Alveolar Hemorrhage Complicating Thrombolysis with Tenecteplase for SCA ST+: A Rare Complication in One Case with a Review of the Literature

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Summary
Alveolar Hemorrhage (AH) is a heterogeneous clinical syndrome with a high mortality rate, characterized by significant bleeding into the alveolar spaces. HA secondary to systemic thrombolysis therapy in acute myocardial infarction is an uncommon but life-threatening complication and can lead to acute respiratory failure. This entity is rarely reported in the literature. We report a case of acute HA after intravenous thrombolysis with Tenecteplase for acute myocardial infarction, and discuss risk factors as well as clinical and radiological evidence supporting the diagnosis. We also review the few previously published case reports in this context, and compare our results with those reported in the literature.

Introduction
Alveolar Hemorrhage (AH) is a rare disease, characterized by the presence of blood at the level of the pulmonary acinus, related to a lesion of the alveolar-capillary barrier (excluding flooding of bronchial origin), more rarely of the pre-capillary arteriole and the post-capillary venule [1].

It is a therapeutic emergency because it can quickly lead to acute asphyxiating respiratory failure with death [2].

The current classifications of HA are based on the determination of the origin of HA according to whether or not it is the result of treatment with corticosteroids or immunosuppressants, thus distinguishing between:
- HA of certain immune origin,
- HA of non-immune origin,
- HA with no apparent cause (idiopathic HA).

Immune HAn on are HA of cardiovascular origin, HA related to haemostasis disorders, HA of medicinal and toxic origin, HA by negative pressure oedema, HA of septic origin, Tumor H A, etc. [1].

Somenon-immune HA may be linked to autoimmune mechanisms, such as drug-induced HA [1].

The most commonly incriminated drugs are amiodarone, D-penicillamine (trolovol®), anticoagulants, antiaggregants and fibrinolytics. Inhalation of certain toxins such as cocaine can also lead to the occurrence of HIA. Silicones used for aesthetic purposes may be accompanied in some cases by intraalveolar haemorrhage [1,2].

Pulmonary alveolar hemorrhage is an extremely rare and life-threatening complication of intravenous thrombolytic therapy. So far, only a few cases have been reported in the literature [3]. We report here a case of acute alveolar hemorrhage complicating thrombolytic treatment in myocardial infarction.

Through our case, we address the risk factors, clinical and radiographic findings that suggest and support the diagnosis, as well as the management issues related to this unusual and life-threatening situation.

Clinical Case
This is a 70-year-old patient with FDRCVx: type 2 diabetes of recent discovery, without any particular ATCD. Admitted to an inferobasal STEMI array, he was immediately given a loading dose of aspirin and Clopidogrel, and then had successful thrombolysis with tenecteplase. 24 hours later, he developed hemoptoid sputum. On physical examination, it was apyretic, hemodynamically stable with BP: 140/75 mmhg, HR: 75 BPM, eupneic with RF: 18 cpm, Sp02: 98% in ambient air.

Pulmonary auscultation revealed crackling rattles limited to the pulmonary bases more pronounced on the right, with no signs of heart failure.

Chest X-ray has objectified bilateral alveolar infiltrates. At the same time, the laboratory work-up showed a decrease in HB levels from 16.6 g/dl to 15 g/dl, with normal platelet and white blood cell counts.

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Chest CT showed foci of alveolar condensation strongly sug-
Faced with the persistence of the VT, the patient received a CEE (200 D) 2 H after the performance of the ATL with return to sinus rhythm.

The evolution was marked by the onset of dyspnea with a polypnea at 30 cm and a desaturation at 85 in ambient air, with the presence of bilateral crackling rails reaching midfield, echocardiographic control showed high filling pressures without added kinetic disorders. The patient was injected on furosemide. A follow-up CT scan was performed showing a stationary aspect of the alveolar hemorrhage.

Two days later, the patient presented with greenish sputum with an increase in the biological markers of inflammation, prompting the introduction of a double antibiotic therapy based on amoxicillin and ciprofloxacin. 48 hours later, the patient worsened his respiratory distress with a desaturation to 70 in the ambient air and appearance of signs of struggle, the chest x-ray showed a worsening of the lesions with bilateral opacities reaching to the summits.

The patient was transferred to the intensive care unit and intubated on the basis of respiratory criteria. The aftermath was marked by the onset of severe ARDS with the death of the patient.

Table 1: Described cases of alveolar haemorrhage after thrombolytic therapy for myocardial infarction.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Age, gender</th>
<th>Thrombolytic Agent</th>
<th>Time Interval</th>
<th>Underlying Context</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obispo et al 1992 [7]</td>
<td>60/H</td>
<td>streptokinase</td>
<td>36h</td>
<td>CPR, defibrillation</td>
<td>Restored</td>
</tr>
<tr>
<td>Hammoud et al 1996 [10]</td>
<td>70/H</td>
<td>r-TPA</td>
<td>12h</td>
<td>Ipsilateral pulmonary trauma two years earlier, defibrillation</td>
<td>Restored</td>
</tr>
<tr>
<td>Gopalakrishnan et al 1997 [13]</td>
<td>24/H</td>
<td>r-TPA</td>
<td>24h</td>
<td>Cardiac catheterization</td>
<td>Restored</td>
</tr>
<tr>
<td>Gopalakrishnan et al 1997 [13]</td>
<td>64/H</td>
<td>r-TPA</td>
<td>12h</td>
<td>COPD</td>
<td>Restored</td>
</tr>
<tr>
<td>Ayyub et al 2003 [16]</td>
<td>35/H</td>
<td>streptokinase</td>
<td>20h</td>
<td></td>
<td>Restored</td>
</tr>
<tr>
<td>Gonzalez et al 2011 [17]</td>
<td>42/H</td>
<td>streptokinase</td>
<td>20h</td>
<td></td>
<td>Restored</td>
</tr>
<tr>
<td>Abousoa et al 2014 [18]</td>
<td>75/H</td>
<td>streptokinase</td>
<td>72h</td>
<td></td>
<td>Restored</td>
</tr>
<tr>
<td>Mahjoo et al 2014 [19]</td>
<td>45/H</td>
<td>streptokinase</td>
<td>12h</td>
<td>Cocaine and tobacco abuse</td>
<td>Deceased</td>
</tr>
<tr>
<td>Prasad et al 2020 [21]</td>
<td>65/H</td>
<td>streptokinase</td>
<td>48h</td>
<td></td>
<td>Restored</td>
</tr>
<tr>
<td>Prasad et al 2020 [21]</td>
<td>60/H</td>
<td>streptokinase</td>
<td>6h</td>
<td></td>
<td>Deceased</td>
</tr>
<tr>
<td>Ben Mrad et al 2021 [3]</td>
<td>63/H</td>
<td>streptokinase</td>
<td>24h</td>
<td>Defibrillation</td>
<td>Restored</td>
</tr>
<tr>
<td>Ben Mrad et al 2021 [3]</td>
<td>61/H</td>
<td>Tenecteplase</td>
<td>48h</td>
<td></td>
<td>Restored</td>
</tr>
<tr>
<td>Mardenli et al 2023 [22]</td>
<td>64/H</td>
<td>streptokinase</td>
<td>12h</td>
<td>Bilateral chest trauma 10 months earlier</td>
<td>Restored</td>
</tr>
</tbody>
</table>
Discussion

The available literature does not cover the exact incidence of this complication, but rather consists of a few case reports [3]. Chang YC et al [4] retrospectively reviewed 2,634 patients with acute STEMI who received thrombolytic therapy and reported that hemoptysis occurred in 11 patients (0.4%).

Four fibrinolytic agents were used in these cases: streptokinase, urokinase and actilyse (Alteplase-rtPA), tenecteplase. Most of these patients received streptokinase. To the best of our knowledge, only one case associated with Tenecteplase (Metalysis) has been previously reported in the literature [3].

Through the analysis of these cases, we find that HA usually occurs from a few hours to 5 days after thrombolysis [13].

The literature review identified 23 cases [3,22]. Surprisingly, all 23 patients (including ours) were male, ranging in age from 24 to 75 years, making male a predisposing factor [3]. Streptokinase was the thrombolytic agent in 16 of 23 patients (69.5%) [3,21]. Streptokinase immune reactions that range from simple allergy to anaphylactic shock may be a contributing factor. It has been suggested that immune-mediated capillaritis maybe a possible etiology of HA following streptokinase administration [3,21,23].

The pathogenesis of HA attributable to thrombolytic therapy remains uncertain and may be explained by pre-existing fibrinolytic states, the presence of parenchymal abnormalities, or an immune response to streptokinase causing pulmonary capillaritis as proposed [20].

It was mentioned that some potential cofactors may predispose to this complication, such as underlying lung diseases (chronic obstructive pulmonary disease, anterior emphysema), recent pneumonia, cardiac catheterization, arrhythmias requiring defibrillation shock or cardiopulmonary resuscitation, heart failure, and substance abuse such as cocaine and tobacco [24]. Green et al [25] described that some patients with alveolar hemorrhage had capillaritis, suggesting an immune reaction since streptokinase is associated with a wide range of allergic reactions, such as anaphylaxis, bronchospasm, and type III immune reactions. Tio et al [8] described the discovery of antibodies to streptokinase in HA patients treated with thrombolytics, which would support this theory. However, in some cases, no predisposing factors have been identified.

For our patient, pneumonia and defibrillation after thrombolytic administration could be the cause of the worsening HA.

Typically, the diagnosis of HA is evoked in the clinical triad of haemoptysis, anemia and radiological pulmonary infiltrates, with a variable mode of onset (insidious to abrupt). Hemothysis is rarely abundant due to its distal nature. It may be associated with coughing or chest pain. Frequent anaemia, possibly of rapid onset with a sudden loss of 10 to 20 g/L, given thealveolar surface during active HA [1].

Chest X-rays may be normal (about 5%). Anemia may also be missing [1]. It varies depending on when it is done in relation to the beginning of the bleeding, and its intensity. In the initial phase, bilateral micronodular images are observed, which will often converge and give predominantly perihilar and peripheral alveolar opacities, sparing the apexes and costophrenic angles [21]. These opacities over time will give way to interstitial opacities (indicating the resorption of the hemorrhagic alveolitis in the interstitium) in principle transient (10 days to 2 weeks) [1].

Chest computed tomography (CT) scans are of little interest in the acute phase and can only be considered in stable patients. It may show areas of bilateral alveolar condensation and/or frosted glass, diffuse, sometimes associated with cross-linking giving a crazy paving appearance [1].

Diagnostic confirmation is based on bronchial endoscopy and AML, the appearance of which varies according to the length of the intraalveolar hemorrhage. A lung biopsy is not necessary [1].

When the diagnosis is suggested, bronchial endoscopy with Bronchoalveolar Lavage (BAL) is the gold standard to confirm the diagnosis. However, this is usually not possible. In cases of post-thrombolysis HA reported in the literature, these examinations have not been performed [3].

The prognosis can sometimes be life-threatening. In some all-cause H series, between 20 and 70% of patients are ventilated and 50 to 90% are on dialysis. Mortality ranges from 20% to 100% with early mortality (first 15 days) attributable to HA of about 10% [1].

To identify patients at risk of hospital death, the following parameters are available in the first 24 hours: resuscitation severity scores (IGS II, APACHE II), an LDH level greater than twice normal, the presence of shock or severe kidney damage [1].

Regarding the cases of post-thrombolysis HA described in the literature, the clinical course was good in about 80% of cases with complete recovery within one to two weeks. The prognosis depends on the extent of the myocardial infarction, the volume of the hemorrhage and the degree of cardiorespiratory involvement.

Prior to our publication, only 23 cases were reported in the literature with five deaths; therefore, the mortality rate was 21%[3].

Symptomatic treatment of acute respiratory failure has no specificity. If mechanical ventilation becomes necessary, it should limit barotrauma. The volume of blood glucose levels should be assessed regularly, as any overload is deleterious, especially in the case of associated renal failure. Any abnormality in haemostasis can aggravate the disease: non-essential antiaggregation or anticoagulant treatments should be discontinued.

In severe cases, some people use desmopressin or corticosteroid therapy, the effectiveness of which is controversial [1]. Antifibrinolytic agents, such as tranexamic acid, were used in one case.

Conclusion

Alveolar hemorrhage is an unusual complication of thrombolytic treatment of myocardial infarction, reported especially with streptokinase. The diagnosis of alveolar haemorrhage is based on a set of arguments, as the signs are not specific and can delay the diagnosis. Diagnosis should be considered in patients with respiratory distress associated with haemoptysis, acute anaemia, and pulmonary infiltrates after thrombolysis. Early diagnosis and therapeutic management are essential to prevent acute respiratory failure and death. Risk factors and a probable etiology of this complication should be investigated.
References