# Ticagrelor Induced Diffuse Alveolar Hemorrhage - A Case Report

Kunwer Naveed[1], Shaheen Bibi[1*], Sumbul Nasir[2], Mehwish Qamar[1] and Maryam Asif[3]

[1]*Department of Nephrology, Liaquat National Hospital and Medical College, Karachi, Pakistan*
[2]*Department of Nephrology, Ziauddin University Hospital, Karachi, Pakistan*
[3]*Dow University of Health Sciences, Karachi, Pakistan*

## Abstract

Drug-induced Alveolar Hemorrhage is a rare cause of Diffuse Alveolar Hemorrhage (DAH). It requires to be considered in the differential diagnosis among patients presenting with DAH and prompt management, including the need for mechanical ventilation in severe cases.

Here we present a case of severe DAH following percutaneous coronary intervention and Ticagrelor therapy that responded well to discontinuation of Ticagrelor.

**Keywords:** *Diffuse alveolar hemorrhage, percutaneous coronary intervention, left heart catheterization, chronic kidney disease, myocardial infarction, drug-eluting stent.*

## INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition that requires prompt diagnosis and appropriate management. The patient may need mechanical ventilation in severe cases. Treatment option depends upon the underlying condition and may require urgent therapeutic plasma exchange (TPE). Most commonly it is associated with vasculitic disorders like anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis and anti-glomerular basement membrane (Anti- GBM) antibody-associated vasculitis. Drugs are also among the important cause of DAH.

Here we are presenting a case of severe DAH following percutaneous coronary intervention (PCI) from Ticagrelor therapy that responded well to discontinuation of Ticagrelor.

## CASE REPORT

A 70 years old male, non-smoker, with functional Class-I (FC-I) at home, presented with shortness of breath (SOB) and palpitation to the emergency room (ER). He had a past medical history of diabetes (DM), hypertension (HTN), ischemic heart disease (IHD) and benign prostatic hyperplasia (BPH). He also had a history of chronic kidney disease (CKD) with baseline Creatinine 4.0mg /dl. On arrival, he was in respiratory distress with a respiratory rate of 20 breaths per minute, blood pressure –of 100/50 mmHg, heart rate of 100 bpm and oxygen saturation of 86% on room air. On initial work up his renal parameters were deranged and had raised troponin I (cardiac enzymes). The rest of his lab workup did not show any abnormality except anemia (hemoglobin 9.6mg/dl) (**Table 1**). The patient was diagnosed with acute renal failure (ARF) on the background of chronic kidney disease (CKD) with Non-ST elevation myocardial infarction (NSTEMI). After loading with Aspirin 300mg, Ticagrelor 180mg and unfractionated heparin 5000 IU, the patient underwent left heart catheterization and had PCI with 2 drug-eluting stents placement followed by hemodialysis *via* temporary double lumen catheter passed *via* left femoral access. He was started on dual anti-platelets with Aspirin 75mg daily, Ticagrelor 90mg twice a day and anticoagulation with Enoxaparin 60mg daily. On the 3rd post-procedure day, the patient developed hemoptysis and due to persistent desaturation despite high flow oxygen, he required intubation and was initiated on mechanical ventilation with 100% FiO2 (fraction of inspired oxygen). His hemoglobin dropped from 9.6 gm/dl to 7.0gm/dl. Chest X-Ray (CXR) showed bilateral infiltrates that gradually worsened on the following day (**Fig. 1**). Considering the possibility of DAH, a combined consensus between pulmonology, cardiology and nephrology was made to hold all anti-platelets and anticoagulation. Work up did not show any coagulation abnormality and also workup for ANCA vasculitis, Anti-GBM and rheumatic diseases including systemic lupus erythematosus (SLE) were negative

**Table 1:** Laboratory values.

| Laboratory Parameter | Results |
|---|---|
| Hemoglobin (HB) | 9.6 mg/dl |
| Total leukocyte count (TLC) | 11.4* 109/L |
| Platelets count | 400 × 109/L |
| Prothrombin time (PT/INR) | 11 seconds/ 0.8 |
| Activated partial thromboplastin time | 21 seconds |
| ANA profile | All negative |
| Anti-DNA | Negative |
| ANCA (p-ANCA & c-ANCA) | Negative |

**Corresponding author: Shaheen Bibi, Department of Nephrology, Liaquat National Hospital and Medical College, Karachi, Pakistan; Email: shaheensultan51@gmail.com*
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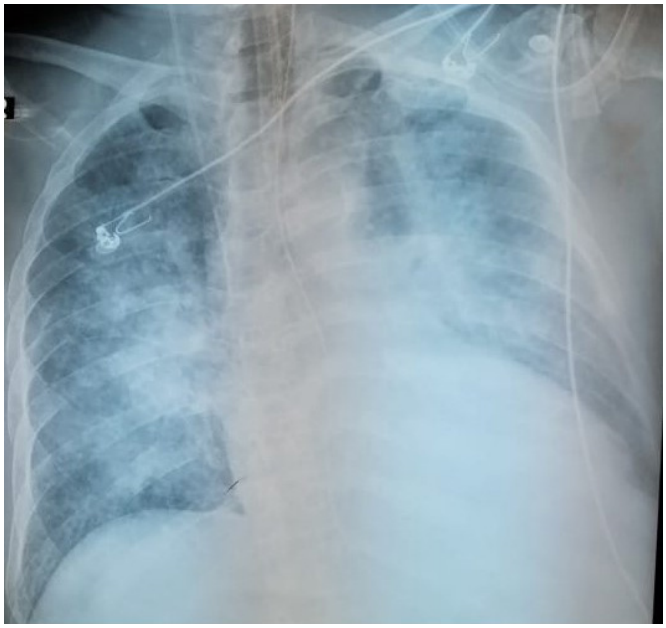

**Fig. (1):** Chest X-Ray (CXR) showed bilateral infiltrates.

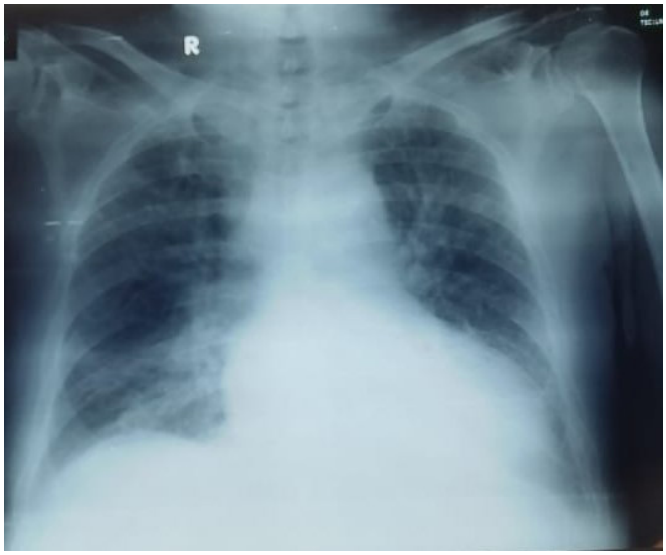


**Fig. (2):** Chest X-Ray (CXR) started improving.

(**Table 1**). Three doses of pulse Methylprednisone was given. Bronchoscopy with sequential bronchoalveolar lavage was performed that confirmed DAH. His bedside transthoracic echocardiogram (TTE) was performed that showed moderate mitral regurgitation with preserved ejection fraction (EF:55%). Given the severity of DAH requiring mechanical ventilation, it was decided to administer therapeutic plasma exchange (TPE). However, after a total 3 sessions of TPE, it was decided to withhold further TPE, with a literature review on drug-induced DAH supporting the role of only stopping the causative drug. The patient also received a total of 3 packed RBCs (red blood cell) transfusions during the hospital stay. After 5 days of stopping Ticagrelor, the patient was extubated successfully. Hemoglobin (Hb) stabilized to 10gm/dl and CXR showed improvement (**Fig. 2**). He improved clinically and only required 2L of oxygen *via* nasal prongs. Only Aspirin was resumed.

## DISCUSSION

DAH is a rare medical emergency and could have a catastrophic outcome. Three histopathologic patterns are described, which include pulmonary capillaritis, diffuse alveolar damage and bland pulmonary hemorrhage [1]. It is characterized by damage to the alveolar capillaries, arterioles, and venules leading to blood leaks into the alveolar spaces and are usually diffuse but can be focal as well. DAH clinically manifests with hemoptysis in 2/3$^{rd}$ of cases. Other possible presentations are anemia, drop in hematocrit, dyspnea, non-specific cough, fever, chest pain and severe respiratory failure. In 1/3$^{rd}$ of the cases, no obvious hemoptysis occurs. It may present with unilateral and bilateral chest infiltrates on radiograph [2]. Depending on the underlying aetiology, DAH can possibly present with or without systemic signs and symptoms. Hence, a high index of suspicion is required if the clinical scenario is suggestive [3]. DAH is most commonly associated with Systemic vasculitides [4]. Its other causes include anti-GBM, idiopathic pulmonary capillaritis, idiopathic pulmonary hemosiderosis, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome, diastolic heart failure, hematopoietic cell transplantation, lung transplantation and bleeding disorders. DAH in approximately 10% of cases is due to drug toxicity [5]. Certain drugs like carbimazole, antiplatelet including Ticagrelor, penicillamine, propylthiouracil, hydralazine, levamisole, cocaine, allopurinol, sulfasalazine are implicated to cause DAH [6]. Other offending drugs are amiodarone, leflunomide, nitrofurantoin, sirolimus, tumor necrosis factor (TNF)-alpha antagonist, abciximab. There is one case of ketorolac-induced DAH in the literature [7]. Sirolimus is another cause of drug-induced DAH in patients with renal transplants. The definite treatment of DAH depends on the underlying disorder. Immunosuppressive therapy is the treatment of DAH in a setting of systemic vasculitis [8]. Recombinant factor VIIa (rVIIa) can be considered for refractory DAH [9]. Therapeutic plasma exchange (TPE) is currently recommended as per guidelines of the American Society for Apheresis in patients with DAH presenting with respiratory failure requiring high flow oxygen and/or ventilator support [10]. However, for drug-induced DAH discontinuation of the culprit drug is advised.

Ticagrelor is an anti-platelet agent, non-thienopyridine; P2Y12 antagonist. Therapeutic indications of the drug include acute coronary syndrome and stable coronary artery disease (CAD). It can be used in the primary prevention of patients with a high risk of CAD. It is also used during PCI. Similar to Sirolimus [11], Ticagrelor, is reported as an important cause of DAH. Case reports of Ticagrelor-induced DAH are available that respond to drug discontinuation [12]. The postulated mechanisms for Ticagrelor-induced DAH are drug hypersensitivity, the anti-thrombotic effect of the drug and drug-induced TTP.

In our case patient developed frank hemoptysis second post PCI day that subsequently diagnosed as DAH on BAL. We assumed Ticagrelor to be the possible culprit of DAH so discontinued it immediately. No definite algorithm for the management of anti-platelet drug-induced DAH is available. In our patient, TPE was started keeping severe nature of DAH but was subsequently stopped. He responded well to drug discontinuation.

## CONSENT FOR PUBLICATION

Informed consent was taken from the patient for publication and informed that none of his personal information will be included in the final publication.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

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