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# A case of diffuse alveolar hemorrhage associated with hyaluronic acid dermal fillers

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Conflict of interest:** None declared

**Patient:** Male, 25
**Final Diagnosis:** Diffuse alveolar hemorrhage
**Symptoms:** Cough dry • short of breath
**Medication:** —
**Clinical Procedure:** —
**Specialty:** —

**Objective:** Unusual clinical course

**Background:** Hyaluronic acid is a substance that is naturally present in the human body, especially in joints and eyes. Hyaluronic acid injectable gels have been available for the general market since 2003 as cosmetic dermal fillers and skin boosters. Diffuse alveolar hemorrhage is an acute event that threatens the life of the patient and can lead to pulmonary fibrosis. Alveolar hemorrhage associated with hyaluronic acid dermal fillers is an entity that to the best of our knowledge has never been described in the medical literature.

**Case Report:** We describe a patient who presented with dyspnea and cough after a subcutaneous injection of hyaluronic acid, with radiographic abnormalities including ground glass opacities and consolidation. The patient underwent flexible bronchoscopy and was diagnosed with diffuse alveolar hemorrhage.

**Conclusions:** This case emphasizes that this life threatening condition may occur with the use of this medication and physicians must be aware of this disorder, as early recognition and management can reduce morbidity.

**MeSH Keywords:** Diffuse Alveolar Hemorrhage • Lung Diseases, Interstitial • Hyaluronic Acid – adverse effects

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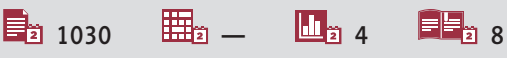

## Background

Diffuse alveolar hemorrhage (DAH) is a life threatening condition, and has been associated with multiple etiologies, including exogenous agents and drugs. Irrespective of its causes, the clinical, radiographic, and histopathological features of DAH may be similar [1]. Generally, the symptoms starts suddenly, with the most common being dyspnea, cough, fever, and hemoptysis. The latter may be absent at the time of presentation in up to one- third of patients because the total alveolar volume is large and can absorb significant amounts of blood [2]. Hyaluronic acid (HA) is an important component of extracellular matrix expressed throughout the body in many different tissues, such as skin, the central nervous system, and blood vessels [3]. The HA molecule is readily soluble in water, producing a gel that behaves as a lubricant, lending it hygroscopic and homeostatic properties. Hyaluronic acid injectable gels have been available on the general market since 2003 as cosmetic dermal fillers and skin boosters. In 2013, the American Society of Aesthetic Plastic Surgery reported that the second-most common non-surgical procedure in the United States is injection of HA. It is generally believed that HA is a safe product with minimal adverse effects, usually involving the injection site.

## Case Report

A 25-year-old male with no significant past medical history presented to the hospital with 5-day history of shortness of breath and dry cough without others systemic complaints. He was a lifelong nonsmoker and did not have any history of recent traveling or sick contacts. He was not taking any medication but recalled a cosmetic intervention in which he was injected with over 50 mL of commercially available HA dermal filler (the usual dose is 1.5 mL to 6 mL) 1 day before start of symptoms. On physical exam, he looks acutely ill. His vital signs were: heart rate regular but tachycardic at 120 beats/minute, blood pressure 116/70 mmHg without orthostatic changes, and respiratory rate 34 breaths/minute. The room air oxygen saturation was 84%, and arterial blood gas analysis in room air revealed hypoxemia (PaO2=53 mmHg) with an elevated alveolo-arterial oxygen gradient (A-a O2 gradient). Lungs auscultation revealed bilateral diffuse crackles and rhonchi. The calf area presented with erythema in some puncture sites but no evidence of superimposed infection. The results of the rest of the examination were unremarkable. Chest radiography showed bilateral patchy lung infiltrates without associated pleural effusion. A CT scan of chest with contrast was performed and showed bilateral pulmonary consolidations and interstitial ground-glass densities with peripheral predominance without abnormally enlarged hilar or mediastinal adenopathy (Figure 1). Results of laboratory tests were: WBC count, 15.2 cells/μL with left shift;

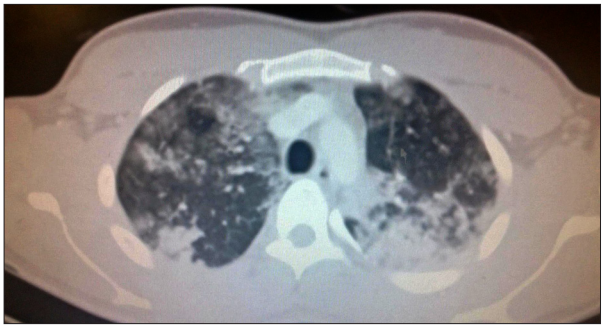

**Figure 1.** Initial chest tomography.

hemoglobin level, 11.4 g/dL; platelet count, 321 000 cells/μL; INR, 1.0. Influenza A and B rapid test results were negative. Complete metabolic profiles were normal.

The patient was admitted to the medical intensive care unit for hypoxic respiratory failure, which stabilizes with supplemental oxygen and non-invasive ventilation. Fiber-optic bronchoscopy was performed the next day and findings were consisted with hyperemic inflammatory changes of airway mucosa associated with bloody secretions (Figure 2). Bronchoalveolar lavage disclosed hemorrhagic features in sequential samples and the pathological analysis confirmed the presence of hemosiderin-filled macrophages. The pulmonary function test showed a moderately restrictive ventilatory impairment (TLC 54% of predicted with FEV1 67% of predicted) with normal gas transfer (DLCO 121% of predicted) (Figure 3). Based on the findings of the bronchoalveolar lavage and the clinical picture without any other discernible cause, he was started on pulse IV methylprednisolone (1000 mg IV daily for 3 days) followed by a tapering dose. The follow-up results of ANA, C-ANCA, P-ANCA, rheumatoid factor, Anti-GM, Leptospira titer, viral serologies (Hepatitis A, B, and C), HIV, and drug screen came back negative or within normal. The test results of bronchoscopy samples for acid-fast bacilli, bacterial, viral, and fungal cultures and other staining were negative. While on treatment, the patient had a favorable response, with gradual clinical and radiographic improvement (Figure 4).

## Discussion

DAH must be distinguished from other causes of pulmonary hemorrhage that are caused by localized abnormalities in the lung (e.g., bronchiectasis, malignancy, infection) and arise from bronchial circulation [4]. The combination of sequential bronchoalveolar lavage samples (from the same location) and an increasing red blood cell count is regarded as diagnostic of DAH [5]. Of the histologies associated with DAH (pulmonary capillaritis, bland pulmonary hemorrhage, diffuse alveolar damage, and miscellaneous histology), pulmonary capillaritis is the most common [6]. Therapy for diffuse alveolar hemorrhage consists of treating the underlying cause.

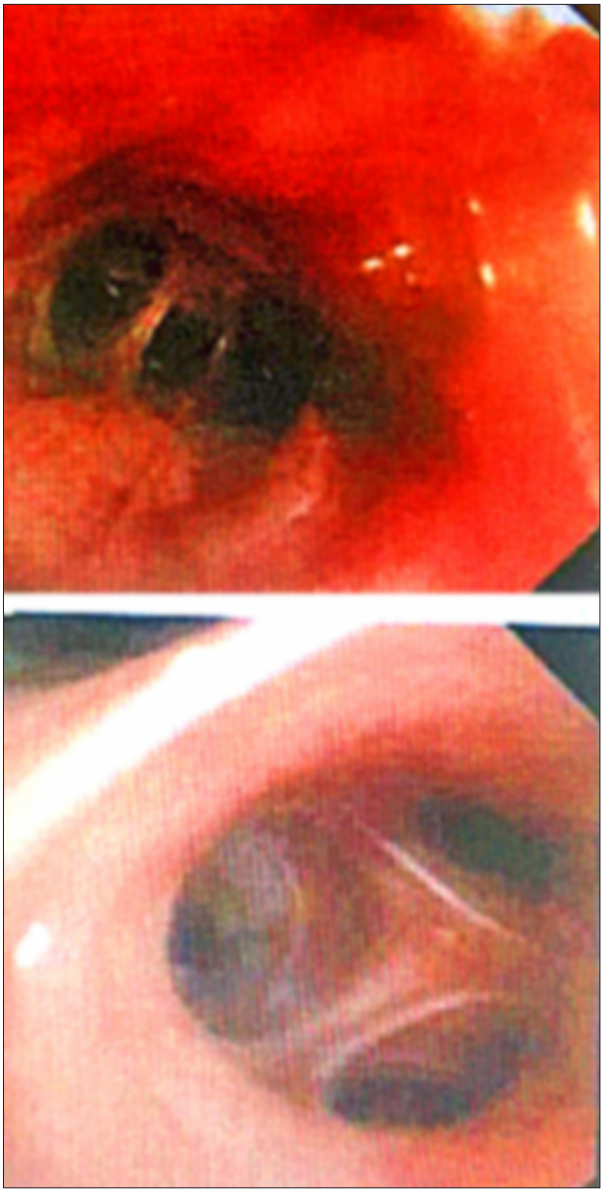

**Figure 2.** Bronchoscopy: Gross-hemorrhagic features in sequential samples and hyperemic mucosa. Micro-hemosiderin-filled macrophages.

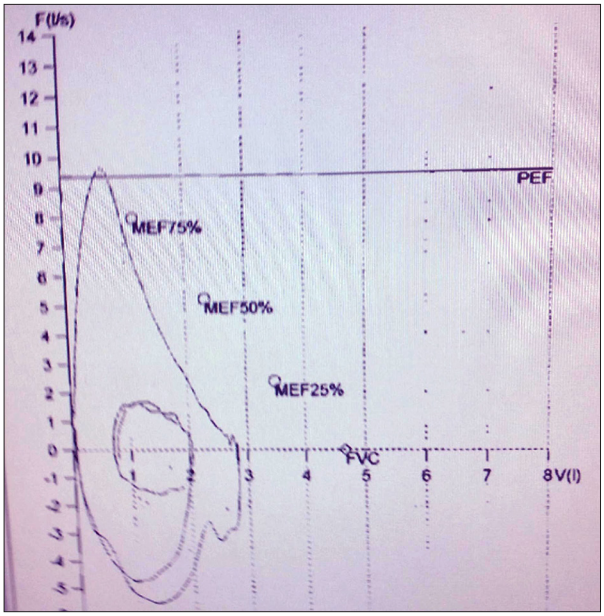


**Figure 3.** Pulmonary function test: FVC 61% of pred, FEV1 67% of pred, FEV1/FVC ratio of 94% of pred, TLC 54% of pred, and DLCO 121% of pred.

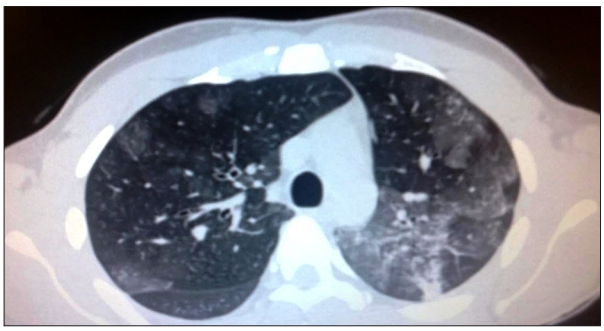

**Figure 4.** Chest tomography after treatment with IV methylprednisolone.

After ruling out other possible etiologies and the lack of co-morbidities, along with a clear temporal association between the use of the medication and the development of symptoms, we believe that in our patient DAH was due to the excessive dosing of commercially available HA. There have been case reports of DAH associated with liquid silicone and warfarin among others, but to the best of our knowledge we report the first case of DAH related to hyaluronic acid, which is a cosmetic filler in increasing use all over the world.

Hyaluronic acid is present in blood in very small amounts, mainly due to active hepatic clearance, which suggests that elevated levels may be deleterious to the organism. A sudden increase in the concentration of HA in blood could dramatically alter normal hemostasis and increase clot formation [7]. LeBoeuf et al. [8] demonstrated that fibrinogen binds to circulating HA, interfering with the usual production and dissolution of fibrin clots. This phenomenon has been described during the inflammation process, wound healing, and high concentration of HA. In our case, a greater rate of clot formation and subsequent dissolution induced by increased concentration of HA could result in a depletion of plasma fibrinogen, eventually leading to an increased risk of bleeding.

## Conclusions

The general public is commonly using various cosmetic agents. Diffuse alveolar hemorrhage associated with the non-approved

use of cosmetic hyaluronic acid dermal filler raises concern about the safety of this easily accessible product. Physicians and other health care specialists must be vigilant for the misuse of these dermal fillers for cosmetics purposes and the possible risk of severe complications, including alveolar hemorrhage.

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