CLINICAL INSIGHT ON WARFARIN INDUCED DIFFUSE ALVEOLAR HAEMORRHAGE : A CASE REPORT

ABSTRACT

Background: Diffuse alveolar haemorrhage (DAH) is a serious condition which requires a medical emergency. A contributing factor to DAH is anticoagulant treatment. Warfarin has been used as prophylaxis and treatment of venous thrombosis, thromboembolic complications from atrial fibrillation or cardiac valve replacement. Warfarin-induced diffuse alveolar haemorrhage is a serious medical condition. Initially, the diagnosis of DAH and for other pulmonary conditions clinical presentation and chest X-ray were enough to suggest the diagnosis.

Case Report: In this report a 72-year-old female patient with a history of Coronary Artery Disease (CAD), Hypertension, and surgical procedure of Aortic Valve Replacement (AVR) and Percutaneous Transluminal Coronary Angioplasty (PTCA). She was on warfarin therapy for 5 years and was admitted to the hospital for severe cough, haemoptysis and dyspnoea. DAH was suspected clinically and confirmed by Computed Tomography (CT) chest and bronchoscopy. The patient required treatment with non-invasive ventilation and fresh frozen plasma and other supportive care. Early diagnosis and treatment are highlighted in our case and an anticoagulation reversal is required. Therefore, it is important to carefully monitor patients receiving warfarin therapy for the main symptoms of such an incident and to start treatment as soon as possible in order to reduce mortality.

Keywords: Diffuse alveolar haemorrhage, warfarin, anticoagulants, bronchoscopy, PT-INR

INTRODUCTION

Diffuse Alveolar Haemorrhage (DAH) is a definite clinicopathologic syndrome of pulmonary haemorrhage that usually originates from the pulmonary microcirculation, which includes the alveolar capillaries, arterioles and venules [1] The occurrence of this is due to the disruption of the alveolar-capillary basement membrane which leads to the collection of red blood cells in the intra-alveolar region. A contributing factor of DAH is anticoagulant treatment. People may have multiple concurrent ailments especially older individuals are affected more, and thus frequently receive multiple medications. Hence, side effects and ADRs are an issue with medication [2].

Warfarin is a once-daily oral anticoagulant medication which is commonly used to treat and prevent blood clots. It competitively inhibits the vitamin K epoxide reductase complex 1 (VKORC1), an enzyme which is responsible for activating vitamin K in the body. The onset of action is 24 – 72 hrs. and peak therapeutic effect is seen in 5-7 days after initiation. However, the patient's International Normalized Ratio (INR) increase within 36 – 72 hrs. after treatment initiation. The dose-response among patients varies and depends on interpatient differences. Significant haemorrhage and bleeding are serious adverse effects of warfarin. Periodic blood testing of the patient's prothrombin time (PT) and international normalized ratio (INR) is recommended to ensure the safety and efficacy of the medication and also to reduce the risk of adverse effect during warfarin therapy [3].

We report a case of DAH associated with warfarin medication. In this case report, we discuss an uncommon and potentially fatal side effect of warfarin: widespread alveolar bleeding.

PRESENTATION OF CASE

A 72-year-old female patient arrived at the emergency room complaining of a cough that had persisted for five days, hemoptysis, and shortness of breath for two days prior to admission. She had previously undergone AVR 24 years prior and PTCA in January 2023. She also had a history of CAD and hypertension dating back 24 years. Since 2017, she had been receiving treatment with warfarin at doses of 3 mg every five days and 4 mg every two days. Her INR was measured once per week, and her doses were modified when necessary. The most recent INR that was recorded was 3.23 one week before hospitalization.

Upon admission vital signs were recorded as follows: BP - 160/90mmHg, PR - 77bpm, RR - 20 cycles/min, SPO2 - 65% without O2 and 97% after initiating 8L of O2/min. On physical examination, she was conscious, and oriented. In Cardiac auscultation, regular S1 and S2 were noted. A pulmonary examination revealed bilateral crepitation and wheezing. Pedal edema was noted on bilateral legs.

At the emergency department, the patient was initially treated with IV antibiotics, diuretics, and nebulization and advised to start intermittent BIPAP with oxygen support. CT Chest did show (Figure 1) confluent patches of consolidation in the right lung with the air-space nodular opacity in bilateral lungs indicating likely infective, cardiomegaly, and few prominent mediastinal lymph nodes. For further management patient was shifted to Intensive Care Unit.

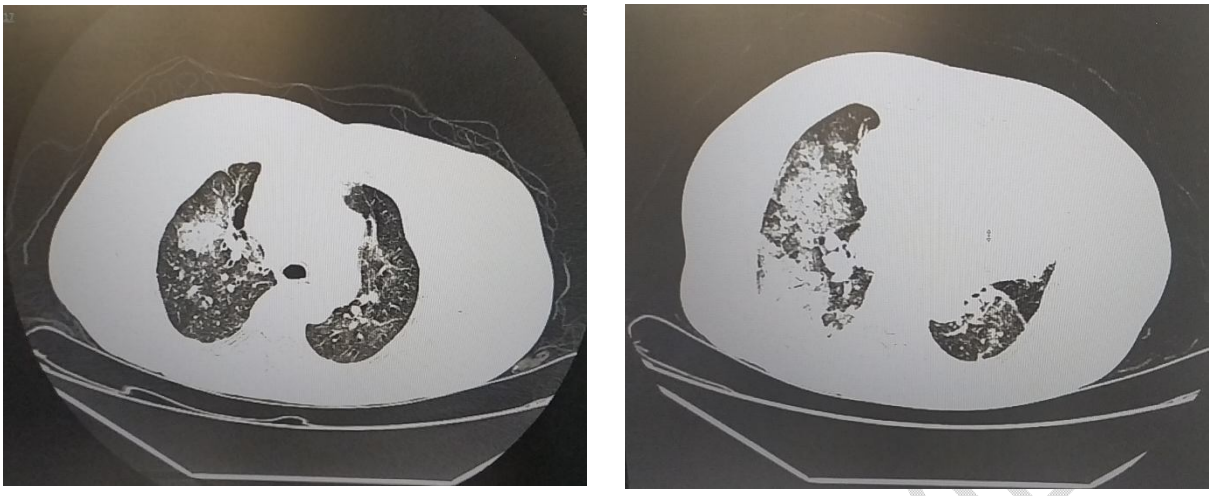

Figure 1: *CT Chest showing confluent patches of consolidation in the right lung with the air- space nodular opacity in bilateral lungs indicates likely infective, cardiomegaly, and few prominent mediastinal lymph nodes (Day 1).*

Laboratory data were reported as Hb - 8.1g/dl(13-15g/dl), TLC - 9140cells/mm^3 (4000-11000 cells/mm^3), Platelet count - 212000cells/mm^3(150000-450000cells/mm^3), Procal - 0.095, CRP – 28mg/L(0-5.0 mg/L), Na – 135mmol/L(136-145mmol/L), K - 4.39mmol/L(3.5-5.1mmol/L), Blood urea – 46mg/dl(13-43mg/dl), Creatinine - 0.83mg/dl(0.9-1.3mg/dl), PT - 31.7sec (11.1-12.9secs), INR 2.72(0.8-1.2) and liver function test were normal.

With DAH as a main diagnosis, due to respiratory distress, the patient was supported with NIV and fed by RT. Initially, the anticoagulant Heparin 2500IU was started followed by the patient experiencing hemoptysis and nasal bleeding thus anticoagulant was withheld. In view of anemia (Hb - 6.7), 1 unit PRBC was transfused and post-Hb was 8.0. Due to no further bleeding complaints, Heparin 2500IU was restarted Q6H on day 4. On day 7, Heparin dose was increased to 5000IU Q8H. As the patient reported mild blood-stained sputum on day 8, Chest X-ray was taken (Figure 2) which shows infiltrates in the right lung, left lower lobe collapse, and cardiomegaly also to rule out blood/mucus clots and Bronchoscopy was done (Figure 3), it showed blood clots occluded in the left main bronchus, thus the anticoagulant dose was reduced again to 2500IU and continued.PT/INR was monitored and its timeline is shown in (Figure 4). The patient was symptomatically better, hence was weaned off from NIV on day 12 to intermittent BIPAP with oxygen support. Repeat Chest X-ray revealed (Figure 2) left lobe collapse consolidation, cardiomegaly hence planned for another Bronchoscopy which showed left lower lobe blood clots occlusion and bronchial toileting done also no active bleed was found. The patient was treated with IV antibiotics, IV PPI, IV steroids, Nebulized bronchodilators, antihypertensives and supportive medications including intermittent BIPAP with oxygen, and other nutritional supplements, RT feed was switched to oral feed on day 15 and clinically better hence planned for discharge. Her course in the hospital was 18 days with an ICU stay for 13 days, a ward stay for 5 days and got discharged. Follow up Chest X-ray was done (Figure 5) after 10 days of discharge and it shows a normal radiographic imaging

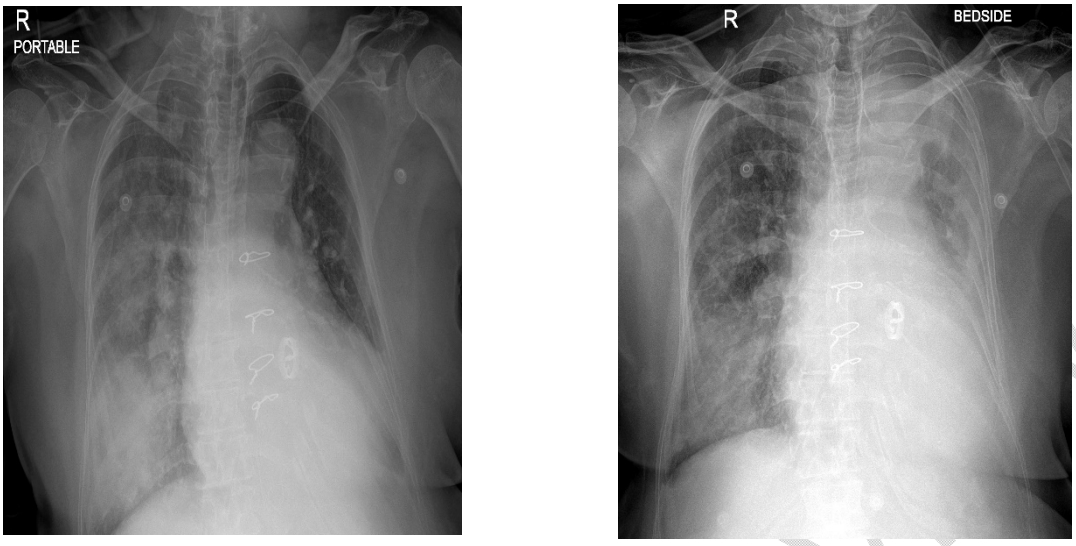

Figure 2: *Chest X-ray on day 4 and day 11 which shows infiltrates in the right lung, left lower lobe collapse, cardiomegaly and left lobe collapse consolidation, cardiomegaly respectively.*

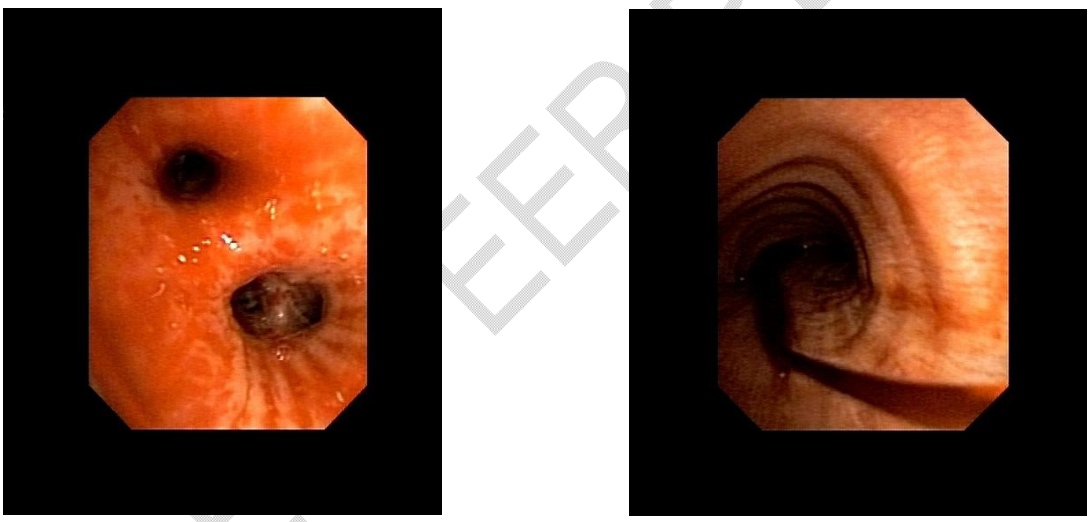

Figure 3*: Bronchoscopy showed blood clots occluded in the left main bronchus (Day 8)*

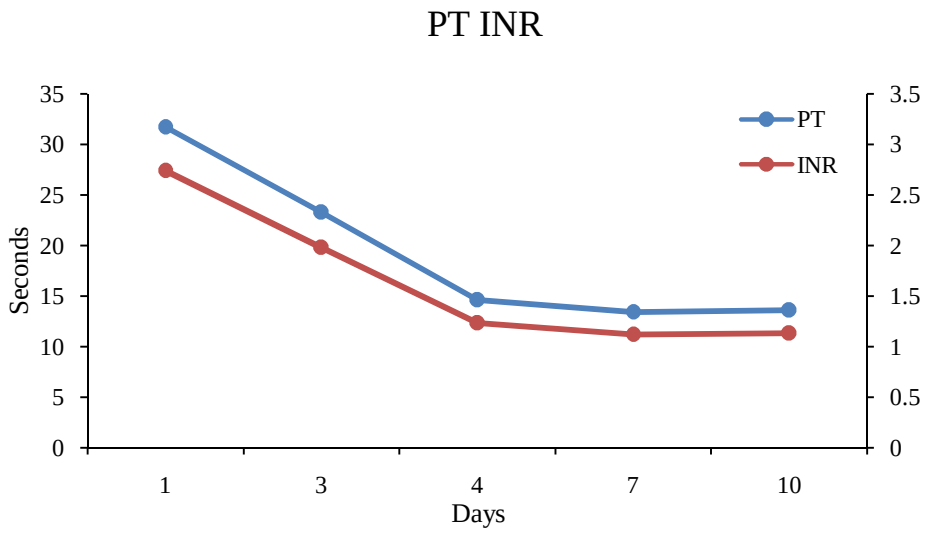

Figure 4: *Coagulation parameters during admission in Hospital. PT-Prothrombin Time; INR-International Normalized Ratio.*

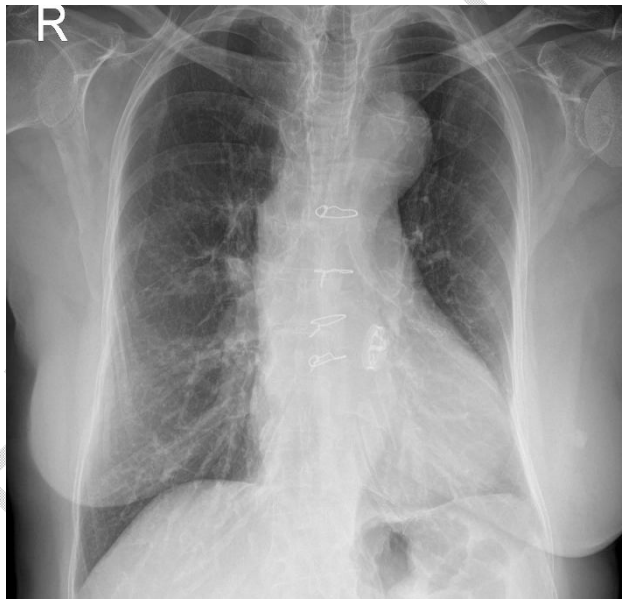

Figure 5: Follow up Chest X-ray was done after 10 days of discharge and it shows a normal radiographic imaging

DISCUSSION

In patients with DAH, the prognosis is often dismal and the in-hospital mortality ranges from 20% to 100% [4]. Clinical conditions which are known to cause DAH includes immunological mediated such as systemic vasculitis, rheumatoid arthritis, systemic lupus erythematosus, Goodpasture syndrome, antiphospholipid syndrome, Bechet's disease and nonimmunological mediated include drugs, toxins, bleeding disorders

and malignancy [5]. DAH is presented with hemoptysis, anemia, diffuse lung infiltrates and acute respiratory failure. Hemoptysis may be absent in one-third of patients with DAH [5]. Diagnosis of DAH is often critical which requires thorough and thoughtful approach to appropriate management.

In a report, Borjian et.al.(2020) have presented a case of DAH in a 41-year-old female patient who had a history of mitral valve replacement 10 years ago and had been under warfarin therapy (warfarin 7.5 mg/ day) since then. Patient claimed no history of altered INR level until prior admission in which she diagnosed with warfarin-induced DAH. After taking amoxicillin for sinusitis con-cominantly with warfarin she developed symptoms of shortness of breath and excessive cough [6]. A similar case reported by Larsen et.al.(2014) also showed a patient presented with dental bleeding and prolonged INR following dental procedure who was treated for a dental abscess along with amoxicillin/clavulanate [7].

Heffler et al. (2016) also described a case of DAH in a patient receiving warfarin therapy (1.25 mg/day) for AF who had hematuria at the time of admission as a result of a self-increased dosage of warfarin (5 mg/day) taken 8 days earlier [8].

In our report, although she was taking warfarin for 6 years (3mg MON-SAT and 4mg SUN) she didn't experience any liable INR as there was proper monitoring of PT/INR, this event occurred only after her surgical procedure of PTCA to LCx where the dose was modified to 4mg MON-SAT and 3 mg SUN. In order to avoid life-threatening complications of warfarin therapy, it is of the utmost importance to be conscious of drug interactions.

Furthermore, the patient was put on intermittent BIPAP with oxygen support which was due to type 2 respiratory failure. Hence ABG was monitored regularly which is tabulated (Table 1) and pressure was modified accordingly.

Initially, the diagnosis of DAH and for other pulmonary conditions clinical presentation and chest X-ray were enough to suggest the diagnosis. Over time, CT scans evolved for the better visualization of parenchymal lung findings. However, BAL samples from flexible fibre-optic bronchoscopy remain a better diagnostic tool for DAH which will show the presence of hemosiderin stains within the alveolar macrophage [9]. In this case, we firmly believe that the instantaneous diagnosis made possible by fibre-optic bronchoscopy and the prompt therapeutic measures helped to save this woman's life.

The patient has type 2 respiratory failure; hence ARDS is one of the possible diagnosis. But type 2 RF, which causes hypercapnia, is a prevalent factor in DAH. Since our patient's medical background did not point to any other possible causes, we determined that DAH was caused by warfarin toxicity.

Table 1. Arterial Blood Gas

Days	pH	pCO2(mmHg)	pO2(mmHg)	pHCO3(mEq/L)
1	7.34	55.8	98.6	29.4
2	7.31	73.3	108	36
7	7.26	96.7	74.8	42.7
10	7.39	62.3	74.4	37.7
13	7.39	56.7	82.5	34.2

ABG was monitored regularly throughout admission. ABG-Arterial Blood Gas

CONCLUSION

Drug-induced coagulation disorder in patients can have life-threatening consequences. The three key aspects of the diagnostic and treatment of drug-induced DAH are highlighted in our case. First, early and immediate diagnosis is required. The BAL was used in our instance to validate the diagnosis because it is frequently regarded as the gold standard. Second, because DAH has a high mortality rate, treatment should start as soon as possible, with coagulopathy reversal serving as the main component of the management plan. Third, better oxygenation to support the patient's respiration and ventilation support if required.

CONSENT

Written informed consent was obtained from the patient regarding the publishing of his anonymized clinical and paraclinical data in the current study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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ABBREVIATIONS:

ABG	Arterial Blood Gas
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
ARDS	Acute Respiratory Distress Syndrome
AVR	Aortic Valve Replacement
BAL	Bronchoalveolar Lavage
BIPAP	Biphasic Positive Airway Pressure
BP	Blood Pressure
CAD	Coronary Artery Disease
CRP	C-Reactive Protein
CT	Computed Tomography
DAH	Diffuse Alveolar Haemorrhage
FRI	Friday
Hb	Hemoglobin
ICU	Intensive Care Unit
INR	International Normalized Ratio
IU	International Unit
IV	Intravenous
K	Potassium
LCx	Left Circumflex
Mg	Milligram
MON	Monday
Na	Sodium
NIV	Non-invasive Ventilation
pCO_2	Partial Carbon dioxide
pO_2	Partial Oxygen
pH	Potential of Hydrogen
PPI	Proton Pump Inhibitors
PR	Pulse Rate
PRBC	Packed Red Blood Cells
Procal	Procalcitonin
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
Q6H	Every 6 hours
Q8H	Every 8 hours
RF	Respiratory Failure
RR	Respiratory Rate
RT	Ryle's Tube
S1S2	Sound 1 Sound 2
SAT	Saturday
SPO_2	Saturation of Peripheral Oxygen
SUN	Sunday

TLC	Total Leukocyte Count
VKORC1	Vitamin K epoxide Reductase Complex 1
X-Ray	Radiography