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Erythema Multiforme Minor: A Revision

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Abstract: The term Erythema Multiforme (EM) includes a wide and controversial variety of clinical expressions at the present time. This study revises the EM minor characteristics according to the most important publications found in literature. Erythema Multiforme is a distinct dermatologic hypersensitivity pathology characterized by cutaneous or mucous lesions and eventually it can also involve both. In their more severe forms, they appear with occasional visceral involvements. In the EM minor only one mucous membrane is affected and usually is the oral mucosa. When occur in the skin, the lesions usually appear symmetrically in the extremities, in a target form, could be continuous or recurrent and none additional systemic involvement is present for both cases. Nowadays, many authors separate etiologically the several manifestations of the EM spectrum. However, no clinical definition is still accepted thoroughly, making more difficult the comparisons of etiological and clinical aspects, histopathological studies and therapeutic protocols. For the present work, we tried to elucidate through an extensive literature revision some historical and current aspects of EM, focusing mainly the EM minor and its frequent association to HSV (Herpes Simplex Virus), with their diagnostic characteristics and current therapeutics, to facilitate the physician understanding and to favor future researches about this disease.

Key words: Erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis toxic, herpes simplex virus

INTRODUCTION

The term Erythema Multiforme (EM) includes actually a wide range of clinical expressions, from exclusive mucous or skin erosions to mucocutaneous lesions (EM minor) and, in its more severe forms, there are a serious involvement of multiple mucosal membrane and skin (EM major, Stevens-Johnson Syndrome) or a large area of the total body surface including mucous surfaces (Toxic Epidermal Necrolysis) with constitutional symptoms and, at times, visceral involvement[1].

The EM minor is a distinctive hypersensitivity disease generally characterized by skin lesions, the mucous membranes of the oral cavity, nose, eyes and genitalia may also be affected [2,3] and eventually it can also happen involvement of both[4]. It's an acute or chronic mucocutaneous inflammatory disorder, self-limited and recurrent, which appears mostly as symmetrical papules that developing plaques with vesicular eruption and erosion, later developing into "target" or "iris" lesions with an erythematous periphery and a central zone of necrosis. The lesions usually appear bilaterally on the dorsal surfaces of the hands and feet[2]. In the scientific literature, EM minor is also called Polimorfic Erythema, Erythema Exudativum Multiforme, Papulous Reumatic Erythema, Ectodermose Erosiva Pluriorificial, Dermatoestomatitis or Herpes iris[1].

This study aims to revise the main EM minor characteristics in agreement with the most important and recent publications found in literature.

Historical aspects and nomenclature: It has been claimed that cases of this nature were early described in France by Nibert and Bazin[2], but, the initial description of EM is attributed to Ferdinand von Hebra, who first described in 1860 a self-limited, mild skin disease characterized by symmetrically distributed skin lesions, located primarily on the extremities and a tendency for recurrences. The primary lesions were characterized by the abrupt appearance of round red papules, some of which evolved into target lesions. The EM described by von Hebra is sometimes called EM minor[1,5].

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In 1916, Rendu described an acute febrile illness (later named *ectodermosis erosiva pluriorificialis*), characterized by severe erosions of mucous membranes and a vesicular skin eruption[1,6,7].

In 1922, Stevens and Johnson described two boys who were febrile with erosive stomatitis, severe purulent conjunctivitis and a disseminated cutaneous eruption. This eruption "consisted of oval, dark to purplish macules separated by normal areas of skin…a few of the largest spots showed a yellow, dry, necrotic center"[8].

The disorders described by Rendu and Stevens and Johnson were probably very close, if not identical. All of these authors believed that they had described a new disease, distinct from EM. Nevertheless, the eponym Stevens-Johnson Syndrome (SJS) is usually classified as an EM major subclass[9].

Only in 1950, it was proposed by Thomas the form described by von Hebra as EM minor and EM major the most severe variety, described later by Stevens and Johnson[1,6].

In 1956, it was described by Lyell the mucocutaneous severe variant exfoliative, called Toxic Epidermal Necrolysis (TEN), producing a clinical situation similar to an extensive burn that is the most serious subdivision of the clinical spectrum in clinical manifestations of the EM[1].

In 1987, the isolated oral manifestations of this disease were also recognized as group variants of EM diseases, being called of oral EM[1]. In 1993, an international dermatologists group tried standardize the terminology, intending differentiate the several clinical manifestations with base in the aspect and extension of the cutaneous involvement of these lesions[1,7].

A few years ago, an international group of investigators began a large case-control study, the Severe Cutaneous Adverse Reactions (SCAR) study, to determine the risk factors for EM, SJS and TEN[10].

The SCAR study was a multinational case-control study conducted through extensive surveillance networks of about 1800 hospital departments and 120 million inhabitants of France, Germany, Italy and Portugal from February 1, 1989, to July 31, 1995. The results of this study on a large number of patients confirm that EM on one hand and SJS and TEN on the other, behave as different disorders, occurring in patients with different demographic characteristics, presenting with different clinical patterns and with different risk factors[10,11].

Therefore, in the current knowledge, the EM spectrum, which includes EM minor usually associate or not to Herpes Simplex Virus (HSV) or others infections, can be separate from the spectrum of SJS (EM major) and of NET[9], that frequently are associate with drug exposition.

Some authors consider the SJS as a subclass of the EM major[9], however, such classification was not considered in our work due to the small number of authors with this concept. Most of the researches links SJS as a synonym of the EM major[1,4].

In agreement with the current literature in the EM minor the skin or mucous surfaces, or both simultaneously, can be affected. However, only one mucous membrane is affected, usually the oral mucosa and none additional systemic involvement is present. This revision study considers the EM minor like a distinct entity from SJS and NET, could be associated or not to HSV.

Epidemiology: Although it can happen in any age, EM minor is more common in patients among 20 and 40 years, in spite of more than 20% of the cases affect children after 3 years old and adolescents[1].

Recently, Torrelo *et al.*[12] described a biopsy-proven case of EM no associated to HSV in a 2-week-old boy. To our knowledge, only one previous biopsy-proven case of EM during the neonatal period has been reported[13]. However, in none of the two cases the authors classify the disease as EM minor, that a lot of times hinder the epidemiologic studies on this disease.

The epidemiologic studies about EM are controversial because almost all no separates the different spectrum of the EM and the incidences shown here link all the different spectrum of the disease.

Although most studies indicate prevalence of the masculine gender[1], others shows feminine predilection of 1,5:1[14,15]. The incidence doesn't show any racial preference[14].

The EM estimated incidence range of 1,1 10^{-6} person-years in Deutchland[1,16], 3,7 10^{-6} person-years in the USA[1,17] and 5/10 10^{-6} person-years in Sweden[1,18].

Recurrences occurs 37% of the cases, they usually happen in the spring and in the autumn, with clinical severity increase of the attacks[1,18,19]. In agreement with Farthing *et al.*[18] EM minor may be recurrent and the oral cavity is often affected.

The reported incidence of mucosal and cutaneous lesions varies considerably and appears to depend in part whether the study is based in an oral medicine or a dermatology clinic population[18].

Prevalence of oral EM minor varies from 35-65% among patients with skin lesions. However, in patients where EM minor was diagnosed by oral lesions, incidence of skin lesions ranged from 25- 33%[2].

A multidisciplinary study reported that seventy percent of cutaneous recurrent EM minor patients had an oral involvement, comprising multiple, large, shallow, extremely painful and debilitating ulcers, which entire oral mucosa affected in over twenty percent[18]. The oral lesions have predilection for the vermilion border of the lips and the buccal mucosa, generally sparing the gingiva[2].

Etiology: The list of etiological associations with EM in the medical literature is endless. It has been suggested that EM minor probably represents a cell-mediated immune response directed against antigens in the skin[20-22].

There is some evidence that sufferers have a defect in delayed-type hypersensitivity and a reduced lymphocyte response. The pathogenesis of EM minor may involve an immune-complex mediated vasculitis[23].

In an investigative study, Kokuba *et al.*[24] described that the Herpes Associated Erythema Multiforme (HAEM) lesions were positive for interferon-γ, a product of antigen-activated $CD4^+$ Th1 cells involved in delayed-type hypersensitivity reactions[25]. On the other hand, drug-induced EM was a mechanistically distinct condition in which keratinocytes were positive for TNF-α, a sign of toxic injury. These findings provide the mechanistic support for prior clinical and histopathology observations that these are separate conditions[24].

A genetic predisposition to EM minor may be of importance, as suggested by the familial tendency that has been reported. Certain HLA phenotypes may predispose the host to develop this disease in response to a range of stimuli. The HLA-B62 is found in a high proportion of patients with recurrent EM minor and also in patients with recurrent HSV infection[26].

Although some rare cases of EM minor can be idiopatics[1], several etiological factors can be associated with its development. Some medicines or topics contactants[22], foods allergy, HBV[9], HSV and EBV infections[2,20], coxsackie infections[26], mumps[6], streptococcal and *Mycoplasma pneumoniae* (Eaton agent) infections[27], coccidioidomycosis[9], candida, hystoplasma, yersinia[23], radiation (mainly the UV)[22], dermatomiositis, leprae[28], diseases as lupus erithematosus, Bowel disease, Wegener's granulomatosis[9], renal carcinoma[22], physical agents (Koebner phenomenon)[4,9] and acute alcoholism are mentioned as etiological factors[23]. A recent report also has suggested that rare cases of EM may be induced by cytomegalovirus infection[29].

Herpes Associated Erythema Multiforme (HAEM): The literature has suggested a strong association between HSV and EM, especially recurrent EM[27]. Investigations associating HSV (1 or 2) as an etiological factor of EM minor was early described in the decades of 30 and 40 of the previous century[1].

The HAEM is a recurrent disease that can be precipitated by sun exposure and does not progress to Stevens-Johnson syndrome[30]. Even in the absence of a clear clinical history of HSV infection, subclinical HSV is likely the precipitating factor, as evidenced by the polymerase chain reaction (PCR) analysis of HSV[5]. Before PCR studies were performed, it was estimated that 15-65% of EM are secondary to HSV infection and that a significant proportion of idiopathic EM was related to subclinical HSV infection[19]. PCR studies actually have been able to detect HSV DNA in 36-75% of EM[31].

Suggesting an explanation for the physiopathology of these lesions, some authors hypothesized that HSV is engulfed by macrophages at the site of the HSV lesion that precedes HAEM development. These phagocyte cells are non-permissive for HSV replication, resulting in a degradation of the viral DNA and dissemination of fragments to peripheral skin[31,32]. HSV DNA fragments with an intact DNA polymerase gene (*Pol*) are deposited at different anatomical skin sites where *Pol* is expressed. Activated T cells are recruited to the site of *Pol* expression resulting in an inflammatory cascade[33].

The skin from HAEM lesions was positive for the viral *Pol* gene in 86% of acute lesions. However, it was not seen in uninvolved skin, adjacent to the HAEM lesions. The skin from 1-3 months healed HAEM also were PCR positive for the viral *Pol* gene[32].

In agreement with Imafuku *et al.*[34] the viral DNA is cleared from the skin within 1-1,5 months of HSV lesion resolution, whereas HAEM lesional skin is still positive 1-3 months after healing. Still in agreement with these authors, the positive HSV-DNA was detected in keratinocytes, germinative cells and epithelial cells from the outer root sheath of the hair follicle and in the epithelial cover for sensory nerve endings. Using *in situ* RT-PCR, these authors also observed the RNA signal in keratinocytes within the basal and spinous epidermal layers with a distribution similar to that of the viral DNA. This signal was cytoplasmic, presumably reflecting the RNA function in translation. The *Pol* RNA was observed in acute but not healed HAEM lesional skin that was positive only for *Pol* DNA. Therefore, the HAEM lesion development is associated with *Pol* gene expression[34].

Some others HSV-specific immune mechanisms are involved in the HAEM pathogenesis. The CD4

lymphocytes are the main cells involved in the lesional skin. There are also the contribution of non-specific effectors cells (neutrophils, basophils, natural killer cells, lymphokine-activated killer cells and macrophages) activated and recruited to the skin by cytokines generated by the antigen-activated T cells[20,32].

Generally, HSV-1 infections and acute diseases of the upper respiratory tract, two recognized triggers of EM, mostly of the minor type, occur in infancy and in the preschool years. On the contrary, *Mycoplasma pneumoniae* infections and drug reactions, also others two recognized triggers of Erythema Multiforme, mostly of the major type, are rather unusual before school age[35].

Clinical characteristics: Lesions of the EM minor can be persistent (continuous), cyclical (acute and self-limiting) or recurrent, the cyclical and recurrent occur mainly in the HAEM[20]. The condition can begin with nonspecific prodromal symptoms such as headache, malaise and fever. Symptoms last from 3-10 days, after which an inflammatory process yields the pathognomonic target, or "iris" lesion.

The EM minor skin lesions usually caused by herpes simplex are predominantly raised and distributed on the extremities and/or the face, with mucosal erosions involving one or several sites. On the other hand, lesions that are widespread flat atypical targets or macules plus blisters were mostly drug induced[36].

In the HAEM, HSV lesions can precede the appearance of target lesions by 2-17 days[27]. Mainly in cases of primary HSV infection, there are frequently systemic signs and symptoms preceding the lesions and the oral ulcers are typically much smaller[14]. The EM minor lesions in HAEM can reach about 200 or more, evolve over 24-48 h and are usually fixed and symmetrically distributed for about a week. These lesions also attacking more that one of the mucous surfaces, could also happen simultaneously with the cutaneous involvement[27].

In the other EM minor induced lesions, the target lesions typically appears on the cutaneous surfaces, including palms, soles and extensor aspect of extremities and less often on the face and neck. The lesions begin as erythematous papules, expanding 2-3 cm in diameter with a dusky purple center, a pale middle zone and an erythematous border. Burning or pruritus, as well as central blistering or crusting, may occur [27]. However, these lesions also may occur in one or more rarely in several mucosal surfaces[36].

When the mucous surfaces are affected, the oral mucous membrane is commonly the most affected, being present in 25-50 percent of all EM minor patients[14,15]. Hemorrhagic crusting of the lips and ulceration mainly of the non-keratinized mucosa characterize oral lesions. When it affects the lips, it results in erosions or serum-hemorrhagic crusts, with pathognomonic blood-stained crusting of erosions on swollen lips, hindering the phonation, the feeding and limiting the oral movement[1]. The intra-oral lesions attack more the anterior part, being the tongue and the buccal mucous membrane the more involved places[37]. Although any place can be affected, the hard palate[37] and the gum are usually preserved (only 16% of the patients)[1,23].

Other mucous membranes that can be affected, mainly in the HAEM cases, are the eyes, nose, genitalia, esophagus and respiratory tract[14]. The ocular lesions are of particular concern because they can result in scarring and progressive blindness[1].

Differential diagnosis: The authors don't have a microscopic or immunopathological specific model of EM and the diagnosis should be made by exclusion of other similar diseases, with a detailed clinical examination and anamnesis of pharmacologic associations[1].

HAEM is clinically different of drug induced EM. It is more commonly characterized by self-limiting and recurrent lesions[32].

The presence of elevated serum IgM to HSV, the isolation of the virus from the oral ulcers and PCR or *in situ* hybridization supported the diagnosis of HSV induced EM[2].

The EM minor can be distinguished from SJS by the presence of true target lesions and no mucosal lesions or lesions involving 1 (oral) mucosa site rather than 2 or more mucosal sites, as seen in SJS. The EM minor also resolves without sequels within 2 weeks, whereas SJS often lasts longer than 2 weeks, leaving scars, could also have visceral involvement, with signs and systemic symptoms[5].

A recent study strongly support the hypothesis that SJS and TEN can be easily separated from EM minor on the basis of simple clinical criteria (pattern and distribution of individual cutaneous lesions) that can be used in individual patients[10].

Stevens-Johnson syndrome and TEN, defined by widespread blisters arising on macules and/or flat atypical targets, are diseases with homogeneous clinical characteristics, a potentially lethal outcome and an elevated probability of being drug induced[10]. The HSV is associated with many cases of EM minor, while SSJ and NET are caused in 80% of the cases by systemic drugs[1].

Importance of the etiology identification of EM minor is in the prognostic and treatment of the condition. In a study performed with history, examination and standard microbiological investigation, the authors ascertain the probable etiology in 81% of cases of EM minor. In this survey infections were found as a definite or at least presumptive trigger of EM minor in 71% of cases. Drugs (or immunization) implicated as triggers of EM minor played a highly suggestive causative role in 10% and a possible causative role in a further 29% of the patients[35].

Differential diagnosis for EM minor includes primary herpetic gingivostomatitis, aphthous ulcers, pemphigus vulgaris, benign mucous membrane pemphigoid, erosive lichen planus[14] and leprosy[28]. In cases of primary HSV infection, there are frequently systemic signs and symptoms, with the oral ulcers typically much smaller. In the aphtha cases, lesions occur exclusively on the unattached oral mucosa[14].

Histological findings: The cutaneous and mucosal lesions of EM minor appear in various forms, but all have identical histological findings. The severity of the histological reaction determines the clinical appearance of lesions. Microscopic examination of skin lesions reveals edema just below the epidermis that when mild or moderate, produces urticarial lesions; when the edema is severe, blisters are formed. Other histological features consist of dilation of blood vessels, accompanied by a perivascular infiltration composed mainly of lymphocytes, nuclear dust resulting from disintegration of neutrophils and eosinophils (leukocytoclasis), edema, acanthosis and erythrocytes extravasations[4].

The characteristic histopathological change of EM minor is epidermal cell death, which is termed “satellite cell necrosis”, mimicking apoptotic cell death. It is not clear whether morphological apoptosis and molecular biological apoptosis defined by DNA fragmentation are identical. Among some apoptosis inducers, the perforin, a pore-making granule from natural killer cells has been suggested[38].

Another apoptotic mechanism that can also be related is the altered expression of apoptotic regulatory proteins. The intense expression of Bcl-2 protein by the inflammatory cells in EM minor support a role for this protein in the maintenance or persistence of the infiltrate in submucosa. An altered or increased expression of Fas antigen throughout the epithelium in correlation with the inflammatory cell infiltrates has been reported in many skin diseases including EM minor[30].

Some apoptosis inducers (i.e., viral infections and glucocorticoids) are common causative agents of EM minor. Epidermal cell death is also a characteristic feature of SJS and TEN. However, compared with SJS and TEN, apoptosis was far less in EM minor, maybe imply a better prognosis[38].

In the early lesions less than 24 h old, direct immunofluorescence showed an unspecific granular deposition of IgM, IgG or C3 in the blood vessel walls of the upper dermis. The transient production of immune complexes plays an important role in the pathogenesis of this disease[39].

It has been proposed that the ulcerative inflammatory lesions of the EM minor may be the result of ischemic necrosis of epithelium as a consequence of immune-mediated vasculitis[30].

Treatment: Before any therapy is prescribed, possible underlying causes, such medications, diet, infections or systemic diseases should be determined and eliminated[27].

The prophylactic and therapeutic use of acyclovir, in cases of HAEM is a common practice[2]. HSV lesions can precede the appearance of target lesions by 2-17 days and intermittent therapy with acyclovir at a dosage of 200 mg twice a day for 5 days, beginning at the first aura of HSV infection (i.e., local tingling and burning), can prevent or minimize the symptoms of erythema multiforme[27,40]. In patients who have recurrent EM associated with HSV, suppressive treatment using acyclovir (400 mg twice a day for 6 months) has also been effective in preventing recurrence. Newer-generation anti-herpes drugs such as valacyclovir hydrochloride and famciclovir are also useful in both intermittent and suppressive therapy[1,27].

The acyclovir administration at the onset of clinical symptoms did not prevent the EM episode. It’s possible that, by the time clinical symptoms are recognized, sufficient viral replication has already occurred to induce a host response to the virus[27]. Therefore, once onset the earliest symptoms, there is none effective treatment[5]. In addition, because EM is self-limited, symptomatic therapy with antiseptics, antihistamines and analgesics is recommended[27].

The oral psoralen plus UV-A (PUVA) therapy has proven to be an equally effective treatment and it is anticipated that it can be used as a long-term maintenance therapy without undue concern for adverse effects. The oral PUVA therapy consists of methoxsalen and exposure of the hands and feet or the whole body to UV-A radiation using a regular schedule of 3 treatments each week. With the remission of the lesions, the treatment may be reduced to weekly

exposures for maintenance in some months. However, generalized exacerbation of the eruption may be triggered by PUVA therapy since EM can occur as a photodermatosis[41].

It has been showed that childhood HAEM may be unresponsive to treatment with oral acyclovir. In this case, corticosteroids should be considered as a mode of treatment[2]. However, some authors believe that treatment with corticosteroids is not indicated in HAEM. Although systemic corticosteroid therapy is frequently used to treat recurrent EM and it may partially suppress the disease, it may also make HAEM episodes more frequent, prolong the duration of attacks and is associated with side effects[5,27,42]. The use of topical and systemic corticosteroids, though, is debatable.

The antimalarials (mepacrine or hydroxychloroquine) have been shown to be occasionally useful when acyclovir treatment failed[42] and azathioprine (IMURAN®) can be used as a last resort to suppress an acute attack in patients with severe disease who do not respond to the other measures[22,27,43,44]. However, it is recommended as second-line treatment due to its side effects[42].

If this treatment fails, mycophenolate mofetil can be tried. It has been shown to be an effective and relatively safe immunosuppressive agent in recurrent EM; however, its use is limited by its high cost[45].

Prognostic: Generally, EM minor doesn't present mortality, however, exists a subgroup of patients with recurrent EM whom frequent episodes of the disease over several years cause significant morbidity. They support two or more attacks per year, each lasting approximately 14 days as in classic EM[42]. In addition, the drug-induced EM tended to have a more severe course than infection induced EM[46]. On the other hand, the mortality for those patients with SSJ is from 2 to 10% and in the patients with NET, it is approximately 34%[36]. In the last cases, sepsis and hypovolemia are the principal cause of death and when this diagnosis is suspected, patients should be referred immediately to a specialized intensive care or burn units[47].

CONCLUSION

In spite of several factors implicated, the exact etiology of EM minor is still uncertain and although several attempts have been made, none specific criteria exist for its diagnosis. The specific pathogenic mechanisms, as well as the multifatorial development hypothesis of the lesions, are still being investigated. The treatment, except for the symptomatic therapy with antiseptics, analgesics and antibiotics, is still being adapted for prophylaxis, control and elimination of the possible related underlying causes.

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