ERYTHEMA MULTIFORME – ORAL MANIFESTATIONS. A REVIEW.

Irena Georgieva[1], Zlatina Tsoneva[2], Teodora Filipova[3], Miglena Balcheva[4]

[1] Department of Periodontology and Implantology, Medical University Varna, Bulgaria
[2]Department of Periodontology and Implantology, Medical University Varna, Bulgaria
[3]Department of Periodontology and Implantology, Medical University Varna, Bulgaria
[3] Department of Conservative Dentistry and Oral Pathology, Medical University Varna, Bulgaria
Corresponding author: *irenahgeorgieva@gmail.com*

ABSTRACT:

Aim of the study Erythema multiforme (EM) is an acute and sometimes recurrent disease with polymorphous eruption on the skin and mucous membranes that can be life-threatening. The etiology often remains unclear but it is believed that is a result of an immunologic hypersensitivity reaction mediated by T-lymphocytes. Predisposing and triggering risk factors can be some bacteria, fungi, viruses, emotional stress, various medications, certain foods, and dyes. The term "multiforme" is originated from the wide variation of different cutaneous manifestations (macules, papules, vesicles, bullae). Oral lesions may appear independently or accompany the skin manifestations. Diagnosis is primarily based on the clinical findings and biopsy. The purpose of this article is to highlight and summarize the potential etiologic agents, pathogenesis, typical clinical oral manifestations, and the most common therapeutic strategies in dental practice.
Material and Methods: This literature review is based on a comprehensive analysis of various scientific studies accessed through databases such as PubMed, Web of Science и Google Scholar.
Results: EM should be carefully differentiated from other acute oral ulcerative conditions. Histopathology helps exclude other autoimmune diseases like pemphigoid or pemphigus. Diagnosis relies on medical history, clinical features, and biopsy findings.
Conclusion: Accurate diagnosis on time and appropriate treatment of EM are crucial for disease control. Dentists may play a key role in early diagnosis, as oral symptoms may be the first or only manifestations.

Key words: erythema multiforme, mucocutaneous disorders, oral manifestations.

INTRODUCTION

Erythema multiforme (EM) is a rare mucocutaneous disorder caused by a hypersensitive reaction due to the presence of cytotoxic T-lymphocytes in epithelium, which subsequently leads to cell necrosis [1]. Although often associated with infections or systemic medication, the pathogenic mechanism remains uncertain, which complicates the development of an effective therapy.

The aim of this article is to emphasize and summarize the potential etiologic factors, pathogenic mechanisms, typical oral manifestations, and the most common therapeutic strategies used in the dental practice.

MATERIAL AND METHODS

This literature review is based on a comprehensive analysis of various scientific studies accessed through databases such as PubMed, Web of Science и Google Scholar. The review summarizes current knowledge on the topic and facilitates the understanding and diagnosis of oral symptoms of this mucocutaneous disorder for accurate diagnosis in the dental practice. The keywords used include: "erythema multiforme", „mucocutaneous disorders", „oral manifestations". All included articles are in English.

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LITERATURE SURVEY

EM is an acute, sometimes recurrent immune-mediated disease with polymorphous eruption on the skin and mucous membranes, potentially life-threatening. It primarily affects young males between ages 20-40 and is less commonly observed in women and children [2].

The etiology remains unidentified in about 50% of cases but is believed to be result from a T-cell-mediated immunologic hypersensitivity reaction. Circulating immune complexes directed against keratinocytes activate the complement system, releasing cytotoxic enzymes, and involving stimulated lymphocytes and neutrophils [3]. Predisposing factors may include some bacteria (streptococci, Mycoplasma pneumonia [2]), fungi, viruses (especially HSV) [4,5], emotional stress, various medications (antibiotics, NAIDs, salicylates, barbiturates, phenytoin, sulfonamides) [2,6], foods, and dyes. One study reported HSV infection in 71% of EM cases [7,8], with lesions typically developing 10-14 days after clinical manifestations of the viral infection [9].

The term "multiforme" is based on the variety of skin lesions – macules, papules, vesicles, bullae. In less than 20% of cases, lesions are limited to the oral cavity, most commonly affecting the lips, buccal mucosa, palatal mucosa, and tongue. Oral manifestations can appear alone or with skin involvement and are often acute mucosal ulcerations.

Lesions' severity varies. Oral mucosa is frequently affected, along with upper and lower extremities. The first episode (rarely the only one, as recurrence is common) begins with general malaise, headache, fever, chills, and lymphadenopathy. A distinguishing feature includes hemorrhagic crusts on the swollen lips and inflammatory eruptions, primarily "target" lesions, on the skin – vesicles or bullae surrounded by a pale ring and a red urticarial zone. In the mouth, these lesions appear as "iris with pupil" patterns due to quick maceration and rupture of the vesicle. Hyperemic papules and macules may also be seen over the skin [10].

Intraoral lesions occur in 25-60% [11] of affected individuals and are very painful, often impairing eating and causing physical and mental exhaustion [12,13]. Large vesicles or bullae may form on the oral mucosa but rupture quickly and turn into deep bleeding ulcers that heal slowly over weeks [14,15]. Buccal mucosa and tongue are the most commonly affected sites, followed by labial mucosa, floor of the mouth, hard and soft palate, and gingiva [12].

About one-third of patients present with oral and labial lesions, and 25% with oral, labial, and cutaneous lesions [3].

Two clinical forms are recognized:

- **Minor form:** self-limiting, moderate, primarily cutaneous, rarely with isolated oral involvement. It affects less than 10% of body surface. Lesions are symmetrical, mostly on extensor surfaces of limbs [16,17]. Erythematous plaques or superficial erosions on oral mucosa and lips can also be observed [3]. Recurrences can occur annually and last around 14 days.
- **Progressive form (major):** severe, with extensive involvement of two or more mucosal sites (oral, ocular, tracheal, gastrointestinal, genital) [18,19], characterized by epithelial necrosis – Stevens-Johnson syndrome [13,20,21,22] The last one should be differentiated from the Reiter and Behçet syndromes. Oral lesions in this form are widespread, larger, and more severe [15,23].

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In terms of clinical course, they can be differentiated by two forms:

- **Recurrent:** multiple episodes yearly, lasting around 14 days each.
- **Persistent:** ongoing appearance of typical and atypical lesions, often papular, necrotic or bullous, though less common [24].

Oral manifestations range from mild erythematous and hyperkeratotic plaques to deep hemorrhagic bullae on mucosa. Later, these multiple bullae rupture and form yellowish fibrinous pseudo-membranes [3,25,26]. Painful superficial ulcers with irregular margins and erythematous halos may also be seen, often covered with desquamated epithelial plaques. Patients may suffer from trismus, dysphonia, and/or dysphagia. In severe cases, lesions may heal with cicatrix and appear as hyperkeratotic plaques mixed with erythematous areas [3].

Other mucosal surfaces (nasal, ocular, pharyngeal, laryngeal, anogenital) can also be affected in this form. Ocular and pharyngeal cicatrices can lead to blindness and be life-threating. Symptoms can vary from slight discomfort to severe pain.

Diagnosis is mainly clinical, confirmed by biopsy. The lesions in EM usually affect lips and skin. Histopathology reveals intra- or subepithelial separation from connective tissue, non-specific perivascular inflammatory infiltrates of CD4+ lymphocytes, neutrophils, eosinophils [27,28], and dilated dermal capillaries.

Direct immunofluorescense is negative in EM but shows non-specific IgM, C3, and fibrin deposits, helping exclude other vesiculobullous disease. Blood tests may show slightly elevated liver transaminases [14,29] and ESR [30]. Oral ulcers may resemble other bullous diseases such as pemphigoid or pemphigus, and must be differentiated from herpetic gingivostomatitis [31,32] and toxic epidermal necrolysis [3,33,34].

Treatment includes gentle oral hygiene mechanical and chemical plaque control, and topical corticosteroids. Mouth rinses with 0,12% or 0,2% chlorhexidine and topical anesthetic ointments help relieve pain. Analgesics and a liquid diet may be advised. Systemic therapy may involve corticosteroids (e.g. methylprednisolone), antihistamines and oxygenating agents. For HSV-assosiated EM, antiviral therapy is recommended – Acyclovir 200 mg, 5 times/day or 400 mg 4 times/day for 6 months starting at lesion on [1]. Healing may take several weeks [12]. In major EM, systemic corticosteroids (prednisolone 0,5-1.00mg/kg/day for 7-10 days, Solumedrol), antibiotics (Clyndamicin/ Dalacin), and hospitalization may be necessary. Immunomodulatory agents such as cyclophosphamide, dapsone, cyclosporine, levamisole, thalidomide or interferon-α can be prescribed [30]. Cyclosporine has shown efficacy in recurrent EM cases [7].

RESULTS AND DISCUSSION

Diagnosing EM is a clinical challenge. Due to the diversity of oral mucosal presentations, EM should be carefully differentiated from other acute oral ulcerative conditions. Histopathology helps exclude other autoimmune diseases like pemphigoid or pemphigus [35]. Diagnosis relies on medical history, clinical features, and biopsy findings [36,37]. Predisposing factors such as viral/bacterial infections [38], emotional stress, alcoholism, and certain medications (anticonvulsants, sulfonamides, barbiturates) [39,40], allergies, vaccines, food, dyes, etc., may be present or absent [2,4,5,6]. Identifying and controlling these triggers is essential in EM treatment.

Most commonly affected individuals are young adults aged 20-40.

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In recurrent EM, relapses may occur 1-3 times annually and lasting 1-3 weeks [12], with individual variation in frequency, duration, and symptoms [41,42]. Lesions typically affect the extremities symmetrically. Severe EM forms can be life-threatening, especially in elder individuals or in cases involving vital organs (liver, kidneys) or neutropenia [43].

Differential diagnosis includes aphthous ulcers, primary herpetic gingivostomatitis, pemphigus, pemphigoid, allergies, lichen planus [44,45], and Behçet's syndrome [46].

Treatment varies by case severity and includes systemic corticosteroids, local anesthetics, analgesics, antibiotics to prevent secondary infection, and oxygen therapy [12,47].

CONCLUSION

In conclusion, accurate diagnosis on time and appropriate treatment of EM are crucial for disease control. Dentists may play a key role in early diagnosis, as oral symptoms may be the first or only manifestations.

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