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Case Report: Systemic Lupus Erythematous Flare with Lupus Nephritis Complicated by Acquired Angioedema Possibly Linked with C1 Esterase Inhibitor Deficiency

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ABSTRACT

This case report describes the hospitalization of a 21-year-old female patient with a history of systemic lupus erythematosus (SLE) and lupus nephritis, presenting with myalgia, low-grade fever, and pricking chest pain. The patient developed angioedema of the face, neck, and tongue, leading to a critical airway compromise. Further investigation revealed significant abnormalities, including severe anemia, complement deficiencies and there may be possible acquired C1 esterase inhibitor deficiency. Treatment involved fresh frozen plasma transfusions, C1 esterase inhibitor Concentrate for angioedema, hemodialysis and immunosuppressive therapy. Administration of C1 esterase inhibitor concentrate was a pivotal in restoring complement system function and alleviating excessive bradykinin effects and also other supportive care measures taken to stabilize the patient condition. End of the day patient's condition improved, and she was discharged with a plan for ongoing hemodialysis, discharge medications and follow-up recommendations.

Keywords: Systemic Lupus Erythematous, Lupus Nephritis, Angioedema, C1 Esterase Inhibitor Deficiency, Hemodialysis, Rituximab

BACKGROUND

Systemic lupus erythematosus (SLE) is an autoimmune disorder with multi-organ involvement. The clinical presentation can manifest in a diverse range, encompassing cardiovascular emergencies such as pericarditis, cardiac tamponade, and myocardial infarction, neurological complications like stroke, pulmonary issues including pulmonary edema, and renal involvement such as lupus nephritis [3].

Angioedema manifests as swelling in soft tissues or mucosa due to heightened blood vessel permeability. This reaction is typically triggered by histamine or bradykinin. Histamine-induced angioedema may be allergic, pseudo allergic, or idiopathic, while bradykinin-induced angioedema can result from drugs, be acquired, or have a hereditary basis.[1]

Hereditary angioedema (HAE) is a rare and severe form of angioedema caused by genetic mutations in the complement C1 inhibitor (C1-INH) gene, leading to reduced C1-INH levels. There are three types of HAE (I, II, and III), each characterized by distinctions in their origins and C1 inhibitor protein levels. Type I involves diminished C1-INH synthesis, Type II features dysfunctional C1-INH protein, and Type III

maintains normal C1-INH levels and activity. HAE presents as recurrent episodes of severe swelling, predominantly affecting limbs, face, and the intestinal tract, with infrequent airway swelling. Unlike urticaria-associated conditions, HAE lacks such a correlation. Acquired angioedema (AAE) with C1 esterase inhibitor deficiency and low C1q, occurring in individuals over 40 without a family history of angioedema, shares clinical features with HAE. This rare disorder manifests as late-onset angioedema without urticaria [2, 6].

Acquired Angioedema (AAE) can be categorized into type 1 & 2, In type 1 AAE, autoimmune diseases or B cell lymphoproliferative disorders (such as non-Hodgkin lymphoma or monoclonal gammopathy) are associated [6]. This variant is believed to arise from the direct activation and depletion of the classical complement pathway by neoplastic tissue associated with lymphoproliferative disorders [7,8]. while type 2 AAE involves autoantibodies against C1-INH. Reported associations include ulcerative colitis, myasthenia gravis, Sjogren syndrome, anti-phospholipid syndrome, anti-thrombin III deficiency, systemic lupus erythematosus (SLE), and immune thrombocytopenia [6, 9].

The proposed explanation for angioedema in these instances continues to be the bradykinin-associated leakage of fluid into connective tissues [9]. Nonetheless, there are documented cases of angioedema in lupus patients linked to a third mechanism involving substantial complement consumption through the major classical pathway and the alternative pathway [9].

Typically, cases of Acquired Angioedema (AAE) stemming from typical C1-INH deficiency exhibit low levels of C4 and C2, while maintaining a normal C3 level. However, a diminished C3 level indicates significant consumption of the major classical pathway-mediated complement. Although rare, angioedema linked to this mechanism has been documented, particularly in correlation with systemic lupus erythematosus (SLE) [9].

In lupus patients experiencing angioedema, the levels and functionality of C1-INH may remain within normal ranges [3].

In lupus patients experiencing angioedema, the observed lack of dysfunction in C1-INH, whether in quality or quantity, mirrors feature found in type 3 Hereditary Angioedema (HAE) or angioedema linked to estrogen. Traditionally, it was thought to be linked to a temporary increase in bradykinin without any pathological alterations in C1-INH's antigenic function or level. Another idea suggests a compensatory rise in plasminogen synthesis, causing transiently elevated bradykinin levels, especially in lupus nephritis patients with glomerulonephritis and subsequent moderate urinary protein loss. This theory gains support from documented cases of tissue plasminogen activator (t-PA)-related angioedema, where in-vitro plasmin and kallikrein form a synergistic positive feedback loop, potentially inhibited by aminocaproic acid. This aligns with the observed effectiveness of tranexamic acid in specific angioedema cases. Additionally, insights from literature on type 3 HAE highlight increased plasmin, factors VII, X, and IX in individuals using hormone replacement therapies (HRT) or oral contraceptive pills (OCP), along with decreased plasminogen activator inhibitor. Despite maintaining normal C1-INH levels and function, individuals in this demographic commonly experience angioedema [10].

This case report highlights the difficulties encountered in the management of a patient with systemic lupus erythematosus (SLE) and lupus nephritis who experienced acquired angioedema, possibly associated with C1 esterase inhibitor deficiency.

CASE PRESENTATION

A 21-year-old female, previously diagnosed with systemic lupus erythematosus (SLE), had a prior admission due to complaints of bilateral pedal edema, orthopnea, frothy

urine, and reduced urine output. The renal biopsy confirmed Stage IV lupus nephritis, with elevated serum creatinine at 3.1 mg/dl. Testing revealed positivity for anti-double stranded DNA antibody (dsDNA), anti-nuclear antibody (ANA)/anti-cell antibody (ACA) IgG, anti-cardiolipin antibody (ACA), and a reduction in complement levels (C3 - 19.6 mg/dl, C4 - <7.4 mg/dl).

The patient underwent pulse therapy with Inj. Methylprednisolone 250mg for 5 doses and started Inj. Cyclophosphamide 500mg therapy. Haemodialysis was initiated via the right internal jugular vein. Upon discharge, the patient continued with Tab. Prednisolone 50mg once daily, Tab. Hydroxychloroquine 100mg once daily, and other supportive drugs.

As of the current admission, the patient had undergone a total of 5 dialysis sessions, with the last session occurring the day before the current admission. On day 1 of the current admission, the patient presented with chief complaints of myalgia, low-grade fever, and pricking chest pain for the past 2 days. A blood sample was provided for culture in the OPD. On day 2, the patient underwent a hemodialysis session.

On the third day, around noon, the patient complained of throat pain and swelling, prompting the physician to prescribe T. Azithromycin 500mg, suspecting an infection. Later in the evening, a medical emergency team (MET) was summoned due to an impending airway compromise. The patient displayed tongue swelling and protrusion, an inability to retract the tongue, an edematous epiglottis, and swollen vocal cords. Urgent interventions, including Inj. Hydrocortisone 100mg, Inj. Adrenaline, and Inj. Pheniramine Maleate, were administered. Despite these measures, the patient required intubation with supportive drugs to stabilize the airway. Subsequently, she was transferred to the renal ICU for further management. The development of angioedema had led to airway compromise, necessitating intubation. On the same day itself Chest X ray done procedure.

On the fourth day, early morning, four units of FFP were transfused over an hour. After a few hours, another unit was administered over 20 minutes because angioedema did not subside even after the intubation procedure. Due to suspected C1 esterase inhibitor deficiency-induced angioedema, a blood sample was sent for testing, but the sample was taken after the administration of FFP. Subsequently, 1000 IU of C1 esterase inhibitor concentrate was administered intravenously. Neb Budecort and Neb Adrenaline were given to enhance airway passage, and to prevent tongue injury from teeth during swelling, two gauze pieces were placed on the dorsal and ventral aspects of the tongue. On the same day, the patient's hemoglobin level was 6.5 mg/dl, so one unit of PRBC was transfused, dialysis was performed in the morning and chest X ray report came as normal.

On the fifth day, an additional dose of Inj. C1 esterase inhibitor concentrate (1000IU) was administered. Concurrently, the final blood culture report, obtained from a sample collected the day before hospital admission, confirmed no growth.

On the sixth day, following three days of intubation, the patient was successfully extubated, maintaining satisfactory room air saturation. The C1 esterase inhibitor test report indicated normal levels.

Moving to day 7, Inj. Rituximab 500mg was administered stat for the SLE flare-up, and there were no adverse drug reaction complications. Preceding this, premedication included Inj. Avil 2ml, Inj. Hydrocortisone 50mg, and T. Dolo 650mg.

On day 8, the patient's condition improved further, allowing for a gradual transition to a normal diet. The patient exhibited good mobility and remained hemodynamically stable.

Finally, on day 9, the patient was discharged with appropriate discharge medication and supportive measures, marking the successful conclusion of the hospitalization journey.

LABORATORY FINDING

Throughout the hospitalization, laboratory investigations reflected fluctuating haemoglobin levels ranging from 6.5 to 8.8gms%, PCV fluctuating between 20% and 25%, RBC ranging from 2.6 to 3.2 million/ul, RWD fluctuating between 19.2% and 21.9%, MCV consistently maintained between 75 and 78 fl, MCH between 25 and 27 pg, and MCHC between 32 and 35g/dl. Platelet counts fluctuated from 90 to 120 10^3/mm^{3}103/mm3, WBC levels ranged between 5.12 and 7.37 10^3/mm^3, neutrophils fluctuated from 90% to 94%, lymphocytes from 3% to 6%, monocytes maintained between 2% to 4%. Serum potassium levels fluctuated from 3.4 to 3.8 mEq/L, and serum sodium level remained at 132 mEq/L. Blood culture showed no growth. Chest report shows no abnormalities. Complement levels (C3 – 39.8 mg/dl and C4 - <7.4mg/dl) were significantly reduced. Notably, C1 esterase inhibitor levels (>388mg/L) might present a false normal value due to the blood sample being taken post fresh frozen plasma (FFP) administration. FFP contains a C1 esterase inhibitor protein, potentially replenishing normal levels and leading to a false normal result before the therapy. Like these parameters were diligently monitored throughout the entire hospitalization period.

DIAGNOSIS AND MANAGEMENT

The patient's initial diagnosis included SLE flare, lupus nephritis on dialysis, anemia due to chronic disease, Bloodstream infection and Acquired C1 esterase inhibitor deficiency was suspected due to angioedema. Therefore, the patient is treated with Fresh frozen plasma transfusion, two doses of Inj.C1 esterase inhibitor 1000IU, Neb. Budecort, Neb. Adrenaline and other supportive measures taken like hemodialysis, blood transfusions, and immunosuppressive therapy were provided as part of the management. the patient showed with resolution of angioedema, stabilization of vital signs with the treatment and she was successfully extubated

The patient received a regimen of medications during hospitalization, including T. Azithromycin 500MG once daily from day 3 to day 7, T. Calcium and vitamin D3 twice daily from day 1 until discharge, T. Nifedipine 10mg twice daily from day 1 until discharge, Inj. Hydrocortisone 100mg thrice daily from day 1 to day 5, T. Hydroxychloroquine 200mg 1/2 once daily from day 1 until discharge, Inj. Ranitidine 50mg twice daily from day 5 to day 9, T. Pantoprazole 40mg once daily from day 1 to day 4, T. Prednisolone 5mg once daily from day 6 to day 9, Neb. Budesonide 0.5mg twice daily from day 3 to day 9, Neb. Adrenaline (diluted to 5ml) twice daily on day 4 and day 5, Inj. Rituximab 500mg one dose administered on day 7 for SLE Flare, Inj. Pheniramine maleate once daily on day 4 and day 5, Inj. Paracetamol 1g four times daily from day 1 to day 3, and Inj. Cefoperazone with sulbactam 1.5g twice daily from day 1 to day 3. It is noteworthy that no major drug interactions or intravenous incompatibilities were identified during the administration of these medications.

DISCHARGE AND FOLLOWUP

Upon discharge, the patient was provided with comprehensive post-hospitalization care instructions to manage her condition effectively. The prescribed diet included a daily salt intake restriction of 4g, coupled with a fluid limitation of 1.5L per day, emphasizing adherence to a normal potassium diet. Hemodialysis was scheduled thrice weekly to maintain renal function.

The discharge medication regimen aimed at the patient's ongoing treatment and included Tab Prednisolone 50mg once daily, Tab Pantoprazole 40mg once daily before breakfast, Tab Calcium supplement once daily, Tab Nifedipine 10mg twice daily, Tab Hydroxychloroquine 100mg once daily, Moisturizing Cream with Aloe Extract & Hyaluronic Acid to be applied once daily, Gel containing Choline Salicylate, Lidocaine, and Benzalkonium chloride to be

applied once daily over the tongue, and Clotrimazole Mouth Paint to be applied thrice daily over the tongue.

To ensure the continuity of care, the patient was scheduled for a follow-up visit, allowing for further evaluation and adjustments to the management plan as needed. This comprehensive discharge plan aimed to support the patient's recovery and enhance her overall well-being beyond the hospital setting.

DISCUSSION

Autoimmune conditions represent the second most frequently observed association with Acquired Angioedema (AAE) [6]. Angioedema, often affecting the larynx and causing upper airway swelling, represents the most severe and potentially life-threatening manifestation. Approximately half of individuals with AAE-C1-INH encounter upper airway edema, leading to anoxic brain injury or fatality due to obstruction in the upper airway [11].

Addressing angioedema is particularly evident in hereditary cases, with treatment options contingent upon the type, severity, and frequency of attacks. During acute episodes, extensively researched interventions include C1-INH concentrate, ecallantide, and icatibant. Moreover, androgens, C1-inhibitor concentrate, and fibrinolytics like aminocaproic acid and tranexamic acid have demonstrated variable effectiveness as prophylactic measures [12].

Treatment for AAE varies by subtype. IH-AAE responds well to increased antihistamine dosages and can be used prophylactically. InH-AE lacks robust treatment evidence, with case reports suggesting varying success with tranexamic acid, steroids, and omalizumab [12]. ACE-I-AAE management involves permanent ACE-I avoidance [13]. Bradykinin-targeted drugs like ecallantide and icatibant demonstrate rapid symptom resolution, enabling early hospital discharge. ARBs in these patients do not exacerbate attacks. C1-INH AAE treatment includes bradykinin-targeted agents, akin to Hereditary Angioedema (HAE), alongside addressing underlying immunoproliferative disorders. Case reports show rituximab reducing attack frequency, severity, and inducing remission [12].

In this case report, the acquired deficiency of C1 esterase inhibitor played a pivotal role in the development of angioedema. C1 esterase inhibitor is a key regulator of the complement system and bradykinin level. Its deficiency can lead to increased bradykinin production. Elevated bradykinin levels contribute to vascular permeability, causing angioedema. Administering C1 esterase inhibitor replacement therapy proved crucial in managing angioedema by restoring the regulatory function of the complement system and mitigating the excessive bradykinin-mediated effects. This underscores the significance of recognizing and addressing acquired C1 esterase inhibitor deficiency in the overall management of complex cases involving lupus and associated complications.

CONCLUSION

This case report emphasizes the complexity of managing SLE with complications such as lupus nephritis and acquired angioedema due to C1 esterase inhibitor deficiency. Timely intervention, multidisciplinary care, and close monitoring of laboratory parameters were crucial for the successful management of this challenging case.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflicts of interest related to this case report.

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