Spontaneous Diffuse Alveolar Hemorrhage in Severe Alcoholic Hepatitis-Case Report

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ABSTRACT

Diffuse alveolar haemorrhage is a clinical catastrophe that presents variably. The commonest etiologies include those of autoimmune and connective tissue diseases, especially granulomatosis with angitis and systemic lupus erythematosus. Infections and secondary disseminated intravascular coagulopathy has also been described to cause this condition. Spontaneous diffuse alveolar haemorrhage is a rare entity that occurs in the course of liver diseases.

Previously, light has been shed on occurrence of alveolar haemorrhage in the wake of hepatitis C virus infection and attendant immunological vasculitis phenomenon. Here we report the first case of diffuse alveolar haemorrhage in a patient of severe alcoholic hepatitis, in whom overt coagulopathy features were indiscernible. This further proves the fact that global and holistic approach hemostasis evaluation in diagnosing coagulation disorders of liver diseases could be the way forward, rather than conventional laboratory evaluation.

Keywords: Alcoholic Hepatitis, Coagulopathy, Diffuse Alveolar Haemorrhage, Thromboelastography

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INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a severe illness that has catastrophic clinical consequences often leading to respiratory failure. Bleeding from the pulmonary tree can originate from the bronchial vessels or the microcirculation of the lung. Pulmonary hemorrhage that originates from the

small, medium and large pulmonary vessels is commonly secondary to systemic vasculitis which also involves the microcirculation. Larger areas of bleeding vessels include those from the bronchi and are usually seen in broncheictasis or endobronchial neoplasms. [(1)] DAH is a syndrome in which there is accumulation of intra-alveolar red blood cells originating from the alveolar capillaries. This commonly presents with hemoptysis, anemia and diffuse pulmonary infiltrates with hypoxemic respiratory failure (type I). DAH is associated with a number of conditions. [(2)]

The most common associated condition is granulomatosis with angiitis (Wegener's Granulomatosis) followed by Goodpasture's Syndrome and Idiopathic Pulmonary Hemosiderosis. ANCA associated vasculitides represent about 40% of DAH. [(3)] DAH presents with different histologic patterns. These include pulmonary capillaritis, bland alveolar haemorrhage and diffuse alveolar haemorrhage. Diffuse alveolar haemorrhage is characterized by interstitial and alveolar edema and alveolar hyaline membrane formation. Repeated alveolar haemorrhage leads to interstitial fibrosis. [(4)] Pulmonary capillaritis is most commonly seen with seropositive systemic vasculitides or a connective tissue disease and bland and diffuse types are seen mostly in a number of conditions, mainly drugs, coagulation disorders and infections. [(5)]

Broncho-alveolar lavage usually is enough to confirm the diagnosis, but a lung biopsy maybe required to confirm the underlying histology. Treatment is typically directed towards underlying condition and includes corticosteroids, immunosuppressive agents and plasmapheresis. [(6)] Alcoholic cirrhosis is well documented in a small proportion of heavy drinkers. Quantity of alcohol along with other factors such as sex, genetic characteristics and environmental factors result in alcoholic liver disease. Alcohol induced liver injury can be of various types. Regular use of alcohol, even for a small period can result in fatty liver or alcoholic steatosis, characterized by macrovescicular triglyceride accumulation within the hepatocytes. [(7)]

This resolves with abstinence. Continued use of alcohol can result in severe alcoholic steatohepatitis and then to fibrosis and eventually cirrhosis. Alcoholic hepatitis (AH) is a severe but treatable form of alcohol related liver injury in which, up to 40% of patients die within 6 months of onset of clinical syndrome. [(8)] This syndrome consists of jaundice and liver failure that occurs after many years of heavy alcohol use (approximately 100g per day). Male patients between 40 to 60 years are commonly affected even though female gender is an independent risk factor for AH. This is also associated clinically with fever, abdominal pain and ascites. [(9)]

Evaluation in such patients usually reveal the presence of aspartate aminotransferase (AST) levels that is more than twice the upper limit of normal, although rarely above 300 IU/mL and those of serum alanine aminotransferase (ALT) levels, which are lower. [10] Histologically, patients with AH shows presence of ballooned hepatocytes that contain amorphous eosinophilic inclusion bodies called Mallory bodies surrounded by neutrophils; this is commonly associated with macrovescicular steatosis in hepatocytes. Intra-sinusoidal fibrosis (or chicken wire fibrosis) is a characteristic lesion in AH. [11]

A number of scoring systems are used to assess the severity of AH such as discriminant function (DF), the Model for End Stage Liver Disease (MELD), the Glasgow Alcoholic Hepatitis Score (GAHS) or the Albumin- Bilirubin-INR-Creatinine Score (ABIC Score). Except for ABIC Score (which is helpful in short term prognosis), the other scores are helpful in determining which patients benefit from treatment. [12, 13] Severe coagulation abnormalities are part and parcel of AH. Bleeding diathesis secondary to severe hypoprothrombinemia, thrombocytopenia and thombocytopathy and disseminated intravascular coagulation secondary to sepsis are well documented in AH patients. In AH patients with underlying alcoholic cirrhosis (acute on chronic liver failure), acute variceal bleed and coagulopathy related mucosal bleeds or intervention related bleeds predominate. [14]

The presence of spontaneous DAH in a patient of severe AH without underlying sepsis and/or chronic liver disease has never been reported before. Prior reports of DAH in liver disease has only shed light on hepatitis C–associated mixed cryoglobulinemia and pulmonary hemorrhage which was resistant to standard treatment and another case of diffuse alveolar syndrome from cryoglobulinemic vasculitis that responded to high dose steroids. Here we present a case of severe alcoholic hepatitis, who developed spontaneous diffuse alveolar hemorrhage during hospital stay with a mildly deranged coagulation profile, a scenario not reported previously among liver disease patients.

CASE REPORT

A 42 year old man, a known alcoholic for 22 years, consuming around 90 to 110 g of alcohol daily who had his last drink about 15 days before presentation to our emergency services facility complained of progressive anorexia and nausea, followed by progressive painless non cholestatic jaundice for duration of 10 days which was associated with high grade fever and with upper abdominal discomfort without abdominal distension, bilateral leg swelling, facial puffiness or decreased urine output. There were no

associated chest symptoms or convulsions, myalgia, arthralgia or skin manifestations or overt bleeding diathesis. He denied other substance abuse, complementary and alternative medicine intake and had no known co-morbidities. There were no similar episodes in the past. His family history was non contributory.

On examination, he was found to be conscious and oriented to place and person, but not to time. He was mildly drowsy and diaphoretic, but responded to simple commands well. The blood pressure was 122/68 mm of Hg on the right upper brachial region and the pulse rate was 122 per minute with a respiratory rate of 28 per minute and temperature of 101 F. Pallor was evident, as was Icterus. His abdomen was distended, soft to touch and tender in the right upper quadrant with the liver palpable 6 centimeters below the right costal margin which was firm to palpation with rounded margins, non nodular surface and without pulsetality or surface bruit. There were no other organomegaly appreciated and free fluid was absent on percussion.

The chest examination revealed fine crackles at infra-mammary region on the right side and decreased vesicular breath sounds in the right basal region. The neurological and cardiovascular systemic examination was essentially normal. His blood work revealed a hemoglobin of 9 g/dL, total white blood cell count of 16800 cells per mm^3 with 90 percent polymorphs and thrombocyte counts of 80,000 per mm^3. The liver function test showed a total bilirubin of 24.8 mg/dL with a direct fraction of 11.2 mg/dL, aspartate transaminase of 220 IU/mL, alanine transaminase of 88 IU/mL, serum albumin of 3.0 g/dL; serum alkaline phosphatase 90 IU/mL and gamma glutamyl trasnferase level of 222 IU/mL. The prothrombin time and International Normalized Ratio (INR) were 24.4 seconds (control 12 seconds) and 2.1 respectively.

An ultrasound of the abdomen revealed an enlarged liver, with a span of 18 centimeters without surface irregularity or lobulations and increased and coarse echotexture, signifying likely severe steatosis. There was mild free fluid in abdomen and the spleen was not enlarged. The patient was initially managed with fluids and empirical broad spectrum antibiotics and high nutritional support to combat severe catabolic state. A chest X- RAY done at admission was normal.

On the second day after admission, the patient developed acute onset dyspnea without cough or expectoration and worsening diaphoresis, without any preceding orthopnea or paroxysmal nocturnal dyspnea. The breathing had become labored and respiratory accessory muscle use was evident with prior chest crackles increasing in intensity and becoming

more wide spread, bilaterally. An arterial blood gas analysis at the time revealed partial pressure of oxygen, 66.8 mm of Hg with a saturation of 92 %. A repeat hemogram revealed a 3 g/dL drop in hemoglobin. An ECG and echocardiogram done at bedside showed sinus tachycardia and an ejection fraction of 60% and without wall motion abnormalities respectively.

In view of worsening dyspnea and type I respiratory failure with progressive deterioration in mental status, the patient was electively intubated and put on mechanical ventilation. A bronchalveolar lavage (BAL) done at the time of intubation was send for investigations and meanwhile, a repeat supine X ray of the chest was done. After stabilization, the patient was shifted for an urgent high resolution tomography (HRCT) of the thorax. The repeat X ray chest revealed presence of bilateral fluffy opacities with patchy areas of consolidation **(FIGURE 1a and 1b)**

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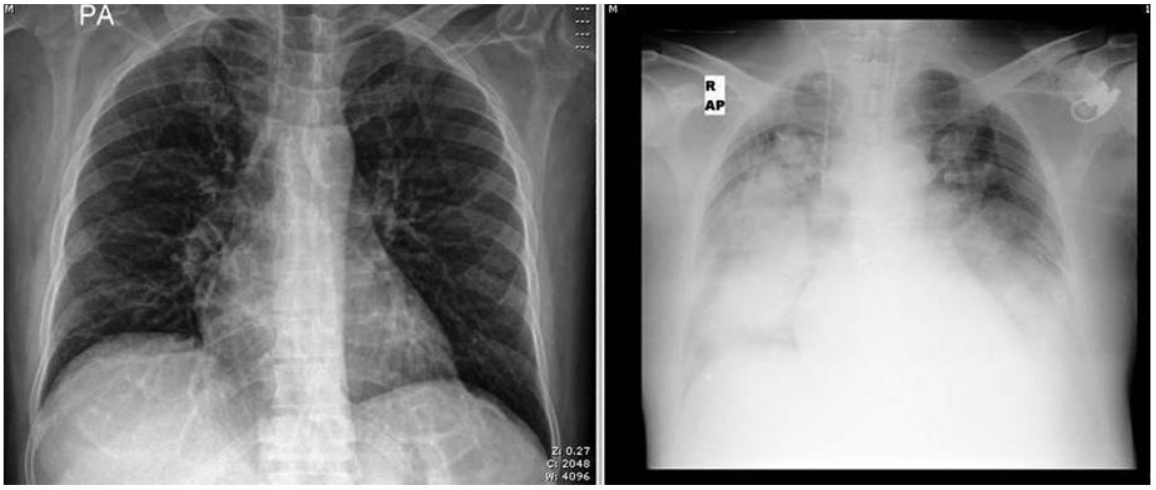

FIGURE 1a and 1b: X Ray of Chest (PA view) of the patient done at admission as compared with that done (AP view) after 3 days post admission. The presence of fluffy alveolar opacities with areas of consolidation with relative peripheral sparing is evident.

The HRCT showed extensive pulmonary air-space opacities seen involving the bilateral upper mid and lower zones with changes being most pronounced in the mid and lower zones along with attendant bilateral air-bronchograms and characteristic sparing of the peripheral subpleural pulmonary parenchyma with mild septal thickening **(FIGURE 2)**, features that were suggestive of adult respiratory distress syndrome, pulmonary edema or DAH.

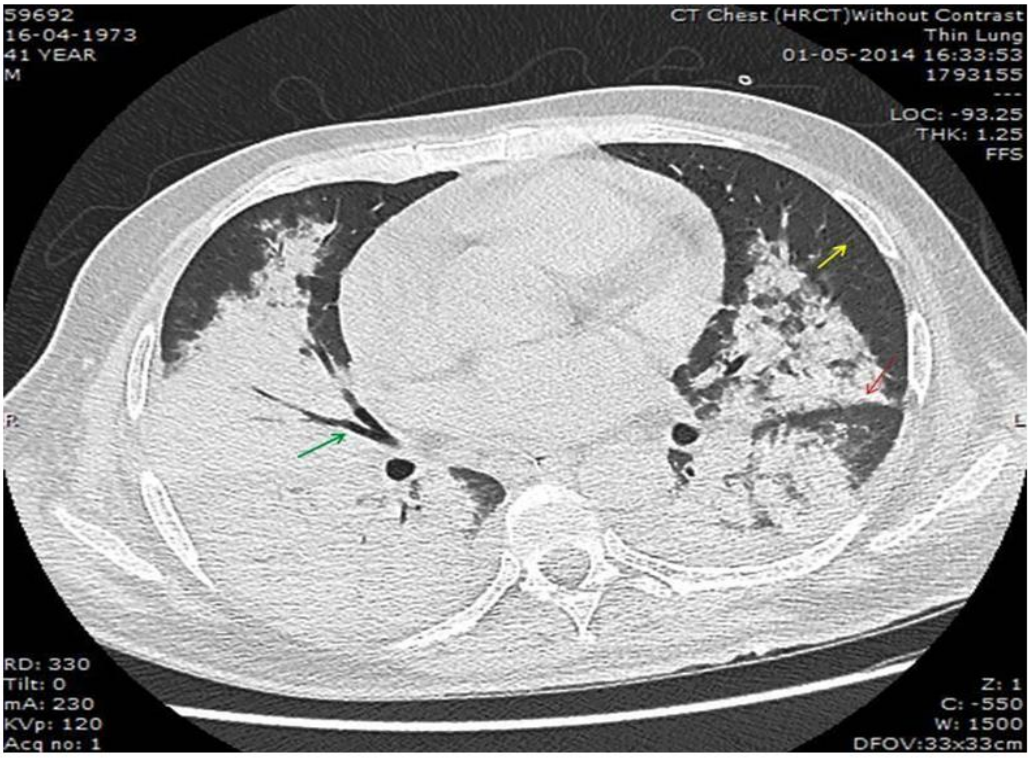

FIGURE 2: High resolution tomography of the thorax. The image shows features of extensive bilateral consolidation with air bronchograms (green arrow) and fluffy alveolar opacities with relative peripheral sparing (yellow arrow) and presence of interlobular thickening (red arrow), most probably due to pulmonary edema or presence of hemosiderin laden macrophages (blood elements) that gravitated.

BAL that was send prior and subsequent serial samples showed the presence of hemosiderin laden macropahges **(FIGURE 3)** thereby confirming a diagnosis of DAH in the patient. Body fluid cultures (including BAL) were sterile and procalcitonin level was less than 0.5 (normal). Serum markers of autoimmunity such as ANA, ASMA, AMA, Rheumatoid factor, anti Citrulinated Cyclic Protein (anti-CCP), c-ANCA and p-ANCA, anti-phospholipid antibodies and infectious diseases serology such as Malaria, Dengue, Leptospira and atypical viral serology including Ebstein Barr virus, Cytomegalovirus and Parvovirus B were negative.

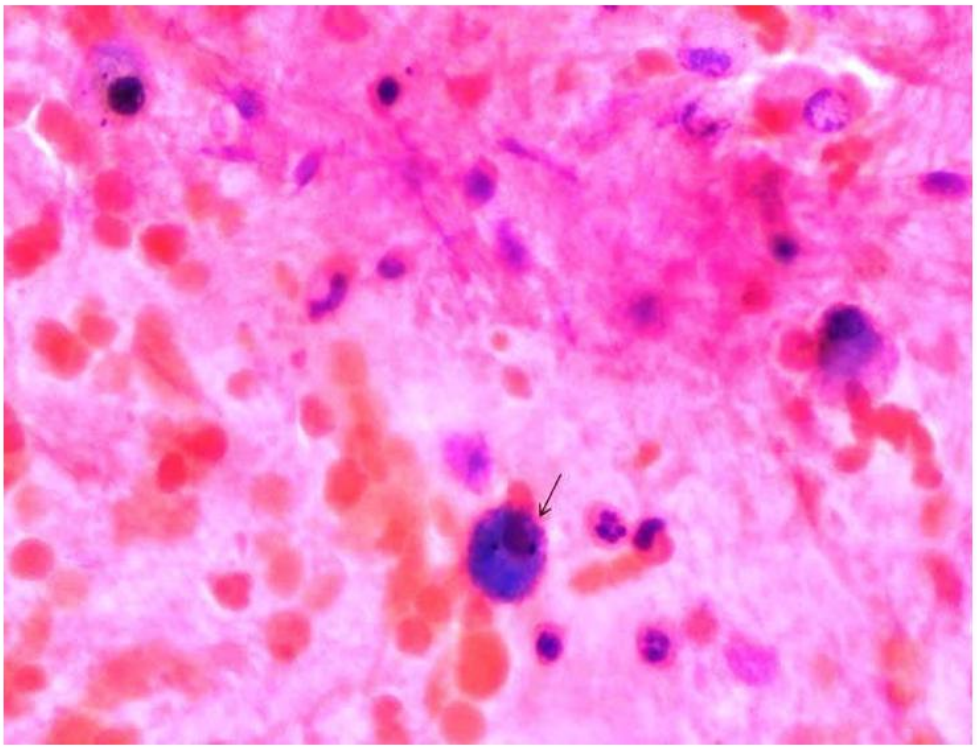

FIGURE 3: Bronchoalveolar lavage fluid smear showing presence of hemosiderin laden macrophages, black arrow (400X, Perl's Stain)

A thromboelastography done revealed grossly deranged parameters such as clotting factor deficiency, platelet dysfunction and hypofibrinogenemia. **(FIGURE 4)** In view of severe AH with a high DF score (81.8 in our patient) and presence of DAH, the patient was started on pulse steroid therapy after confirming that sepsis screen was negative. Even after two pulses of steroids, the patient hemodynamically worsened and kidney injury intervened. He was started on inotropic support which eventually progressed to high doses and he succumbed to his illness six days after admission due to cardio-respiratory arrest.

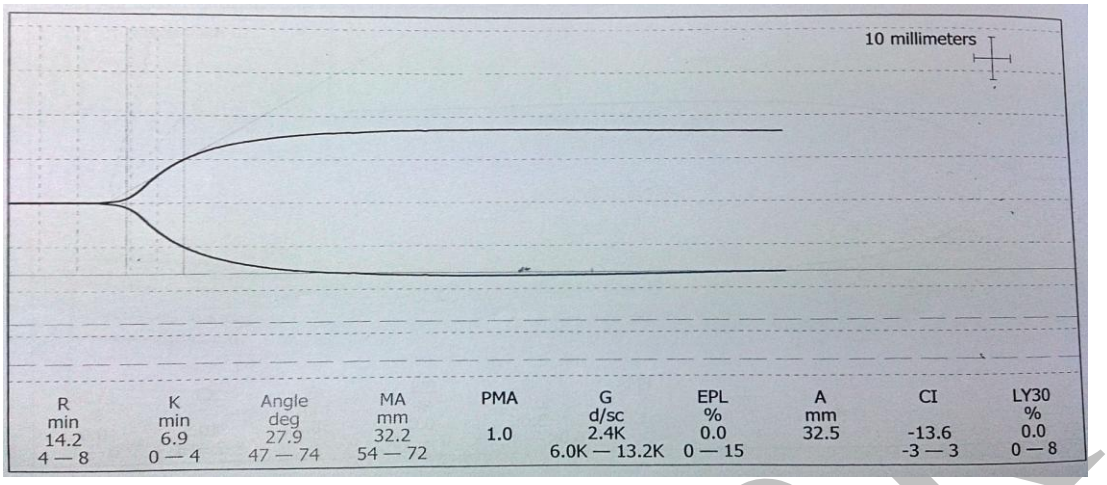

FIGURE 4: Thromboelastography of the patient revealing gross derangements in hemostatic profile.

DISCUSSION

Diffuse alveolar haemorrhage can appear at any age and often with an associated disease. It can also present as the initial manifestation of an underlying disease. The cardinal sign of DAH is haemoptysis, sometimes occurring dramatically or evolving over few days to weeks; but can be absent in up to 33% [(15)] of DAH cases as was the case with our patient. Other associated symptoms include fever, cough and dyspnoea and symptoms pertaining to underlying condition. In addition to history and physical examination, routine laboratory tests and targeted serological studies is useful for establishing the diagnosis. In patients who present without haemoptysis, a falling hematocrit along with worsening dyspnoea/hypoxia and rapidly developing pallor points towards the diagnosis of DAH. [(16)]

The chest radiograph findings are non specific and consist of alveolar opacities that can be patchy, focal or diffuse in nature. Computed tomography of the chest more accurately can define extend of the disease. In many cases it may show areas of widespread ground glass opacification and crazy paving pattern with or without areas of consolidation. In sub acute phases of the disease, there may be fine diffuse nodular densities and in later stages, there may be evidence of interlobular septal thickening due to intralymphatic accumulation of hemosiderin. [(17)] Flexible bronchoscopy needs to be performed to establish the clinical diagnosis of DAH and to exclude infections. Progressively hemorrhagic serial BAL samples are diagnostic of DAH but do not reveal the underlying cause. Alveolar haemorrhage, that too spontaneous, in the setting [(18, 19)] of liver disease has been rarely reported in

literature. Reports on association of DAH with liver disease has been described previously in cases of hepatitis C related liver chronic liver disease with underlying secondary cryoglobulinemia related vasculitis, one that responded to high dose steroid therapy and another that led to progressive and catastrophic DAH and hepatic failure brought on by flare of hepatitis C virus infection secondary Rituximab use, when steroid therapy failed to control symptomatic cryoglobulinemia.

In a series by Amital et al with 125 patients with cryoglubulinemic vasculitis, only about 3% of the patients developed diffuse pulmonary haemorrhage. This association is an adverse prognostic indicator for patients with Hepatitis C with in-hospital mortality approaching 100% in a series by Ramos-Casals et al of 29 patients, 4 of whom had alveolar haemorrhage. [20, 21] Most patients are treated with immunosuppressants like high dose steroids but there is no evidence in literature about the optimal dose or duration. The coagulopathy of liver disease is a complex entity in which both procoagulant and anticoagulant factors play a role to produce a 'rebalanced hemostatsis'. [22] Tipping of this balance can occur in either direction with bleeding predominating or thrombotic events occurring, depending on multiple factors including patient profile and severity of underlying liver disease.

The platelet counts, prothrombin time and coagulation factor measurements, none correlate well with bleeding risk in liver disease patients. [23] Newer modalities of global haemostatic measurements like Thromboelastography will soon become major tools in point of care management in liver disease patients. [24] Even then, a dependable tool in assessing and predicting bleeding risk in liver disease patients has not yet been formulated. In patients of liver disease, especially ones with severe disease such as alcoholic hepatitis, fulminant hepatic failure or severely decompensated cirrhotics, the differential diagnosis of diffuse alveolar haemorrhage must be kept in mind, in a patient of rapidly developing anaemia, progressive hypoxia and worsening sensorium, even in the absence of haemoptysis or classical chest symptoms and signs.

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