

Review Article

Immunopathological aspects of oral erythema multiforme

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ABSTRACT

Background: Erythema multiforme is an acute disease on the skin and mucous membrane. This lesion can erupt in mucous membranes of the oral cavity. Improper and late treatment may cause Stevens Johnson syndrome which may cause patient mortality, therefore proper and accurate diagnosis are needed. **Purpose:** The immunopathological aspect of oral erythema multiforme through literature study can help us to find the definite diagnosis and to know the differential diagnosis. **Review:** In immunopathology, minor type of erythema multiforme is vasculitis caused by the immune complex hypersensitivity reaction among antigen antibodies. The mayor type of erythema multiforme may appeared from autoimmune reaction and from untreated minor type of erythema multiforme. **Conclusion:** Immunopathological approach of erythema multiforme is important beside the clinical manifestation, histology, and the differential diagnosis to find the definitive diagnosis.

Key words: erythema multiforme, hypersensitivity, autoimmune

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INTRODUCTION

Erythema multiforme is an acute disease on skin and mucous membrane which may cause several skin lesions, therefore named multiforme.¹ This disease is an immunologic reaction of hypersensitivity reaction. Erythema multiforme is characterized with an ulcerated lesion on mucous or target lesion on skin in the form of reddish macula surrounding vesicular or bulla in the center. Target lesions are also called iris lesion.²

Severe cases of erythema multiforme are also called as Stevens Johnson syndrome. This syndrome involves the mouth, eyes, genitalia, and skin. Twenty to thirty percent of erythema multiforme cases occur in oral mucous membrane, in the form of multiple vesicular lesion which burst and leave wide eroded area covered by white pseudomembrane.^{3,4} This disease often happen in young adults and children, especially in males and seldom occur in elderly.¹⁻⁵

There are two types of erythema multiforme: minor and mayor erythema multiforme. Mayor type of erythema multiforme has higher degree of severity which is called as Stevens Johnson Syndrome. This disease may worsen

and cause extensive skin peeling, and often cause mortality through secondary infection and electrolyte liquid imbalance.^{1,3,6}

The etiology of erythema multiforme is still unclear to this day. Erythema multiforme is considered as an immunologic disease.⁴ This is probably happen because of predisposing factors as side effect reaction against certain microorganisms, radiotherapy, systemic diseases, malignancy, and food or drug allergy.¹⁻⁷ Common drugs which often cause erythema multiforme are antibiotics, barbiturates, phenylbutazone, and carbamazepin.¹

Immune system is a body mechanism which is used to maintain homeostasis condition against diseases.⁸ The body's ability to eliminate foreign bodies depend on the ability of the immune system in recognizing strange molecules or called immunogens. Response against foreign bodies is done by immunocompetent cells in the body which has three characteristics: specific recognition on certain immunogens, function to differentiate non-self bodies, retaining memory and amplification by remembering known previous immunogens by differentiation.⁹

Today, the development of science and technology is focused on increasing disease diagnosis more accurately. This literature review describes the immunopathogenesis of erythema multiforme and its identification through immunopathological approach not only to get accurate diagnosis but also to give proper therapy.

Erythema multiforme

The clinical manifestation of this disease are acute, begin with general symptom of fever, dizziness, and malaise. In less than 24 hours, an explosive lesion will occur in the skin and mucous membranes, where the lightest manifestation is formed as macula and papula in 0.5–2 cm diameter, whereas in the oral cavity it is started with easily ruptured vesicular and bulla. This condition is a distinctive clinical description which happened in 20–30% of cases (Figure 1).¹



Figure 1. Lesion as crusts, bleeding, and desquamation.¹⁰

Minor erythema multiforme often occur in the oral mucous membrane and skin, seldom happen in oral mucous membrane only. Multiple vesicular and easily rupture lesions leave an eroded area which hurt and covered with white pseudo membrane. Minor erythema multiforme also happen on other mucous membrane in genitalia mucosa but seldom happen in conjunctiva, while on skin usually appeared as reddish macula papula. This lesions are often occur as target lesion (Figure 2).⁴



Figure 2. Lesion as bulla and target lesion.¹⁰

Major erythema multiforme occurs more often on oral mucosa. At the beginning it seemed as a reddish area which turn quickly into vesicle and soon rupture leaving a reddish eroded area covered by white pseudomembrane and crust from bleeding. Other mucous parts could be found on the eyes, genitalia, pharynx, larynx, esophagus, and bronchial; especially in severe cases. On skin, this lesion often found as redness edematous lesion, forming a target lesion.⁴

Diagnosis was based on characterized clinical manifestation, as broad and quick lesion, easily ruptured bulla, bleeding, and crusts on lips.^{4,6} Biopsy for histopathology examination was done to bring ultimate diagnosis of erythema multiforme. Morphological changes usually show hyperplastic and spongiosis epithelial cells. Apoptosis on basal and parabasal layers are always seen. Vesicular could be found on superficial epithel on supporting tissues and sometimes in intraepithel. Necrotic epithel could always be found. Changes on supporting tissues showed lymphocyte and macrophage infiltration on perivascular and papilla supporting tissue area.³ Even though histopathological features are unspecific, the presence of perivascular lymphocyte infiltrates, epithelial edema and hyperplasia, were enough to considered the suspect of erythema multiforme.¹

Histopathology examination on mucosa affected by erythema multiforme showed specific characteristic, which is not always present. Inflammations with inflammatory cell infiltration such as lymphocyte, neutrophil, and eosinophil are more often seen. These cells are organized parallel with perivascular. Immunopathologic feature on erythema multiforme is less specific, therefore it is not grouped into vesicobulous diseases. Ultimate diagnosis of erythema multiforme usually can be set through anamnesis and clinical examination (Figure 3).¹¹

Systemic therapy given on erythema multiform is antihistamine if there is hypersensitivity reaction of drug and to avoid predisposing factors.¹² Administration of oral corticosteroids, especially after the second to fourth days will decrease the eruption period of acute symptoms. On minor type, oral corticosteroids were given 20–40 mg/day for 4–6 days in tapering dose not more than two weeks.^{1,4} On major type corticosteroid therapy is needed orally 40–80 mg/day for 2–3 weeks and antibiotic to avoid secondary infection risk, and high calorie and protein soft diet. Topical therapy can be done by using oral rinse with topical anesthesia, oral rinse containing antibiotic and topical corticosteroids to reduce patient discomfort.⁴

Hypersensitivity reaction

Specific immune system is like a two sided knife, in one side it is a body defense system, but in other side it can promote tissue destruction.¹³ All kind of immune system trauma is a hypersensitivity reaction.¹⁴ Hypersensitivity is a disease caused by over reaction of immune system. This reaction happen on second contact with antigen, which sensitized previously.⁵

Coombs and Bell classified hypersensitivity reaction into 4 groups. Type I, II, and III are reactions which

depend on antigen and antibody interactions, while type IV depend on increasing receptor expression on the surface of lymphocyte.¹³ Type I hypersensitivity reaction is called as anaphylactic type which is quickly set, where allergen bound IgE antibody in releasing vasoactive amine, other mediators from basophil and mast cell, which lead to other inflammatory cells recruitment, prototype distraction as anaphylactic and other type of bronchial asthma.⁹

Type II hypersensitivity reaction is a cytotoxic hypersensitivity reaction which depend on antibody. This reaction happened because of free antibody interaction with antigen from tissue or cell surfaces. This antigen can originate from part of cell or host tissue and can also be absorbed from the outside which stick to cell or tissue, such as in hemolytic anemia autoimmune and erythroblastosis foetalis.¹³

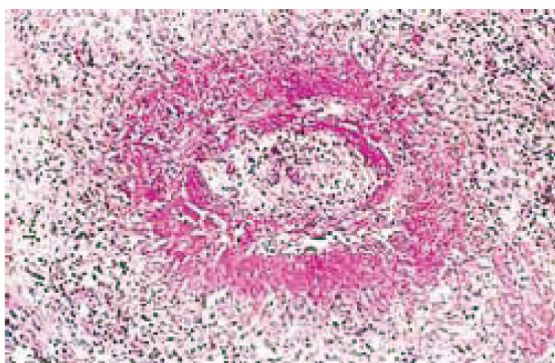


Figure 3. Vasculitis on immune complex process.¹⁴

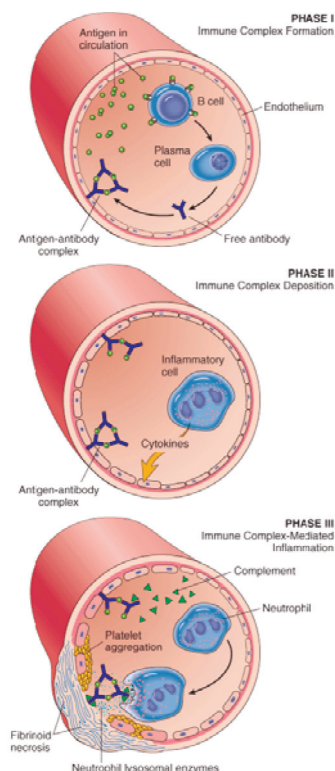


Figure 4. Stages of immune complex formation.¹⁴

Type III hypersensitivity reaction is called as immune complex disease (Figure 3). The mechanism begun with the formation of antigen antibody complex which activate complement to attract neutrophil, lysosim enzyme release, oxygen free radicals, etc., as in arthus reaction, serum sickness, and systemic lupus erythematosus (Figure 4).¹⁴

Type IV is a cellular hypersensitivity, where T lymphocyte with receptor on its surface, will be activated from macrophage contact which bound with antigen. This will sensitize T cell and make it release cytokine as mediator in slow type of hypersensitivity reaction, as in tuberculosis, contact dermatitis, and transplant rejection.^{9,13}

Hypersensitivity reactions often occur in the oral cavity, involving part or all of oral mucosa. Angioderma alergica which is a type I hypersensitivity reaction, stomatitis contacta of toothpaste or topical anesthesia are examples of hypersensitivity reaction in part of the oral cavity, while stomatitis alergica, erythema multiforme, and lichen planus are examples which involve all part of the oral cavity.⁵

Autoimmune

Autoimmune is an immune response which considers host tissue as antigen. These processes involve cellular and humoral reaction. The process or mechanism inside the host that lead to tissue destruction is not yet known precisely (Figure 5). In this problem there are many theories which still in debate.⁵ In every autoimmune disease there can be more than one defect and this defect may vary from one disturbance to other disturbances. Disturbances on tolerance and autoimmune initiation involve interaction between immunologic factors, genetics, and microbial infections.^{9,13,14}

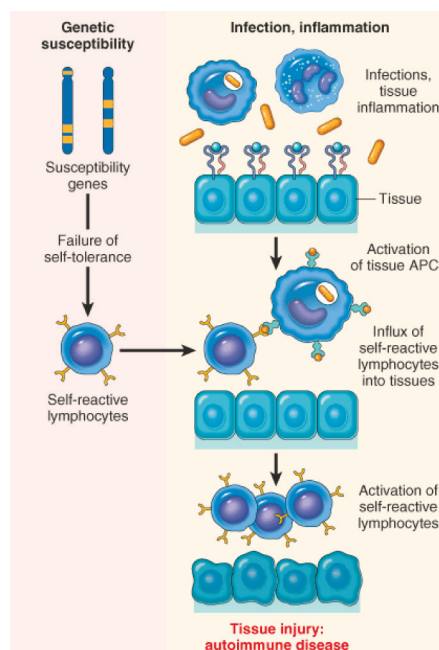


Figure 5. Infection activate autoimmune disease which lead to tissue destruction.¹⁴

Immunology factor mechanism from the tolerance failure such as: the failure of cell death induced by T cell activation which is auto reactive persistently, the activation of B cell without initiation stage which will form autoantibody, the failure of suppression mediated by T cell because of the reduced function of T cell, activation of polyclonal lymphocyte (non specific antigen) B cell because of microorganism production, and foreign antigen release because of tissue inflammation which arrange the induction of immune response and epitop spreading.¹⁵

The phenomenon of autoimmune is often connected with genetics. There are genetic components which are identical to HLA specificity, as in systemic lupus erythematosus (SLE) with Class II HLA gene especially on HLA-DQ locus.^{13,14} In relation with microbes, some bacteria, microplasm, and virus are able to trigger the autoimmune reaction through several mechanisms, such as: epitop recognition which cross linked with host antigen, microbial antigen and auto antigen combined forming an immunogenic unit to activate the tolerance of T cell, some virus and bacteria as a mitogen to T cell or B cell non specific polyclonal which can induce the formation of antibody, and microbial infection with tissue necrosis and inflammation which can activate antigen presenting cell (APC) stimulation in tissues.¹⁴

DISCUSSION

Erythema multiforme is an acute disease which occur on skin and mucosa with many manifestations, there are papula, bulla, or vesicular and target lesion on skin, whereas ulceration with white pseudomembrane on mucosa and specific desquamation with bleeding and crusts on lips.^{1,3,4}

The etiology is often triggered by drugs side effects and can also caused by infection from herpes simplex virus and Mycoplasma pneumonia.⁴ This can result the type III hypersensitivity reaction and lead to minor type of erythema multiforme. This minor type of erythema multiforme may worsen, affected by body autoimmune factor and become major type which usually called Stevens Johnson Syndrome.

From immunopathological aspect, minor erythema multiforme is caused by type III hypersensitivity reaction, which involves immune complex reaction of antigen and antibody. Biopsy on blood vessel wall of erythema multiforme patient found the increasing level of IgM, complement and fibrin deposits.³ This vasculitis caused by immune complex reaction of antigen and antibody. The pathogenesis is divided into three steps: the formation of antigen-antibody complex in circulation, the deposit of immune complex in numerous tissues, and the appearance of inflammatory reaction in many parts of the body.¹⁴

On the first stage, when antigen enters the body, specific antibody will be produced. And then in the circulation system these two form antigen-antibody complex. If the antigen could not be eliminated or phagocyte cells fail to do

its function, antigen will be in the circulation for a longer time. This situation can also be caused by malfunctioned macrophage, leading to deposition of immune complex in many parts and causing vasculitis.¹³

Immune complex which leave circulation and deposit inside or outside blood vessel wall, will cause the increase of blood vessel permeability. This condition is marked by immune complex which bound with inflammatory cells through Fc and C3b receptors and trigger the release of vasoactive and cytokine mediators.¹⁴

On condition when immune complex deposit within the tissues, third inflammatory reaction occurs. In this stage appears symptoms such as fever, urticaria, arthralgia, and lymphoid gland expansion.^{1,15} This can happen in the beginning of erythema multiforme to quickly appear its clinical manifestation, but the prodromal symptoms which precede it may not as severe as in diseases of viral infections.

Severe erythema multiforme (major type) is mostly caused by autoimmune process. In histopathology examination, autoantibody on desmoplakins 1 and 2 are found, which show the involvement of humoral immune system.³

The formation of autoantibody could happen through several mechanisms. They are cross reaction, virus, drugs, synthetic error or abnormal lysosome which modify body constituent molecule into autoantigen.⁹ Drug administration is considered as foreign antigen which will be absorbed by cell surface and trigger chemical reaction with hapten which could change the immunogenicity. Drugs like NSAID, carbamazepin, antibiotic and barbiturates can trigger autoimmune reaction which can cause erythema multiforme both major and minor type.

The involvement of microbial infection between simplex herpes virus and Mycoplasma pneumonia will cause microbial endotoxin release. This microbial endotoxin stimulates B cell through non specific second induction signal without T cell help (T cell independent), and later produce autoantibody detectable in serum.^{14,16} Other cause of autoimmune is the failure of autoregulation in antigen presentation, infection which increase Major Histocompatibility Complex (MHC) response and low level of cytokines. The surveillance of several autoreactive cells is predicted dependent to T suppressor (Ts) cell. If the T supressor (Ts) cells fail, T helper (Th) cells can be induced and therefore promoting autoimmune.⁹

The immunopathology of major erythema multiforme is characterized by T cell with autoreactive potential when meeting with autoantigen without constimulation. This situation is caused by infection or tissue necrosis and local inflammation.¹⁴ This might occur if therapy is not done immediately on minor erythema multiforme or not well maintained and worsen, leading to major type of erythema multiforme.

Until now, the diagnosis of erythema multiforme is still based on specific clinical manifestation and histopathology examination result. For accuracy, immunology test is

needed to support more precisely and adequate therapy. Immunity system repair is needed to achieve homeostasis condition for successful disease treatment of immunity disturbance.

On minor erythema multiforme, immunology diagnosis is based on vasculitis as immune complex reaction caused by type III hypersensitivity reaction, while on major type of erythema multiforme is often found desmoplakins autoantibody 1 and 2 which involve humoral immune system, showing an autoimmune reaction. This can be used as a way to help the diagnosis of erythema multiforme, to be differentiated by its differential diagnosis.

The differential diagnosis of erythema multiforme in the oral cavity is primary herpetic stomatitis. Both often occur acutely as ulceration, begin with prodromal symptoms such as malaise, fever, arthralgia, and occur in the oral cavity and lips. The difference between them is the appearance of erythema multiforme as ulceration with white pseudomembrane on oral mucosa. This white pseudomembrane is fibrin formed by vasculitis bleeding and the crusts on lips with bleeding, while these are not occurred in primary herpetic stomatitis. The location of ulceration differs, where erythema multiforme do not always occur on gingival, while primary herpetic stomatitis often occur on gingival. Prodromal symptoms starting erythema multiforme are not as severe as in primary herpetic stomatitis, therefore to establish the diagnosis, deep anamnesis must be carried out.

Corticosteroid is used to avoid the causing factor. Mouth wash with topical anesthesia and antibiotic is aimed to avoid secondary infection.

Through this literature review, it can be concluded that erythema multiforme is classified into 2 types, the minor type which is caused by hypersensitivity reaction by vasculitis on antigen antibody complex reaction, and the major type which is caused by autoimmune process. Immunopathological approach on oral erythema multiforme

could help in taking the definitive diagnosis and providing adequate therapy.

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