AN ASSOCIATION OF HERPES VIRUS REACTIVATION AND ERYTHEMA MULTIFORME

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Abstract
Introduction: Erythema multiforme is a skin disease manifested with "target lesions" as an iris that affects skin and mucous system. It is an acute hypersensitivity reaction with various etiological factors and mostly due to infections such are herpes simplex virus, medications, autoimmune diseases, and malignancies. The diagnosis is based on clinical manifestations, symptoms and histopathology.
Case Presentation: In this article we report the case of a patient diagnosed with Erythema multiforme associated with reactivation of Herpes simplex virus. The biopsy of the skin confirmed the diagnosis of EM during the reactivation and positive serology of HSV. The treatment of the case consisted on the treatment of symptoms and the prophylactic treatment with acyclovir or valacyclovir for 6 months.
Conclusions: The prophylactic treatment of EM due to reactivation of HSV is a must for any clinician that treat patients with Erythema Multiforme.

Keywords: Erythema Multiforme, Herpes Simplex Virus, CD34+, Herpes Associated. Erythema Multiforme.

SHOQËRIMI I RIAKTIVIZIMIT TË VIRUSIT HERPES ME ERITEMËN MULTIFORME.

Abstrakt
Hyrje: Erythema multiforme eshte nje semundje lekure qe manifestohet me 'lezione target" qe mund te prekin lekuren dhe mukozat. Eshte nje reaksion hipersensibiliteti me etiologji te ndryshme si semundje infektive, Herpes Simplex virus, medikamente, semundje autoimmune dhe semundje malinje. Diagnoza bazohet ne manifestimet klinike, simptomat dhe histopatologjine.
Prezantim rasti: Ne kete artikull ne raportojme nje rast klinik te diagnostikuar me Erytheme multiforme shoqeruar me riaktivizim te Herpes simplex virus. Biopsia e lekures konfirmon diagnozen e EM nderkohe qe ne serologji kemi rezultate pozitive per HSV. Trajtimi konsiston ne trajtim simptomatik dhe trajtim profilaktik me acyclovir ose valacyclovir per 6 muaj.
Konkluzione: Trajtimi profilaktik i EM nga ri aktivizimi i virusit HSV eshte nje domosdoshmeri per cdo mjek klinicist qe trajton pacient me EM me etiologji nga virusi HSV.

Introduction

Erythema multiforme is a recurrent disease manifested with "target lesions" as an iris that affects skin and mucous system. It is an acute hypersensitivity reaction with various etiological factors

and mostly due to infections and drugs. Etiopathology is not well understood, but the most frequent etiologic factors reported are Herpes Simplex Virus, medicaments, autoimmune diseases, premalignancy conditions. (1,2) EM may occur at any age, and several reports suggest that males are affected more than females. (3) Clinical manifestations reported are erythema with different shades within the element, vesicula or bulla on the center. The disease affects or not oral cavity or other mucous area, genital, ocular, laryngeal, and esophageal mucosae.

Case prescription

A 28-year-old female patient presented to the Dermatology Department complaining of pruritic skin rashes on the face since the last 5 days after symptoms of weakness and fatigue in the prior days. On physical examination, there were multiple annular erythematous papules with central bullae and peripheral erythematous margins, localized on the face, and trunk. (Fig.1)

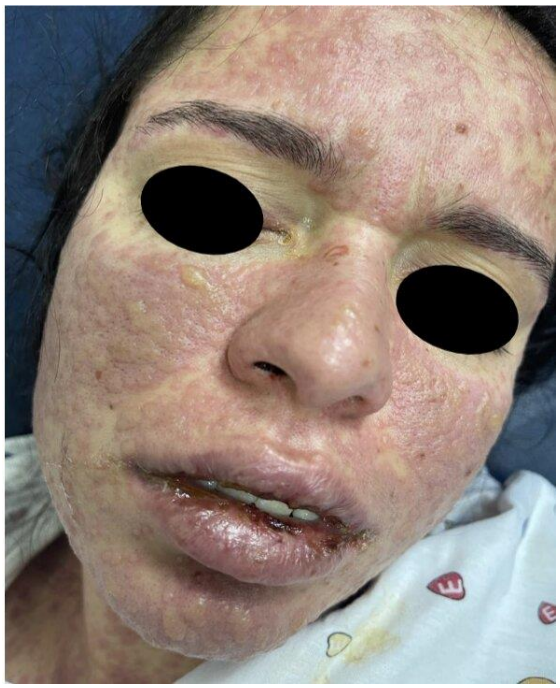

Figure 1: Erythematous papules with central bullae and peripheral erythematous margins, localized on the face and erosive lesions on the oral mucosa.

Intraoral examination revealed numerous painful erosions in the palate, buccal mucosae and on the lips. The patient referred for a history of recurrences of these oral lesions that were presented very often these last four years. Laboratory examinations showed normal levels of complete blood count, liver function, serum creatinine and electrolytes levels as well as the serological tests for Hepatitis B and C viruses and HIV infection. Serological test for Herpes Simplex Virus (HSV1) was positive. The main differential diagnosis was Erythema Multiforme, Pemphigus Vulgaris. To confirm the diagnosis a skin biopsy was performed on the oral mucosa. Direct immunofluorescence was also performed to exclude Pemphigus Vulgaris. The histological examination revealed dermal inflammatory infiltrate and edema of the lamina propria with perivascular infiltrate of mononuclear cells, features compatible with Erythema Multiforme.
Referring the anamnesis, clinical manifestations, and biopsy the diagnosis was Erythema Multiforme after the reactivation of Herpes Simplex Virus (Herpes Activation Erythema Multiforme HAEM). The patient was treated with prednisone 50 mg a day for 10 days, supportive

IV fluids, local antiseptics. Referring the history of recurrences, the patient was treated with valaciclovir 500 mg a day for 6 months. On a follow up after 3 months the patient denied any sign of recurrence.

Discussion

EM is diagnosed based on clinical manifestation (target lesions) and histopathology examination. Target lesions are erythematous lesions with 2-3 different concentric shades of pigment. On the center of the lesion is evident a bulla or vesicula. Based on the affection of mucous area EM is classified in EM major (with manifestations on skin & mucosa) and EM minor (without lesions on oral cavity or other mucosae). (4) Manifestations on oral cavity can be alone or may precede lesions on other sites. (3) At the beginning of the disease different differential diagnosis have to be taken in consideration; primary herpetic infection, hand-foot-and-mouth disease, erosive lichen planus, urticaria, lupus erythematosus, fixed drug eruption, cutaneous vasculitis, Sweet syndrome, mucositis due to methotrexate. (4, 5, 6,7) In cases of erosions of lips and oral mucosae direct immunofluorescence may help to differentiate with pemphigus vulgaris, paraneoplastic pemphigus, mucosal bullous pemphigoid, and linear IgA dermatosis.

Lesions may progress through erythematous macules presented to the skin and mucosae, to bullae, erosions and crusted lesions to the lips and mouth. Herpes Simplex Virus infection was reported as a most common cause in many publications. (8) Asier et al reported that 23% of patients were found to have associated HSV infection. (2, 3) EM typically follows a lesion of recurrent herpes simplex within 1 to 3 weeks. The interval usually is about 10 days. There is reported that lips are the most common site of preceding HSV infection in recurrent EM implicating HSV-1. (1) Other factors implicated in etiopathogenesis of EM are bacterial, viral, and fungal infections, drugs, radiation therapy, and emotional stress. (2,4,6)

Table 1. Etiological factors of Erythema Multiforme.

Infectious agents	**Medications**
Herpes Simplex	Sulfonamides
Epstein Bar virus	Penicillins, Cephalosporins
Citomegalovirus	Quinolones
Varicella Zoster virus	Anticonvulsants
Mycoplasma pneumoniae	Analgesics
Streptococci	Anti-inflammatory Nonsteroidal
Fungal agents Parasites	Antifungals

The diagnosis is based on clinical view and histopathology examination as in our case report. The histopathology concluded in necrosis of some keratinocytes and epidermal damage. This damage is particularly noticed on the center of the target lesions of EM. (9, 10) In more severe cases with bulla and erosions were reported necroses of the whole dermis. (11)

The differences between EM and Steven Johnson Syndrome are not just referring the etiology where SJS is mostly caused by medicaments bur either referring the severity of the disease and the surface of the body affected in SJS that is around 10% or less. (1,6) Making the right decision for the treatment of EM is based on severity of the disease, mucosal involvement, reactivation, and risk factors. Most EM minor forms may regress within 2 to 4 weeks. If the manifestations are not severe it is recommended conservative care. In case of oral mucosal involvement, the symptomatic treatment includes topical analgesics and anesthetics and liquid foods. Patients are recommended to avoid spicy foods, acidic foods, and liquids. Systemic treatments, besides the supportive therapy

consist of corticosteroid therapy and in cases of secondarily infected lesions systemic antibiotics are also indicated.
When the suspected etiological factor is a specific medication, the main step of management is to stop the suspected drug and avoid the use of other drugs to prevent cross reactivity reactions. In cases of recurrent HSV episodes, antiviral therapy is indicated in order to prevent further recurrences. (12) In a double-blind placebo-controlled study conducted by Tatnall et al., which involved 20 patients with recurrent EM, where of 15 had a proven HSV association; it was shown superiority in the use of acyclovir in the prevention of EM episodes. Furthermore, the discontinuation of acyclovir resulted in clinical remission on some patients, instead of recurrences in all the patients treated with placebo. (13) For individuals facing HSV-related erythema multiforme (EM) who do not respond to standard antiviral treatments, alternative approaches include oral cyclosporine. Thalidomide, despite its known risk of birth defects, can also be used due to its ability to modulate TNFα. (4) Additionally, corticosteroid-sparing medications like dapsone, azathioprine, methotrexate, and mycophenolate mofetil are options worth considering for managing these difficult cases. (5) How is it explained the etiopathogenesis in the case of HSV and Herpes Associated EM? In a paper published by Miura et al 1992 was concluded that HSV persists in the skin sited of previous lesions for up to 3 months and as a conclusion was noted that the difference in Herpes Associated Erythema Multiforme HAEM patients were an inability to clear the virus. (15) A group of authors reported the implication of CD34+ cells in HAEM pathogenesis. HSV-associated EM (HAEM) lesions are virus-free (15, 16), but they contain HSV DNA fragments, most often comprising sequences that encode the viral DNA polymerase (Pol). (15, 17-23) The percentages of circulating CD34+ (and CD34+/CLA+) cells were significantly higher in HAEM patients at the time of acute lesions. A similar increase was not seen for HSV patients. (24)

Conclusions

The prophylactic treatment of EM due to reactivation of HSV is a must for any clinician that treat patients with Erythema Multiforme. The use of antiviral therapy minimizes the recurrences of the disease and has a great impact in the quality of life of the patients.

Conflict of interests: No conflict of interests is declared**.**

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