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Case Report

Management of Angioedema and Mucositis as Oral Manifestations of Juvenile Systemic Lupus Erythematosus

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Abstract

Angioedema and mucositis are rare in juvenile systemic lupus erythematosus (jSLE) and increase morbidity and mortality in an individual under 18 years. This case report aims to describe the management of an 11-year-old female patient with a history of jSLE, presenting with swelling of her lip, difficulty in speaking, oral pain since a month ago, and self-medicating, which led to the swelling becoming worse. Full blood count, immunology, and antigen laboratory examination indicated anemia normocytic normochromic, leukopenia, hypoalbuminemia, vitamin D deficiency, proteinuria, neonatal lupus erythematosus, and Sjogren's syndrome. Methylprednisolone, mycophenolate mofetil, and hydroxychloroquine sulfate were given by the pediatrician. Medications consisted of topical application of 0.1%triamcinolone acetonide in orabase for angioedema and mucositis, benzydamine hydrochloride oral rinse before meals, chlorhexidine gluconate and 0.025% hyaluronic acid mouthwash after meals and before bed. Oral complaints and lesions have improved within 10 days. High caution, specific examinations to determine the type of angioedema, collaboration with pediatric rheumatologists, and systemic treatment of SLE must be supported by topical therapy to treat AE and mucositis, which are oral manifestations of SLE.

Keywords: angioedema; mucositis; juvenile Systemic Lupus Erythematosus

INTRODUCTION

Angioedema (AE) is an acute onset and immune-mediated swelling of submucosal and subcutaneous tissue, typically the periorbital tissue, lips, and airways, and increases fatality and mortality rate if definitive diagnosis and appropriate treatment are delayed. Angioedema is divided into allergic (mast) and non-allergic (bradykinin) types. Non-allergic type of angioedema consists of acquired, drug-induced, hereditary, idiopathic, and pseudo-allergic angioedema. [1,2]

The prevalence of hereditary angioedema (HAE) ranges from 0.0001% to 0.001%, and AAE ranges from 0.0002% to 0.001%.[3,4] Many HAE results from changes in the DNA sequence in the †SERPING-1 gene generating HAE type 1 with a deficit C1 esterase inhibitor (C1-INH) in about 85% of cases and HAE type 2 with abnormal function of the C1-INH around 15%. There is no gender predilection between males and females and between ethnicities.[1,2,4]

Juvenile-onset systemic lupus erythematosus (jSLE) is a rare chronic, autoimmune multisystem inflammatory disease that is associated with significant morbidity and mortality in an individual under 18 years of age. The incidence of jSLE varies depending on ethnicity and location, with a range from 0.3-2.5/100,000

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per year and a prevalence of 3.3-24/ 100,000.[5]

The pathogenesis of jSLE mechanisms is a combination of hormonal, environmental, and genetic factors.[5,6]The jSLE patients have a higher level of severity in organ systems involvement, reduced quality of life, adverse effect of treatment, and recurrence compared to adult patients. Clinical signs of jSLE can be diverse and varied, consisting of lupus nephritis, hematologic disorders, photosensitivity, neuropsychiatric, and mucocutaneous involvement. [7]

Multidisciplinary medical collaboration and immunosuppressive agents for the treatment of jSLE are similar to adult SLE, although in a more aggressive pattern to achieve disease outcomes and prognosis. Ethnicities, poor compliance, social views on health, and the expense of medicine and treatment influence the result and response to lupus treatment. [5,8]

Several reports of Angioedema in adult SLE patients, which is a complication of SLE, have been reported, as well as in children, although it is still infrequent and has been increasing lately. [2,9] this case report aims to describe the management of an 11-year-old female patient with a history of jSLE, presenting with swelling of her lip, difficulty in speaking, oral pain since a month ago, and self-medicate, which led to the swelling becoming worse.

CASE REPORT

An 11-year-old female was hospitalized at the Paediatric Allergy Immunology Rheumatology Centre and consulted the Oral Medicine Department with a history of juvenile systemic lupus erythematosus complained of swollen eyelids and lips with difficulty eating, drinking, and speaking (hoarseness) almost for a week. During the last 3 days, she had noticed a new onset of oral ulcer, which caused pain and led to worsening swallowing and speaking. History taking showed no history of insect stings, consumed seafood, drug allergies, or similar diseases in the family line.

The patient's vital signs consisted of temperature at 36.2ºC, heart rate at 80 times per minute, blood pressure at 90/60 mmHg, respiratory rate 20 times per minute, and oxygen saturation at 98% on room air. No tracheal or laryngeal obstruction sign was noted. No dermatological abnormalities were identified on the exam.

On extra oral examination, she appeared weak, with mild facial swelling around her face, bilateral eyelids, and lips (figure 1A). The painless swelling was non-tender. She had submental and bilateral soft submandibular lymphadenopathies that were non-tender. Intraoral examination showed irregular ulcers in the anterior hard palate upper and lower labial mucosa with exfoliative area in the upper and lower lips (figure 1B).

Blood, antigens, albumin, urine chemistry, and urinalysis investigation results can be seen in Table 1. Laboratories interpretation indicated anemia normocytic normochromic, leukopenia, neonatal lupus erythematosus, Sjogren's syndrome, SLE, hypoalbuminemia, vitamin D deficiency, and proteinuria.

The oral diagnosis was angioedema and mucositis, which are manifestations of juvenile systemic lupus erythematosus. The pediatrician initiated intravenous methylprednisolone 48 mg every 8 hours for 24 hours, and the oral lesions were treated with benzydamine hydrochloride 7.5 mg oral rinse 10 minutes before meals for 60 seconds, 0.2% chlorhexidine gluconate was compressed after meals on the labial mucosa and the anterior of palate three times a day followed application of 0.1%triamcinolone acetonide in orabase.

On the 4th day, oral examination revealed oedematous upper and lower lips and unpainful ulceration concurrently with hemorrhagic crusts on the upper and lower labial mucosa (figure 1C and 1D). On the 3rd day, 30 mg IV methylprednisolone daily with mycophenolate mofetil 500 mg twice

a day were given; lisinopril 5 mg and hydroxychloroquine sulphate 200 mg each once a day for the presence of lupus nephritis.

Six days after hospitalization, swelling on the upper and lower lips subsided (figure 2A) with sloughing and mixed ulcerations of upper and lower labial mucosa, hard palate, and bilateral buccal mucosa (figure 2B). Ten days after the initial visit, the swelling of lips and periorbital; oral lesions had healed, remaining dry, exfoliative lips and mild sloughing on buccal mucosa (Figure 3).

The patient's symptoms continued to improve, with only mild abdominal pain. Albumin administration due to low albumin level was performed by intravenous (IV) infusion, and she allowed for outpatient treatment on a methylprednisolone taper starting at 48mg, mycophenolate mofetil 500 mg twice a day, hydroxychloroquine sulphate 200 mg, and lisinopril 5 mg for two weeks. The parents gave informed consent, allowing the publication of her data, and they approved the publication of the case.

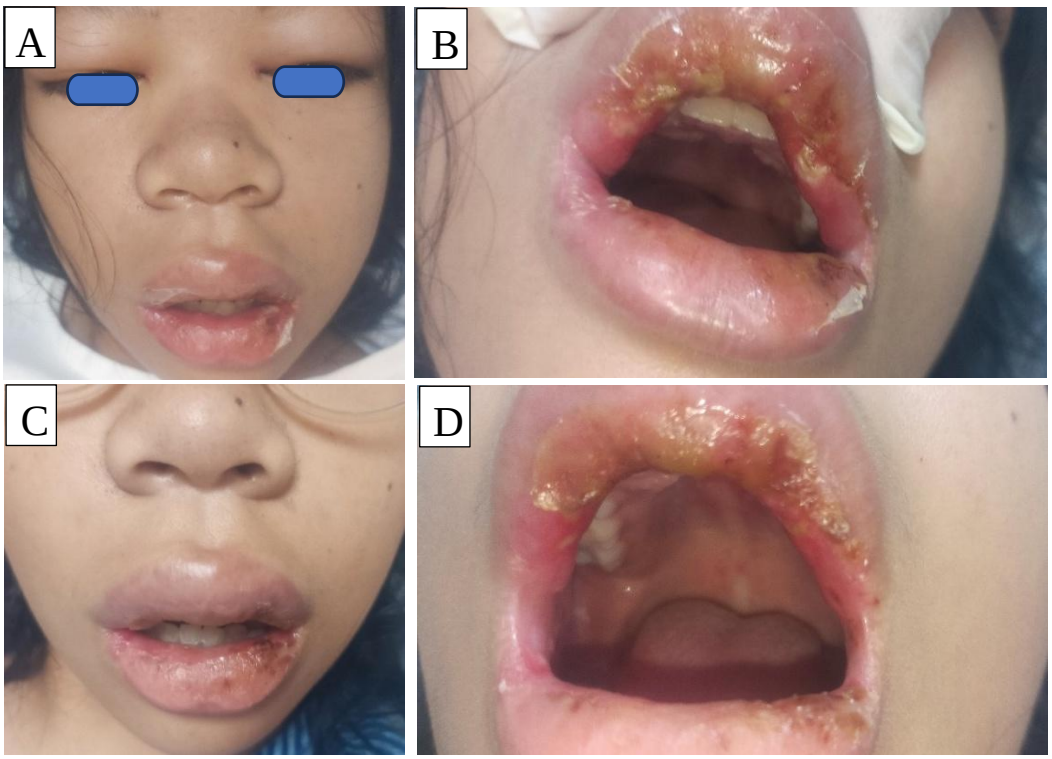

Figure 1. The patient at first presentation with bilateral periorbital oedema (A). Ulcerated, hemorrhagic crusts and oedematous upper lip and dry crust on oedematous lower lip. Oral ulcer on the anterior palate upper labial mucosa, along with multiple ulcerations on the oral mucosa (B). On the 4th day of hospitalization, oedematous upper and lower lips, unpainful ulceration, and hemorrhagic crusts on the upper and lower labial mucosa (C, D).

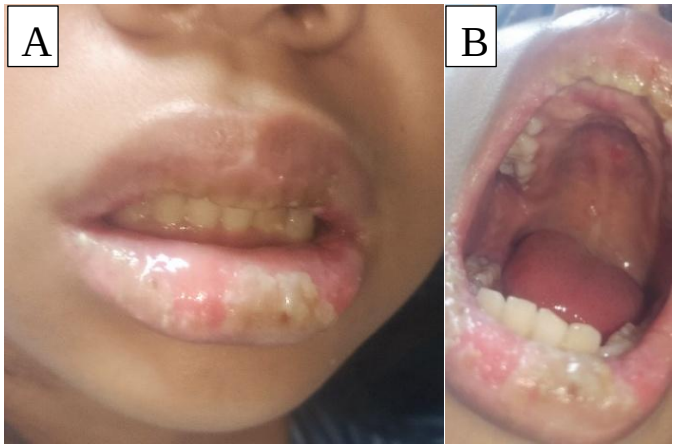

Figure 2. Swelling on the upper and lower lips subsided (A) with sloughing and mixed ulcerations of upper and lower labial mucosa, hard palate, and bilateral buccal mucosa on the 6th day of hospitalization (B).

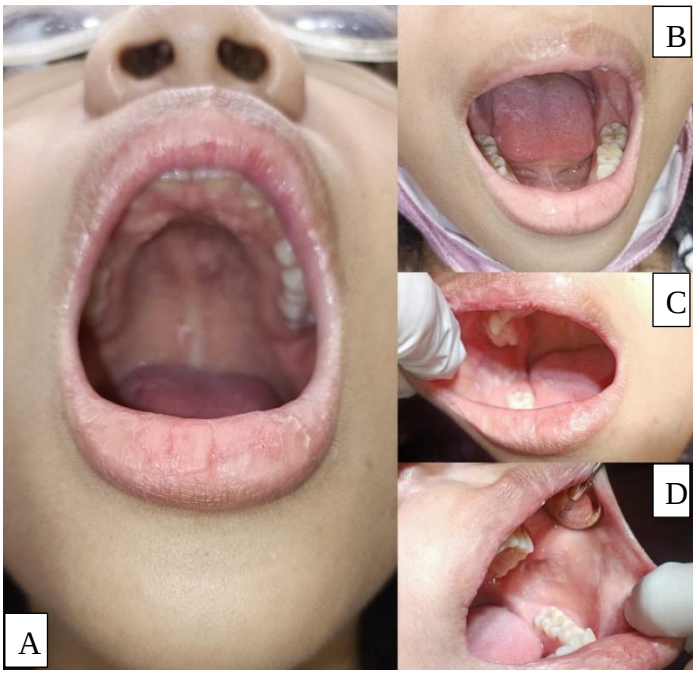

Figure 3. Lip swelling and ulceration recovered completely (A, B). Mild sloughing presented as white patches on bilateral buccal mucosa (C, D) after 10 days of treatment.

Table 1. Laboratory Findings

Full Blood Count	Result**	Reference Values
Haemoglobin	10.4 (L)	11.8-15.00 g/dL
Haematocrit	32.0 (L)	35-47 %
Total of erythrocytes	3.9 10^6/uL	3.8-5.2 10^6
Total of leukocytes	4.2 10^3/Ul (L)	4.5-13.5
Total of platelets	219 10^3/uL	150-440
Differential Count	Result	Reference Values
Basophil	0%	0-1
Eosinophil	0 (L)	2-4
Neutrophil rod	2	0-6
Neutrophil segment	46 (L)	50-70
Lymphocytes	46	30-60
Monocytes	6	2-8
Erythrocyte index	Result	Reference Values
MCV	82.7 fL	80-100

MCH	26.9 pg	26-34
MCHC	32.5 g/dL	32-36
Erythrocyte Sedimentation Rate	80 mm/hour (H)	0-20
Immunology	Result	Reference Values
C-Reactive Protein	1.0	0-5 mg/L
Rheumatologic workup		
Antigen	Intensity	Class
SS-A native (60 kDa) (SSA)	33	++
Ro-52 recombinant (52)	30	++
DFS70 (DFS70)	34	++
dsDNA (DNA)	17	+
Nucleosomes (NUC)	24	+
Histones (HI)	18	+
Vitamin D Total (25-OH)	3.0 ng/mL (L)	<20: deficiency
Chemistry	Result	Reference Values
Albumin	1.66 g/dL (L)	3.8-5.4 g/dL
Urine Biochemistry		
Urin volume	4600 mL (21)	
Protein urine 24 hours	9.338 g/24 hours (H)	0.04-0.23 g/24 hours
Urinalysis		
Qualitative Protein urine	203 mg/dL (H)	<12
Sediment		
Erythrocytes	1.8	0.2-10.1 /uL
Leukocyte	1.5	0.10-6.55
Epitel	0.4	0.10-7.81
Cylinder	0.3	0.0-0.4
Crystal	0.0	
Bacteria	10.8	1.06-107.82
Glucose, ketones, bilirubin, nitrite, leukocyte esterase;	Negative	Negative
Urobilinogen	Normal	<1 mg/dL
pH	7.0	5.0-7.4

**L: low; H: high

DISCUSSION

Various research results on the relationship between SLE and hypersensitivity diseases differ and are still controversial, although there is a higher risk of hypersensitivity disease due to atopic disorders in AE patients with SLE. Chronic urticaria, with its pathogenesis of mast cell degranulation in SLE patients, can manifest with AE.[4] The American College of Rheumatology (ACR) supports criteria grouped one of the typical oral lesions correlated with LE is palatal erythematous ulcers, which was found in the current patient, while aphthous ulcers, lupus cheilitis and several types of oral lesions grouped as nonspecific LE oral ulcers. [10]

The patient was suspected had an AAE due to systemic lupus erythematosus. The absence of a family history of similar symptoms, i.e., a history of angioedema, suggests a clinical diagnosis of AAE.[11] Acquired angioedema (AAE) has two forms, AAE-I and AAE-II. AAE-I can be linked with lymphoproliferative disorders with increased catabolism of C1-INH, AAE-II is an autoantibody-mediated pointed to the C1-inhibitor molecule for example, recently systemic lupus erythematosus (SLE). Patients with concomitant SLE and Angioedema usually occur in younger women of African-American with a tendency to HAE is more common than AAE. Visceral pain is another important symptom due to swelling of the gastrointestinal mucosa. The definitive pathophysiology of AAE in SLE is currently undetermined. [9,12]

C1-INH, as part of the complement system, coagulation, and fibrinolytic cascades, plays a role as a regulator protein

and downregulates the production of the vasodilator bradykinin in the plasma kallikrein-kinin system. On the contrary, the low level of C1-INH antigen and function, complement factors 3 and 4 (C3 and C4) generate an increased level of bradykinin, followed by advanced capillary permeability as can be seen in swelling of the lips. [13]

Frequent occurrence attacks of visceral pain and rapid loss of saturation are suspected due to edema of the laryngeal lips, and the significant reaction to steroids and, subsequently, immunosuppressive treatment can be closely related and described with angioedema. The C1q level examination in angioedema to distinguish between HAE and AAE subtypes was not performed due to the unavailability of this investigation in our hospital and limited insurance limits.[11] Autoimmune inspection for SLE indicates elevated serum inflammatory signs, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as can be seen in the laboratory results of the case. Concurrent therapy of SLE with AAE with corticosteroids, cyclophosphamide, hydroxychloroquine, etc., has exhibited overall improvement in symptoms, emphasizing the existence of the association.[9,12]

Oral ulcerations are a common finding in SLE, specifically juvenile SLE, including other oral mucosal lesions such as lupus cheilitis, central erythema on palatal area, and fungal infection, as oral manifestations are one of the criteria in ACR used to establish the diagnosis which also can be seen in this case. Painless palatal ulcers and aphthous ulcers on the buccal mucosa of SLE are more common compared with lips lesions, which many are associated with discoid lupus, and the least lesion is angioedema or crusted cheilitis.[14–16]

The vascular permeability factor (VPF), as a potent angiogenic factor, is essential for organizing angiogenesis. Thus, the dysregulation of the VPF pathway causes apoptosis and leads to ulcers. There are differences between haplotypes in the polymorphism of differentiation group CD34 in SLE, which can influence the immune system and trigger the pathogenesis of oral ulcers.[14,17]

Treatment options for SLE include nonsteroidal anti-inflammatory drugs, antimalarial, glucocorticoids, immunosuppressive, and biologic agents. References regarding definite treatment and medication for oral lesions are limited, although topical glucocorticoids have been widely used as the main treatment preference. The selected formulation of medication is adjusted to ease of use and access to the lesion.[18,19]

The first-line regimen in the treatment of jSLE is glucocorticoids and hydroxychloroquine; the second most common regimen is mycophenolate mofetil.[20,21] Hydroxychloroquine recently is the main preference in initial and continuous primary therapy and prevention for SLE. It reduces an exacerbation of jSLE and multiplies the complete renal reaction to mycophenolate, and it is expected to alleviate organ destruction and cardiovascular and metabolic diseases compared with glucocorticoids. [22] Mycophenolate mofetil, as an immunosuppressive agent, has become the choice in the therapy of SLE with extrarenal involvement and its anti-inflammatory features. All these systemic medications indirectly treat oral lesions because oral lesions are a manifestation of SLE. [18,23] It is highly recommended when doing outdoor activities to avoid exposure to UV rays if possible, and regularly maintain lip moisture and use a lip protector that contains anti-UV.[23,24]

If angioedema recurrence in SLE or undetected SLE frequently occurs, it is recommended to perform a C1-INH level examination to determine the type of angioedema and accurate treatment. [2,10] Mental health disorders related to anxiety, depressive disorders, and ineffective family coping difficulties in children and

adolescents with SLEs must be addressed and become the focus of health workers and the patient's family.[25,26]

CONCLUSION

High caution, specific examinations to determine the type of angioedema, collaboration with pediatric rheumatologists, and systemic treatment of SLE must be supported by topical therapy to treat AE and mucositis, which are oral manifestations of SLE.

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