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BACTERIAL INFECTIONS-INDUCED ORAL ERYTHEMA MULTIFORME IN A SEPTIC CHILD: A RARE CASE REPORT

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ABSTRACT

Background: Sepsis is a medical emergency condition that triggers an immune response due to an infectious process. Causative organisms in sepsis including viruses, bacteria, fungi, and parasites. Microorganism infection is one of the etiologies of erythema multiforme. **Objective:** This case report was aimed to describe the bacterial infection as a trigger for oral erythema multiforme in a septic child. **Case:** A 12-years-old boy was referred to the Oral Medicine Department. Extraoral showed a symmetric face and he was using a nasogastric tube. There were erosive lesions and tend to bleed, hemorrhagic crusts on the upper and lower lips. Laboratory test results revealed increasing in leukocyte (15,880/ μ L), procalcitonin (24.58 ng/mL), and C-reactive protein (3.67 mg/L). The identified microorganisms in pus specimens including gram-positive coccus and gram-negative rods as well as the isolated bacterial colonies were *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Citrobacter koseri*. The diagnosis was oral erythema multiforme induced by bacterial infections. **Case management:** The medications given by the Pediatric Department were cefotaxime vial 1 gram, metronidazole 500 mg/100 ml, and paracetamol 1 gr/100 ml. The Oral Medicine Department gave the instructions for compressing the lips with gauze soaked in 0.9% Sodium Chloride solution four times a day to remove crusts and accelerate wound healing. Oral lesions showed significant improvement after 7 days of therapy. **Conclusion:** Oral erythema multiforme in a pediatric patient could be induced by sepsis of bacterial infection. The microbial infection causes the release of endotoxins that trigger erythema multiforme.

Keywords: *Bacterial infection, Oral erythema multiforme, Sepsis.*

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INTRODUCTION

Erythema multiforme (EM) is a mucocutaneous inflammatory disease that manifests on the skin and mucosal surfaces. The term EM was first declared by Ferdinand von Hebra in 1860. EM occurs in young adults aged 20 to 40 years, more common in women than men with a ratio of 1.5:1. The genetic predisposition of EM occurs in certain Asian ethnic groups. The prevalence of oral EM lesions varies from 35% to 65% in patients with cutaneous lesions.¹ EM is caused by the presence of infections from certain microorganisms, radiotherapy, systemic diseases, malignancies, immunizations, genetic factors, and drug or food allergies.^{2,3} Human Leukocyte Antigen (HLA) phenotype can be a genetic predisposing factor for the occurrence of EM.⁴

Erythema multiforme can be classified into EM minor and EM major. EM minor involves the skin less than 10%. EM minor lesions are characterized by the presence of a single mucosal ulceration and characteristic target lesions on the skin. EM major involves more extensive of the skin and oral mucosa and other mucous membranes.^{2,5,6} The involvement of oral mucosal and lip lesions without skin lesions have been reported in several previous studies.^{1,7} Some researchers classified these lesions into a new variant called oral erythema multiforme. Oral EM is characterized by the presence of some typical oral lesions but no target lesion on the skin.⁸

The clinical manifestations of EM including papular, bulla, or vesicular lesions and target lesions on the skin. Oral mucosal lesions

occur in more than 70% of EM cases.¹ Oral manifestations of EM including superficial erythematous lesions, hyperkeratotic plaques, bullae, and haemorrhagic erosions. Oral lesions begin as oedema, erythema, erythematous macules on the lips, and buccal mucosa followed by the formation of multiple bullae and vesicles that easily rupture then produce a pseudomembrane layer.⁹

Sepsis is a syndrome involving biochemical, physiological and pathological abnormalities caused by infection.¹⁰ Sepsis is a medical emergency condition that triggers an immune response due to an infectious process, resulting in septic shock, multiple organ dysfunction, and death.¹¹ The causative organisms that cause sepsis including viruses (29%), bacteria (27%), and parasites (1%). Viruses which involved in sepsis are influenzae virus, dengue virus, rhinovirus, adenovirus, hantavirus, and norovirus. The main pathogens that cause sepsis in adults and children including gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Enterobacter* spp.) and gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus suis*, and *Streptococcus beta-hemolytic* spp.).¹⁰ Microorganism infection is one of the etiologies of erythema multiforme. The purpose of this case report was to describe a bacterial infection as a trigger for oral erythema multiforme in a septic child.

CASE

A 12-year-old boy with traumatic spinal injury was referred to the Oral Medicine Department to find the focus of infection. The diagnose of this patient was septic shock and had been treated intensively in the hospital for 10 days. He had loss of consciousness and could not communicate well. He was shot by a gun on his buttocks and had paralysis of the lower limbs since 7 months ago. His lips began to bleed 1 week ago. Extraoral revealed a symmetrical face and he was using nasogastric tube. There were erosive lesions with haemorrhagic crusts which bleed easily on the upper and lower lips (Figure 1). The treatment given by the Paediatrics Department including 1 gram cefotaxime vials, metronidazole 500 mg/100 ml, and paracetamol 1 gr/100 ml.



Figure 1. Clinical manifestations at the first visit. There were erosive lesions with haemorrhagic crusts that bleed easily on the lips, upper and lower labial mucosa.

Laboratory tests showed the leukocyte values (15,880/ μ L), procalcitonin (24.58 ng/mL), and C-reactive protein (3.67 mg/L) were increased. The identified microorganisms were gram-positive cocci and gram-negative rods as well as the bacterial colonies isolated in pus specimens were *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Citrobacter koseri*. The chest x-ray image showed a metal density opaque projected as high as the Th10 – Th 11 of the vertebral corpus (Figure 2). Based on clinical and laboratory examination, the diagnose was oral erythema multiforme induced by bacterial infection.

Test	Result	Reference Range
Hemoglobin	8,2 g/dL	14 – 17,4 g/dL
Erythrocyte	3,15 x 10 ⁶ / μ L	4,5 - 5,9 x 10 ⁶ / μ L
Thrombocyte	12,000/mm ³	150,000-450,000/mm ³
Leukocyte values	15,880/ μ L	
Segmented neutrophils	66%	47 – 55%
Procalcitonin	24.58 ng/mL	<0.05 ng/mL
C-reactive protein	3.67 mg/L	0-5 mg/L

Table 1. Laboratory tests at the first visit



Figure 2. Radiographic of the thorax after being shot by a gun bullet.

CASE MANAGEMENT

The Oral Medicine Department instructed the family to compress the patient's lips with gauze soaked in 0.9% Sodium Chloride solution 4 times a day to remove crusts and to accelerate wound healing. Petroleum jelly was applied to the lips after the crust had disappeared. Oral lesions had not improved after 3 days of therapy. The family was instructed to continue compressing his lips with gauze soaked in 0.9% Sodium Chloride solution. The erosive lesions on the lips and labial mucosa began to improve significantly after 7 days of therapy. The patient had respiratory failure and died 1 day later.



Figure 3. Clinical manifestations at three days of therapy



Figure 4. Clinical manifestations at seven days of therapy. Oral lesions began to improve significantly.

DISCUSSION

Erythema multiforme (EM) is an acute mucocutaneous condition caused by a hypersensitivity reaction. The most common cause of EM are infections which found in about 90% of cases and herpes simplex virus infections are the most dominant in 70% to 80% of cases.¹ Some other pathogens that can trigger EM are *Mycoplasma pneumoniae*, *Chlamyphila pneumoniae*, virus hepatitis, virus Epstein-Barr, Orf virus, HIV, *Mycobacterium leprosy* and some vaccination agents such as *small pox*, rabies, *human papillomavirus*.^{12,13}

There are no specific diagnostic tests to establish the diagnosis of EM. The diagnosis of EM is based on the history taking and clinical examination. Some EM cases do not require further diagnostic tests. Punch biopsy can be used to get a definitive diagnosis in patients with bullous autoimmune disease. The advantage of punch biopsy is that the procedure is fast and does not require suturing.¹⁴ Direct and indirect immunofluorescence may also help to differentiate EM from other types of vesiculobullous lesions, such as bullous pemphigoid. Direct immunofluorescence detects several molecules such as immunoglobulin and complement in biopsy specimens. The results of the EM lesions immunofluorescence showed the presence of immunoglobulin M and C3 components in perivasculitis.¹

Haematological examination revealed an increase in leukocyte count, procalcitonin, and C-reactive protein. Procalcitonin (PCT) is a hormone produced by hepatocytes and plays a role in

calcium homeostasis.¹¹ PCT is detected after infection and followed by elevated levels of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and IL-6. There is an increased of the CALC-1 gene expression on chromosome 11 which causes the release of PCT during inflammation and sepsis.¹⁵ C-reactive protein (CRP) value also increased. CRP is a homopentameric protein that plays a role in the acute phase reaction in sepsis. An increase in CRP values can be caused by an infection or inflammation in the body.¹ Induction of IL-1 β , IL-6, and TNF- α by macrophages causes an increase in CRP levels in septic patients.¹⁶

The patient had a sepsis condition due to a bacterial infection. The identified microorganisms including gram-positive cocci and gram-negative rods as well as isolated bacterial colonies in pus specimens were *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Citrobacter koseri*. Microbial infection causes the release of endotoxins which stimulate B lymphocyte cells to produce autoantibodies in the serum, and triggering erythema multiforme.¹⁷

Endotoxins are small hydrophobic molecules and part of the lipopolysaccharide (LPS) complex that forms the outer membrane of gram-negative bacteria. These molecules are released into the host when the bacterial cell wall is damaged.¹⁸ Endotoxins can bind to *LPS-binding protein* to form the CD14+ complex. The bond will activate *toll-like receptor 4* (TLR-4), initiate inflammatory response, activate macrophages, monocytes, and produce pro-inflammatory cytokines (TNF- α , interleukin-6, and interleukin-23). Endotoxins can also trigger septic shock.^{18,19}

Erythema multiforme is a disease triggered by an immune reaction mediated by T cells. The immune reaction causes a cytotoxic immunological response followed by the formation of vesicles, blisters, and erosions in the subepithelial and intraepithelial.^{12,13} The epidermal layer is infiltrated by CD8 T lymphocytes and macrophages at the early stages of the disease. These cells release cytokines that can mediate inflammatory reactions and epithelial cell apoptosis. There is a T-helper type 1 (Th1) cell cytokine response that produces interferon gamma (IFN- γ). IFN- γ upregulates cytokines and chemokines that amplify the inflammatory response and release autoreactive T cells into the epidermis. The release of autoreactive T cells causes keratinocyte cells to undergo lysis and

apoptosis, resulting in damage to the epidermal layer.¹

Topical treatment for this patient were compressing the lips using gauze soaked in 0.9% Sodium Chloride solution and applying petroleum jelly on the upper and lower lips after the crust had disappeared. Sodium Chloride solution controls the wound exudate and help to control the infection. This solution can cause an osmotic action to clean the wound naturally. Using the right Sodium Chloride concentration (0.9 – 1.8%) triggers fibroblast cell migration and extracellular matrix production thereby accelerating wound healing.²⁰

The lesions began to heal at seven days of therapy. Sepsis causes the wound healing process being delayed in this patient. The impaired wound healing is caused by decreased expression of cytokines and matrix metalloproteinase-7 (MMP-7) which are important in the wound healing process. MMP-7 plays a role in the process of re-epithelialization and angiogenesis in the wounds. MMP-7 releases TNF- α and TGF- β which activate the growth factors to support the process of tissue remodelling. MMP-7 deregulation is one of the causes of an inadequate inflammatory response and results in impaired wound healing during septic conditions. The cytokines expression that are important in the wound healing process is deregulated after sepsis induction. Restoration of normal cytokine response locally in the wounds could be a good strategy to enhance wound healing in septic conditions.²¹ Oral erythema multiforme in paediatric patients can be induced by sepsis of bacterial infection. Microbial infection causes endotoxin release which initiates an inflammatory response that triggers erythema multiforme. Endotoxins also activate some pro-inflammatory cytokines and induce septic shock condition. We would like to thank the patient and his family who participated kindly in this study. This study was approved by Oral Medicine Department, Faculty of Dentistry, Padjadjaran University.

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