the use of anticoagulants [(1)]. Warfarin therapy is a rare cause of DAH [(1)]. We aimed to present a 69 year-old male patient who developed diffuse alveolar hemorrhage as a complication of warfarin therapy used for valve replacement. After diagnosis of DAH, warfarin treatment was discontinued and fresh frozen plasma, metilprednisolone, vitamin K were administered during mechanical ventilation therapy. The patient was responded well and INR decreased to therapeutic value. DAH should be remembered during warfarine therapy to avoid challenging situations.

Keywords: *Warfarin, hemoptysis, respiratory insufficiency*

ÖZ

Diffüz alveoler hemoraji (DAH) akut solunum yetmezliğine neden olabilen bir tıbbi acil durumdur. DAH tanısı ve tedavisi mümkün olan en kısa sürede yapılmalıdır. Vaskülit, enfeksiyon, pestisit zehirlenmesi, barotravma, yaygın alveolar hasar, pulmoner emboli ve antikoagülan gibi çeşitli nedenleri vardır [(1)]. Varfarin tedavisi DAH'ın nadir bir nedenidir [(1)]. Biz aort kapak replasmanı için varfarin tedavisinin bir komplikasyonu olarak diffüz alveoler hemoraji gelişen 69 yaşında bir erkek hastayı sunmayı amaçladık. Varfarin tedavisi kesildi ve mekanik ventilasyon tedavisi sırasında taze donmuş plazma, metilprednizolon, K vitamini verildi. Hasta iyi yanıt verdi ve INR terapötik değere kadar azaldı. Varfarin tedavisi sırasında DAH olasılığı mutlaka hatırlanmalıdır.

Anahtar kelimeler: *Varfarin, hemoptizi, solunum yetmezliği*

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INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a condition associated with alveolar capillary-induced lung hemorrhage. Cases of anticoagulant- related lung bleeding have been reported in the literature [(2)]. Diffuse alveolar hemorrhage as a complication of warfarin therapy used for valve replacement is associated with a high mortality rate. When anticougulants are administered, INR monitorization should be maintained carefully to prevent life -threatening bleeding.

In this paper, we describe a 69-year- old man with a history of aortic valve replacement (AVR) treated with warfarin, who was admitted to our institution's emergency department. Diffuse alveolar hemorrhage was suspected clinically and radiologic findings were subsequently confirmed by bronchoscopy. The patient required aggressive treatment with fresh frozen plasma, vitamin K and mechanical ventilation with a resultant successful outcome. We emphasise early diagnosis and fast therapeutic intervention in rare and potentially lethal complication of over-anticoagulation.

CASE PRESENTATION

A 69-year-old man with a medical history of AVR, hypertension (HT) and diabetes mellitus (DM) was

admitted to our institution's emergency service with complaints of respiratory distress, and bloody cough over the previous 24 hours.

The patient's medications on the day of admission were metoprolol 50 mg PO, valsartan/hidrochlorothiazide 80/12,5 mg PO, warfarin 5 mg PO, and metformin 1000 mg PO.

On examination, he was noted to be in severe respiratory distress and peripheral oxygen saturation was 80% with respiratory rate 26 / min, pulse rate 110 bpm and blood pressure 110/85 mm Hg. On auscultation rhythmic metallic heart sound, and diffuse wet crackles over both lung fields were heard. The patient was intubated and mechanical ventilation support was initiated because of respiratory insufficiency. Blood-tinged secretions was suctioned from the endotracheal tube.

The chest x-ray showed diffuse bilateral alveolar infiltrates suggestive of diffuse alveolar hemorrhage (Figure 1).

The patient was transferred to intensive care unit (ICU) immediately. Mechanical ventilation mode was SIMV, with FiO_2 90%, PEEP 9 cm H_2O, fr: 14, TV 500 ml. Results of his arterial blood gas measurements in ICU were as follows: pH 7.29, pCO_2 47.3, pO_2 70.3, BE -3.6, SO_2 84%, HCO_3 21.3.

All biochemical and hematological tests were performed in ICU. The patient's laboratory findings were as follws: , hemoglobin 10,1 gdl^{-1}, hematocrit 31.4%, platelets 332x103 mm^{-3}, leucocyte 20110 mm^{-3}, random glucose 110 $mgdL^{-1}$, serum sodium 137 $mmoll^{-1}$, serum potassium 3,8 $mmoll^{-1}$, serum creatinine 1,2 $mgdl^{-1}$ and blood urea nitrogen 36 $mgdl^{-1}$. INR 5,58, PT 49,7 s, aPTT 41,6 s. Urinalysis showed no pathologic findings.

The rest of the laboratory results including cardiac enzymes were unremarkable. For differential diagnosis of collagenous disease, serum levels of C-ANCA, P-ANCA, ANA, and anti-ds-DNA were investigated and these parameters were within normal limits. The patient had no rheumatological disease that would ordinarily cause DAH. Transthoracic echocardiography showed normal left ventricular ejection fraction and a normal mechanical aortic valve prosthesis with normal gradient.

The diagnosis was confirmed by computed tomographic (CT) and bronchoscopy (with bronchoalveolar lavage (BAL)). Bronchoscopy showed bilaterally presence of fresh blood up to segmental bronchi. A large number of hemosiderin-laden macrophages were observed during the examination of lavage samples. Open lung biopsy could not be performed due to the risk of bleeding.Thoracic computed tomography revealed newly developed ground-glass opacities with crazy-paving appearance on both sides of the lungs (Figure 2).

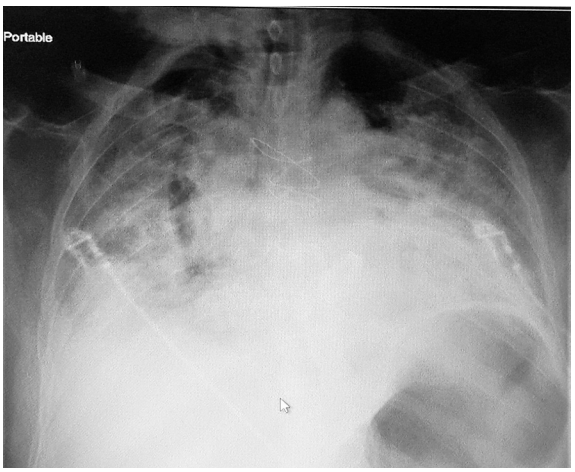

Figure 1. The chest x-ray showing diffuse bilateral alveolar infiltrates.

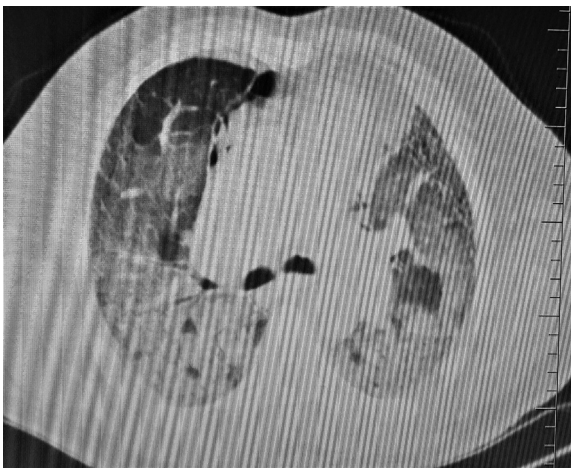

Figure 2. CT scan of chest showing 'crazy paving' appearance.

The warfarin treatment was discontinued. For DAH therapy high dose methyl prednisolone (1 g/d) was given for 72 hours. As prophylaxis meropenem (1 g IV tid) therapy was initiated. Fluid replacement was performed at an appropriate dose. On the day of admission two units of fresh frozen plasma were transfused along with vitamin K 10 mg IV. At the 24th and 48th hours of hospitalization INR values were 2,08 and 1,23, respectively (Table 1). Warfarin, 5 mg therapy was initiated simultaneously with enoxoparine 2x0.6 mg SC On the fourth day of follow-up, mechanical ventilation was no longer needed, so the patient was weaned from the ventilator. On the 7th day of follow-up, a chest X-ray and CT scan revealed significant improvement with resolution of infiltraion (Figures 3 and 4). After seven days of therapy with corticosteroids, antibiotics, and fresh frozen plasma, the patient recovered his healthy status and transferred to the cardiology department. Warfarin dose was increased to 7,5 mg daily and enoxoparine was stopped when therapeutic INR was reached at the 14th day of hospitalization.

Table 1. INR,aPTT and PT values of the patient before and after admission in the ICU.

Laboratory findings	Before admision of the ICU	24 hours after admission of the ICU	48 hours after admission of the ICU
INR	5.58	2.08	1.23
PT (sec)	49.7	23.1	15.4
aPTT (sec)	41.6	30.3	29.6

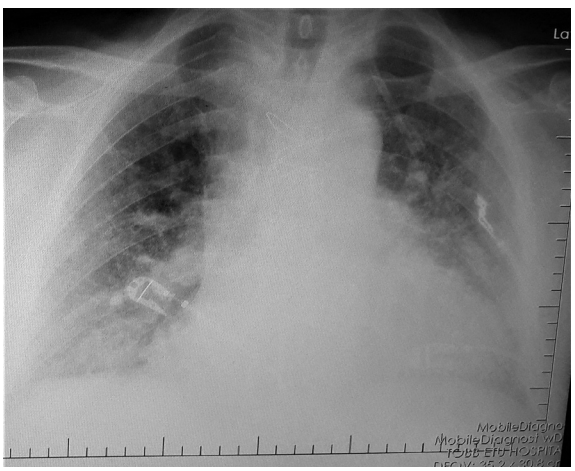

Figure 3. A chest X-ray on the 7th day showing significant improvement with resolution of infiltraion.

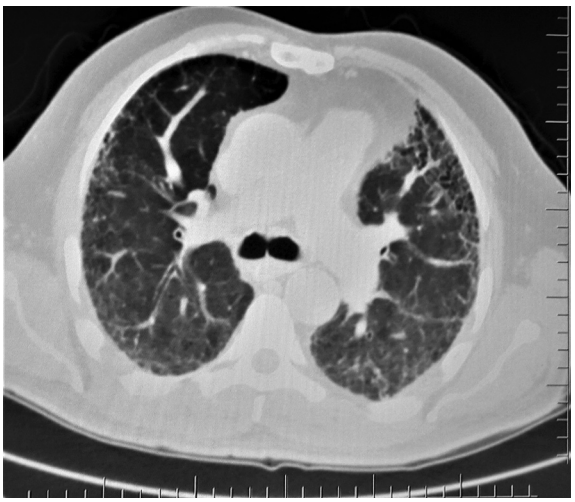

Figure 4. CT scan of the same patient on the 7th day after admission of the ICU.

DISCUSSION

DAH is a clinical syndrome characterized with dyspnea, anemia, and hemoptysis that is caused by pulmonary alveolocapillary membrane damage due to many etiologic factors.. Although the most important step in the diagnosis of DAH is clinical suspicion, imaging methods and detection of hemosiderin-laden macrophages in a bronchoalveolar lavage fluid are important in diagnosis. Immune system diseases like systemic vasculitis (Wegener's granulomatosis and microscopic polyangiitis), systemic lupus erythematosus (SLE), idiopathic pulmonary hemosiderosis are the most common causes [(3)]. Rarely, it can develop due to medication use. Although the mortality rate varies according to the etiology, it has been reported to range between 25% and 50% [(4,5)]. DAH develops as a rare complication of anticoagulants as warfarin, dabigatran, apixaban and edoxaban [(6-9)].

Warfarin is a commonly prescribed anticoagulant all over the world [(10)]. In the present case, warfarin was withdrawn from therapy, and 10 mg vitamin K, fresh frozen plasma, antibiotics, and high dose prednisolone were administered intravenously. The patient had a good prognosis over subsequent 4-7 days and was discharged home in stable condition.

Congestive heart failure, cerebrovascular disease, hepatic or renal disease, diabetes mellitus have been associated with elevated risks for bleeding in anticoagulant treatment [11]. In these cases, the risk of increased bleeding should be considered when oral anticoagulant is used [12,13]. Our case had a past medical history of AVR, so he received an oral anticoagulant therapy.

Warfarin (Coumadin) is a frequently prescribed oral anticoagulant. Complication (such as bleeding) can occur in any organ. Alveolar hemorrhage is a rare complication [14]. Since the first case of DAH caused by warfarin intoxication reported by Brown et al. [14] in 1965, few other reports have been cited in the literature. Warfarin-induced DAH is usually severe and can be lethal. The use of anticoagulants due to surgery and different diseases is increasing.

Our patient had abruptly increased INR . We investigated for possible causes of DAH (concomitant drugs, trauma, or infections). Firstly, it is very important to confirm the condition clinically in suspected patients with hemorrhage, because it can be lethal due to anemia and respiratory problems [15]. Supportive care and antidote administration are recommended for warfarin-induced hemorrhage, as with other new oral anticoagulants [12].

CONCLUSION

Although warfarin-associated DAH is rare, respiratory complications may be fatal.

In order to prevent complications in cases of overdose of warfarin, early diagnosis and aggressive treatment are required.

INR and PT test's should be performed at least 2 times in a month to prevent bleeding complications. According to these tests dose should be adjusted.

Vigilance should always be maintained to monitor INR's when anticougulants are administered so as to prevent bleeding complications as seen in this case.

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