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A Fatal Case of Systemic Lupus Erythematosus Complicated with Diffuse Alveolar Hemorrhage

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Abstract: Introduction: SLE is a multisystem autoimmune disease with variable clinical presentation. DAH is a rare but catastrophic manifestation of SLE with high mortality, requiring early, intensive therapy. Case Presentation: A 31-year-old female presented with low-grade fever and joint pains for six weeks associated with alopecia, anorexia, and weight loss. She had pale and had cervical lymphadenopathy, moderate hepatomegaly, and splenomegaly. Hb level was 9.2mg/dL, with a platelet count of 144 × 103/µL. The ESR was 65mm/hour, and the CRP level was 36 mg/L with a UPCR of 332mg/g. She had low C3, C4 levels, positive ANA, and dsDNA titer. A renal biopsy revealed class 3 lupus nephritis. Twenty days after, she was readmitted with acute onset of pleuritic chest pain, cough, and dyspnea, where she was hemodynamically unstable with SpO_2 of 85% on air. The Hb level was 8.6 g/dL with a platelet count of 106 × 103/µL. Her condition deteriorated despite standard medical care, where the Hb level and SpO_2 dropped to 5.6 d/dL and 65%, respectively, even after blood transfusions, intubation, and artificial ventilation. The chest X-ray revealed bilateral large whitish hazy shadows, and the HRCT scan revealed diffuse bilateral pulmonary hemorrhages. Then she was transferred to the ICU, and there she was started with broad-spectrum antibiotics, methylprednisolone, and plasmapheresis. However, after one week of ICU stay, her renal functions worsened, and she was initiated on CRRT. However, despite all the resuscitation efforts, she succumbed following a cardiac arrest. Conclusion: DAH is a rare catastrophic complication of SLE, which usually presents in patients with an established diagnosis of SLE, even on medical therapy. The diagnosis of DAH is problematic because it mimics a severe pulmonary infection. Early detection and aggressive management are warranted to improve affected patients' outcomes and quality of life.

Keywords: Systemic Lupus Erythematosus, Diffuse Alveolar Hemorrhage, Pulmonary Hemorrhage

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, occasionally limited to one or a few organs, diagnosed on clinical grounds in the presence of characteristic serological abnormalities. It has variable clinical presentation, course, and prognosis [1]. Pulmonary complications in SLE can occur in 50–70% of affected individuals during their illness. The spectrum of pulmonary manifestations includes pleuritis, interstitial lung disease, acute lupus pneumonitis, diffuse alveolar hemorrhage, pulmonary embolism, pulmonary hypertension, vasculitis, shrinking lung syndrome, pulmonary nodules, bronchiolitis obliterans, infections, and diaphragmatic weakness. The most common manifestation is pleuritis, which can be associated with pleural effusions [2]. Diffuse alveolar hemorrhage (DAH) is a rare but potentially catastrophic manifestation with high mortality, with reported frequency ranging from 1% to 5.4% of lupus cohorts [2, 3]. It requires early, intensive therapy and is associated with high mortality ranging from 23% to 92% in those who developed DAH [3, 4]. We present a female presented with

SLE and later developed DAH who succumbed even with the standard treatments.

2. Case Presentation

A 31-year-old previously apparently well lady was admitted in December 2019 with a history of low-grade fever, joint pains, and weight loss for six weeks. She had low-grade intermittent fever without significant diurnal variation, without chills and rigors, and the fever had initially responded to paracetamol. She had bilateral small and large joint pains with mild morning stiffness lasting for about half an hour. She also complained of gradual hair loss, loss of appetite, and significant weight loss of about 6 kg during the last six weeks. Furthermore, she had anemic symptoms such as exertional dyspnea, episodic palpitations, and lightheadedness. She was amenorrheic for two months, though she did not have a cough, abdominal pain, low urine output, or frothy urine. There was no history of altered bowel habits or bleeding manifestations such as bruises or petechiae.

She did not have any history of a similar illness, autoimmune diseases, malignancies, or exposure to tuberculosis or hepatitis. Blood transfusions had not been done to her previously. She was a housewife and mother of two children, the youngest aged one year. Her husband was working abroad, and his last visit was six months ago.

On examination, she was an averagely built lady who was pale, not icteric, had no rashes or skin pigmentation, no peripheral evidence of infective endocarditis and clubbing, and had no ankle edema. She had cervical lymphadenopathy, few palpable nodes in the posterior neck, which were non-tender. Nevertheless, she had no axillary, epitrochlear, or inguinal lymph nodes. Her lungs were clear, her heart rate was 96 beats per minute, and her blood pressure was 110/70mmHg. Her abdominal examination showed moderate hepatomegaly and splenomegaly, but she did not have clinically detectable free fluid.

In initial investigations, the white cell count was 6.1 × 109/ μL with neutrophil predominance. The hemoglobin (Hb) level was 9.2mg/dL with a mean corpuscular volume of 80fL and a platelet count of 144 × 103 / μL. Her blood picture showed ovalocytes. There was no evidence of bleeding or hemolysis in the blood picture, and anemia was likely due to chronic disease/acute illness. The erythrocyte sedimentation rate was 65mm/h, and the c-reactive protein level was 36 mg/L. She had a serum creatinine level of 86 mmol/L, aspartate transaminase (AST) level of 24 U/L, and alanine transaminase (ALT) level of 36 U/L. Her urinalysis revealed protein 3+ and urine protein-creatinine ratio of 332mg/g. Her C3 level was 31.6 mg/dL, and her C4 level was 1.4 mg/dL, showing low values. Her serum antinuclear antibody (ANA) titer was 1:80, above the population's cut-off level. Her dsDNA titer was 1:100, which is also above the cut-off for the population. Her 2D echocardiogram revealed an ejection fraction of 61% with good left ventricular and right ventricular function. She was discharged after seven days of hospital stay, and she was planned to be reviewed as an outpatient in a week. A renal biopsy was performed during her ward stay to review the report during the clinic visits, but she did not attend the clinic.

However, 20 days after the discharge, she presented to our ward with pleuritic chest pain with shortness of breath and orthopnea for 6 hours. She had a mild dry cough and said that she noticed frothy urine during last week, and her joint symptoms were also worsened during this period. On admission, she was pale, dyspneic with 30 cycles per minute respiratory rate, with peripheral oxygen saturation (SpO_2) of 85% on air. She was given oxygen 10 L/min, where her SpO_2 picked up to 97%. Her heart rate was 120 beats per minute, and her blood pressure was 90/60mmHg. The abdominal examination revealed moderate hepatosplenomegaly with a distended bladder, and therefore she was catheterized. We traced her renal biopsy report at that time, and it revealed a microscopic appearance that showed cores of renal tissue containing nine viable glomeruli, two cores each measuring 0.3cm in length. All the glomeruli had mesangial proliferation. Thickened basement membrane resembling wire loop lesions were present in glomeruli, with three showing focal segmental necrotizing lesions. Tubular atrophy of 10% and lymphocyte-mediated tubulitis were present with interstitial lymphocytic infiltrate of 30% and interstitial fibrosis of 10%. The blood vessels did not show any pathological changes. Immunofluorescence- IgG - 2+ capillary and mesangial, IgA – negative, IgM – negative, C3 – 3+ granular capillary and mesangial. The renal biopsy findings were consistent with lupus nephritis class 3: activity index of 9/24 and the chronicity index of 2/12. Her initial arterial blood gas (ABG) revealed pH 7.44, pO2255 mmHg, pCO_2 31 mmHg, lactate level 0.6 mmol/L, and bicarbonate level (HCO_3) 22.1 mmol/L. ECG was compatible with sinus tachycardia. Her bilateral lower limb duplex scan was negative for deep venous thrombosis, and her abdominal ultrasound scan revealed hepatosplenomegaly with bilateral renal acute parenchymal changes. Her white cell count was 8.4 × 109 / μL with neutrophil predominance. Hb level was 8.6 g/dL with a mean corpuscular volume of 75fL and platelet count of 106 × 103 / μL. Her serum creatinine level was 134mmol/l. The in-ward chest X-ray revealed few patchy bilateral shadows.

On the following morning, she became more dyspneic with a respiratory rate of 36 cycles per minute, and she was noted to be more pallor than the previous day. On auscultation, her lungs were filled with rhonchi. However, her SpO_2 was maintained at more than 95% with oxygen. Then her Hb level was found to be 5.6g/dl, and she has immediately transfused two units of leucodepleted blood. Her dyspnea improved after blood transfusions. Then her ABG revealed pH 7.39, pO_2 171 mmHg, pCO_2 36 mmHg, and lactate 0.5 mmol/L. Her procalcitonin level was negative (0.16 ng/mL) despite a high c-reactive protein level of 80 mmol/L. Her second chest X-ray revealed bilateral large whitish hazy shadows compatible with the severe infection involving both lungs and pulmonary hemorrhages. (Figure 1) After 2 hours again, she became dyspneic, and her SpO_2 dropped to 85%, and she became confused. So we electively intubated her due to the impending respiratory arrest where the SpO_2 dropped to 65%. Then we

performed a high-resolution CT (HRCT) scan of the chest, and it revealed evidence of diffuse bilateral pulmonary hemorrhages, and there was no evidence of pulmonary embolism. (Figure 2) Then she was transferred to the intensive care unit (ICU) for further care.

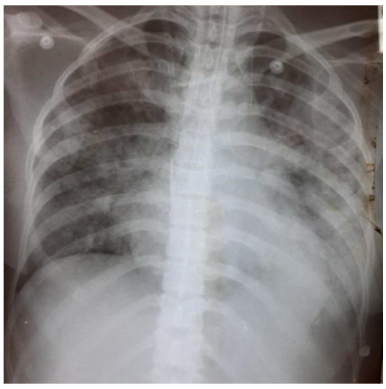

Figure 1. *Chest X-Ray showing bilateral large whitish hazy shadows.*

During the ICU, she was further transfused with five units of blood and was given supportive ventilatory care. She was started on intravenous broad-spectrum antibiotics; meropenem 1g eight hourly, and teicoplanin, 400mg twelve hourly for the first day and after that 400mg daily. She was also started on intravenous methylprednisolone 1g daily for the first five days, and then she was initiated on plasmapheresis every other day as she did not improve and had persistent lung hemorrhages as found on X-rays did daily. Meanwhile, she was also investigated for any other possible cause that could have been attributed to lung hemorrhages. Serum antineutrophil cytoplasmic antibody (ANCA) level, anti-glomerular basement membrane (anti-GBM) antibody level, and antiretroviral antibody level were below the cut-off for the population. The cultures of blood, urine and endotracheal secretions were negative. Procalcitonin level was also within the normal range. From the 7th day of ICU stay, her serum creatinine started to rise from 110 mmol/L to 340 mmol/L, and her urine output started to reduce from 1.5 L / 24 h to 0.5 L /24h. The ABG became acidotic with a pH of 7.2 and HCO_3 of 15 mmol/L and hyperkalemic with a potassium level of 6.5 mmol/L. Then she was initiated on continuous renal replacement therapy. However, despite all the resuscitation efforts, she passed away following a cardiac arrest on the 9th day of ICU stay.

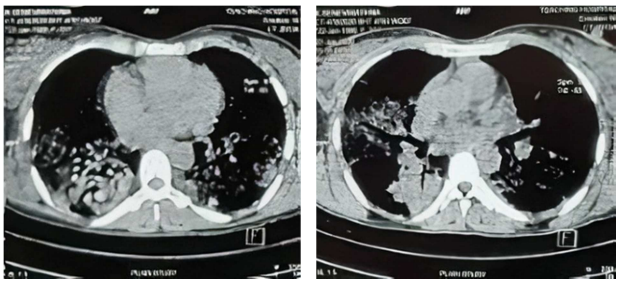

Figure 2. *High-Resolution CT scan showing bilateral ground-glass opacification suggestive of diffuse bilateral pulmonary hemorrhages.*

3. Discussion

SLE is a chronic autoimmune disease affecting almost every organ system, such as the skin, joints, kidneys, nervous system, heart, lungs, and serous membranes. Its presentation and clinical course are highly variable, ranging from indolent to fulminant. The incidence of SLE varies by sex, age, race, and ethnicity. SLE occurs more commonly in women, consisting of more than 90% of cases, frequently starting at childbearing age [5]. Pulmonary hemorrhage is an uncommon complication of SLE with reported frequency ranging from 1% to 5.4% of lupus cohorts. However, it is often severe, requiring early intensive therapy and high mortality ranging from 23% to 92% [6]. It was first described in 1904 by Dr. William Osler and is one of the most devastating complications of SLE [7].

Diffuse alveolar hemorrhage (DAH) is caused by various disorders attributed to three characteristic patterns that reflect the nature of the underlying vascular injury. They are DAH with capillaritis, DAH without capillaritis, and DAH associated with other conditions. Causes for DAH with capillaritis include small vessel vasculitis, immune complex-mediated vasculitis, and secondary vasculitides such as SLE, rheumatoid arthritis, and antiphospholipid antibody syndrome (APS) [8]. However, DAH in SLE is secondary to pulmonary capillaritis and non-inflammatory bland alveolar hemorrhage [7].

The pathology of DAH in SLE occurs in three distinct but sometimes overlapping histologic patterns; pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage [9]. Pulmonary capillaritis is characterized by interstitial infiltration of neutrophils and fibrinoid necrosis of the alveolar and capillary walls. The infiltrating neutrophils undergo cytolysis, and nuclear debris accumulates within the interstitium, causing a subsequent loss of the integrity of the alveolar-capillary basement membrane. Disruption of the alveolar-capillary basement membranes results in bleeding into the alveolar spaces. This process can occur as a result of systemic vasculitides and connective tissue disorders [4]. Bland pulmonary hemorrhage presents microscopically with an accumulation of erythrocytes and fibrin in the alveolar spaces without inflammation or destruction of alveolar structures. Lastly, diffuse alveolar damage is characterized by edema of alveolar septa and the formation of hyaline membranes. Among these three pathological patterns, the commonest one is pulmonary capillaritis [9].

Clinical presentation of DAH consists of a classic triad; hemoptysis, an abrupt fall in the Hb level, and pulmonary infiltrate evidenced by imaging. Acute dyspnea, cough, rales, chest pain, tachypnea, and fever are frequently present, leading to diagnostic confusion with bacterial and opportunistic pulmonary infections [6]. Since infection is a far more common cause of new pulmonary symptoms in patients with SLE, this must be aggressively excluded or empirically treated before intensifying immunosuppressive therapy for DAH [6]. However, patients with DAH usually present with dyspnea, cough, fever, blood-stained sputum, and sometimes hemoptysis,

with symptoms developing rapidly in hours or over a few days [7]. Our patient presented with clinical features suggestive of SLE in the first admission, and after twenty days of discharging from the hospital, she again presented with acute onset of pleuritic type chest pain, dyspnea, orthopnea, and dry cough. She also had frothy urine and joint pain which represented the features of SLE. She was also pale, tachypneic, and was in a circulatory collapse. Therefore this clinical picture directly resembles the classical clinical features of DAH. Hemoptysis was not present in our patient, and the absence of hemoptysis is not unique for DAH in SLE, having been reported for other etiologies of DAH [10].

Since the clinical picture of DAH resembles a pulmonary infection, investigations play a significant role in diagnosing the condition. New infiltrates on radiography accompanied by an abrupt drop in Hb appear to be more sensitive signs of pulmonary hemorrhage. The range of Hb drop ranges from 1.1 to 3.5g/dL [3]. Our patient had a Hb level of 9.2 g/dL on the first admission. On the second admission, she initially had a Hb level of 8.6 d/dL, which subsequently dropped to 5.6 g/dL. The first chest X-ray done on our patient revealed a few patchy bilateral shadows, and the second chest X-ray revealed bilateral large whitish hazy shadows where the appearance was compatible with a severe infection or pulmonary hemorrhages. The subsequent HRCT scan of the chest revealed evidence of diffuse bilateral pulmonary hemorrhages. In DAH, chest radiographs typically show bilateral central opacities with peripheral sparing [11]. Chest X-ray sometimes can be normal or show bilateral, rarely unilateral, airspace opacities which are patchy, focal, or diffuse. CT scan may show diffuse, bilateral, and patchy alveolar infiltrates, asymmetrical, ground-glass opacities, or diffuse nodular opacities, and it is more accurate than chest X-ray to evaluate the extent of the disease [12]. Bronchoalveolar lavage (BAL) is another investigation of choice in DAH where progressively hemorrhagic BAL found in serial samples is diagnostic of DAH [4].

Another aspect of the clinical assessment in this patient is to diagnose SLE. According to the European League Against Rheumatism/American College of Rheumatology, classification criteria for systemic lupus erythematosus published in 2019, the entry criterion for SLE diagnosis is ANA titer ≥ 1:80 [13]. Our patient had an ANA titer of 1:80 in the first presentation, fulfilling the entry criterion. Then there are further criteria on clinical domains and immunological domains with a scoring system, where the patient needs to have a score of ≥ 10, including at least one criterion on either domain to diagnose SLE [13]. In the first presentation, our patient had a fever (2), joint pain (6), proteinuria (4), thrombocytopenia (4) which comes under the clinical domains. She also had low C3 and C4 levels (4) and positive dsDNA (6) under the immunological domains, obtaining a total score of 24, which is diagnostic of SLE. The diagnosis was further confirmed by renal biopsy findings of class 3 lupus nephritis, which amounts to a score of 10 [13]. An increased risk of DAH has been reported during active renal disease, mainly when manifesting as lupus nephritis [7].

There is a lack of randomized control trials regarding the management of DAH in SLE. Therefore the management is individualized in most medical centers [14]. The most frequently used therapies are methylprednisolone, cyclophosphamide, and plasmapheresis. Other options include azathioprine, intravenous immunoglobulin (IVIg), mycophenolate, the B cell-targeting therapy rituximab (RTX), and stem cell transplantation. The usage of methylprednisolone is recommended until the cessation of the hemorrhage. It is found that the survival rate is higher for patients receiving a dose of methylprednisolone above what is conventionally used [7]. The combination of methylprednisolone and cyclophosphamide is associated with an increased survival rate [2]. Cyclophosphamide treatment is associated with better survival rates than other treatment options such as plasmapheresis [15].

As immunosuppressive therapy is the preferred treatment for DAH and pulmonary symptoms in SLE often are due to infections, antibiotic therapy is highly recommended until the microbial cause of the disease has been excluded. Infections are responsible for 22–25% of SLE patients' deaths, which has in part been attributed to the therapies used. Hence, untimely usage of immunosuppressants can facilitate microbial growth leading to disease exacerbation. When infection is suspected, broad-spectrum antibiotics should be considered as they might reduce mortality [7]. Plasmapheresis is efficacious therapy for causes of DAH such as ANCA-associated vasculitis, cryoglobulinemic vasculitis, anti-glomerular basement membrane disease, and APS. The therapy is thought to remove the pathogenic immune complexes that are responsible for vascular inflammation. Immune complexes and pathological antibodies are probably responsible for capillaritis in lupus DAH [16].

Our patient was treated with intravenous methylprednisolone, plasmapheresis, and intravenous antibiotics, the accepted treatment modalities for DAH in SLE [7]. She was also transfused with blood two times due to dropping in the Hb level. Circulatory and respiratory support was given when necessary. However, while in the ICU, she developed acute renal failure and passed away owing to a cardiac arrest. The presence of acute or chronic renal failure in patients having DAH with SLE was reported. Furthermore, renal involvement in clinical nephritis, nephrotic syndrome, or acute renal failure is common in SLE, where acute renal failure requiring hemodialysis was reported in 50% of the cases when it is complicated with DAH [10].

When an SLE patient develops DAH, the prognosis is generally poor [10]. However, it depends on the number of organ systems involved and the degree of renal disease [8]. When there are concurrent infections, the prognosis further worsens [7]. DAH associated with connective tissue diseases (CTDs) shows a worse prognosis than idiopathic DAH; however, among CTDs-associated DAH, SLE patients seem to have a better prognosis [12]. Pulmonary hemorrhage alone is responsible for most deaths, and then either cardiopulmonary or pulmonary failure. Infections are also considered a leading cause of death in DAH with SLE [15]. However, early recognition and management of SLE-related

respiratory manifestations are essential to prevent complications and improve disease prognosis [12].

4. Conclusion

DAH is a rare catastrophic complication of SLE with poor prognosis and high mortality despite increasing available modern therapies. It usually presents in patients with an established diagnosis of SLE even on medical therapy but can be the initial manifestation of undiagnosed SLE patients. The diagnosis of DAH is problematic because it mimics a severe pulmonary infection. However, it should be suspected in patients presenting with worsening respiratory symptoms, dropping hemoglobin levels, and pulmonary infiltrates on chest imaging. Early detection and aggressive management are warranted, including supportive care, immunosuppressive therapy, and plasmapheresis to improve affected patients' outcomes and quality of life. Future studies on this topic are essential for a better understanding of this condition.

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