ERYTHEMA MULTIFORME - ETIOPATHOGENIC, CLINICAL AND THERAPEUTIC ASPECTS

Anca Creţu¹, Andreea Dimitriu¹, D. Brănişteanu²*, Daciana Elena Brănişteanu⁴

“St. Spiridon” Emergency Hospital – Iaşi
1. Department of Dermatology
University of Medicine and Pharmacy”Grigore T. Popa”- Iasi
Faculty of Medicine
2. Department of Surgery
3. Department of Medical Sciences (II)

* Corresponding author: E-mail: dbranisteau@yahoo.com

ERYTHEMA MULTIFORME - ETIOPATHOGENIC, CLINICAL AND THERAPEUTIC ASPECTS (Abstract): Aim: To present the epidemiological, etiopathogenic, clinical and therapeutic aspects in Erythema multiforme (EM). Material and methods: This is a 3-year retrospective study based on medical records of patients with EM admitted to the Dermatology Clinic. Forty patients were included in this study. The obtained data allowed the classification of patients according to their distribution by sex, age group, area of residence, etiology, clinical aspects, and type of administered treatment. Results: The prevalence of EM during the 3 study years was 0.4%. EM prevailed among the rural population, more frequently in women. The minimum age at which EM was diagnosed was 12 years and maximum age 78 years, with a peak incidence between 20-40 years old (37.5% cases). In 42.50% of the cases EM was drug-induced, and in 17.50% of cases it was caused by infection with herpes simplex virus (HSV). There were 18 cases of erythematos–papular EM (45%), 14 cases of erythematous–vesiculobullous EM (35%) and 8 cases of recurrent EM (20%). All patients received treatment with antihistamines and nonspecific desensitizing agents. Systemic corticotherapy was used in 22 cases. Three patients received treatment with acyclovir. Conclusions: Erythema multiforme is a rare skin condition, easily diagnosed based on its characteristic clinical appearance, but remains a challenge for the physician in terms of establishing its causal agent. Keywords: ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME, LYELL’S SYNDROME.

Polymorphic erythema or erythema multiform is part of the group of cutaneous–mucosal hypersensitivity reactions, a disease with multiple etiologies, with typical cutaneous and/or mucous clinical manifestations, the episode being self-limited, sometimes recurrent (1). The etiology and pathogenesis are not fully elucidated yet. Its various clinical manifestations range from the simple papular form (the characteristic lesions being erythematous papules, acral in distribution and symmetrical), and erythematous-vesiculobullous form (lesions are erythematous plaques with a vesicle or bulla arranged centrally that can develop a pathognomonic “target-like” or "cockade" appearance) to the severe bullous form (severe damage to the mucous membranes,
the damage to the skin membranes varying in extent and severity). The papular form is also called *Erythema multiforme* minor, and the other two forms, erythematous – vesiculobullous and severe bullous, are included into the *Erythema multiforme* major. Among the precipitating factors are medications and infectious agents. Recurrence may be common, most patients experiencing 1-2 recurrences per year. This is explained by the fact that in some cases EM can be associated with a persistent antigenic stimulation leading to repeated manifestations of the disease. In the medical literature EM is often confused with Stevens – Johnson syndrome (SJS) and Lyell’s syndrome (toxic epidermal necrolysis = TEN). It was only in 1993 that a consensus regarding the classification of these three conditions was reached: SJS was separated from the EM and included in TEN, SJS and TEN being considered variants of the same disease, different only by the degree of severity (<10% of body surface area affected corresponds to SJS, and >30% to TEN) (2).

The not completely understood pathogenesis and multiple etiology are other factors that make the knowledge of this disease to be of particular interest in medical practice.

**MATERIAL AND METHODS**

For this retrospective, open-label study we studied a group of patients admitted with a diagnosis of *Erythema multiforme* to the Dermatology Clinic of the Iasi "St. Spiridon" Emergency Hospital in the interval January 1, 2006 – December 31, 2008. The aim was to gather data on clinical manifestations, investigation methods and therapies used. Included in the study were 40 patients (some patients with multiple admissions during the 3 study years). The data obtained allowed the classification of patients according to their distribution by sex, age group, area of residence, etiology, clinical aspects, association with other diseases, type of administered treatment and its efficiency. To interpret the data different statistical concepts were used: arithmetic mean, percentage distribution.

**RESULTS**

During the interval January 1, 2006 – December 31, 2008 a total of 11,204 admissions (of which 5,311 day admissions) were recorded. Of these, 45 admissions were for the diagnosis and treatment of erythema multiforme, corresponding to a number of 40 patients. The prevalence of *Erythema multiforme* over the 3-year study period was 0.4%.

The distribution by area of residence revealed that EM was more common among the rural population (65% vs. 35%), corresponding to an urban/rural patient ratio of 1:1.86.

There was a higher rate of EM among female patients, the male: female ratio being 1:1.35 (fig. 1). According to the literature men are more frequently affected than women, more precisely with a male/female ratio ranging from 3:2 to 2:1.

The minimum age at which the occurrence of EM was recorded was 12 years and the maximum age 78 years. Our data were in agreement with literature data according to which all ages are affected, with a peak incidence between the 2nd and 4th decade of life, about 20% of patients being children and adolescents. In our study the peak incidence was indeed between 20-40 years, 37.5% of cases, but the highest percentage of all cases, 27.5%, was recorded in the 30-40 year age group. Fifteen percent of our patients were children and adolescents aged 56.
less than 20 years, close to the 20% mentioned in the literature. However we found a significant percentage of cases in patients older than 50 years (32.5%), although EM is considered rare under the age of 3 and above 50 years (fig. 2).

The onset was sudden in most cases, with rapid, progressive extension of lesions. Eight of the 40 patients had prodromes with constitutional symptoms (moderate fever or subfebrility, headache, asthenia, nausea, vomiting, etc.), some similar to a viral syndrome prodrome. As a result of this, some patients decided to self-medicate to relieve these symptoms, making it difficult to differentiate the possible etiology of EM in these cases.

As to the medication administered before the disease onset, of the 45 admissions 17 patients confirmed taking various drugs, including antibiotics, NSAIDs, antipyretics, combinations of NSAIDs and other compounds (acetylsalicylic acid in combination with paracetamol and caffeine), sedatives, estrogen receptor modulator, antifungal agents. In several cases the patients took more medicines simultaneously, making it more difficult to establish the one responsible for EM.

Another factor considered to be responsible for the occurrence of EM is herpes simplex virus (HSV) infection. From patient history we found that 7 patients showed signs of labial herpes simplex infection. Of these 7 patients, 4 were diag-
nosed with recurrent EM, 3 patients presenting the erythematous-vesiculobullous form and 1 the erythematous-papular form. These 4 patients presented signs of EM for 8 months to 13 years. Bacterial and fungal infections were also detected: due to beta hemolytic streptococcus (2 cases of streptococcal pharyngitis), candida infection (4 cases of oral candidiasis) infection with dermatophytes (tinea pedis = 4 cases, onychomycosis = 1 case). Other possible causes of EM resulting from patient history were: solvents, detergents and other irritant solutions, printing ink, sun exposure, pregnancy (fig. 3).

Of the total of 45 admissions, 2 patients had a check-up admission one month after the first presentation to the clinic, while other 2 patients with recurrent EM had 3 and 2 admissions, respectively, for distinct EM episodes, thus totaling 40 EM patients with 43 admissions. Twenty-two patients presented manifestations of EM erythematous-papular form, while 21 patients EM erythematous-vesiculobullous form. Of these, 8 patients were diagnosed with recurrent EM. One of the 2 patients with multiple admissions had 1 episode of erythematous- papular EM and 2 episodes of erythematous-vesiculobullous EM, while the other patient had 1 episode of EM erythematous-papular form and 1 episode of erythematous-vesiculobullous EM. Thus of the total of 43 admissions, 18 cases had erythematous- papular EM, 14 cases erythematous-vesiculobullous EM and 8 cases recurrent EM, totaling 40 patients (fig. 4). Of the 8 patients with recurrent EM 4 had symptoms of erythematous-papular type and the other 4 of erythematous-vesiculobullous type. In 4 cases (3 with erythematous-vesiculobullous form and 1 case with erythematous-papular form) the etiology was herpetic, in one case a contact reaction and in the other 3 cases the causal factor was not detected. Special attention deserved the 2 EM pregnant women (pregnancy weeks 28 and 31, respectively). One of these women was diagnosed with EM erythematous-papular form, and other with EM erythematous-vesiculobullous form. No other causal factor other than pregnancy could be related to the occurrence of this disease.

Typical acral distribution (fig. 5, 6) was present in 42 of the 43 cases, oral mucosa was affected in 7 cases (fig. 7), lesions on the trunk were present in 9 cases and genital lesions were found in 3 cases.

Fig. 5. Target-like lesions on palms
Fig. 6. Target-like lesions on soles
The lesions occurred progressively, symmetrically, with centripetal spreading, which is consistent with literature data. Acral involvement, another important feature in the diagnosis of EM, was present in 98% of cases; most commonly affected being the back of the hands, palms and soles in 70, 59 and 40% of the cases, respectively.

Pruritus was present in 12 cases, and pain in 6 cases, of which 3 with oral and genital mucosal involvement and 3 with the erythematous-vesiculobullous form. Burning sensation was present in 4 cases.

Twenty-two cases of minor EM and 21 cases of major EM were recorded.

Thirty-one (77.50%) of the 40 study patients presented associated diseases, the most common being *tinea pedis*, oral candidiasis, chronic venous insufficiency, essential hypertension, dyslipidemia.

All patients received treatment with antihistamines and nonspecific desensitizing agents (Ca + vitamin D$_3$, vitamin C). These were used as adjuvant agents in the treatment of EM which in this study consisted of topical therapy (dermatocorticoids) and systemic therapy (systemic corticosteroids). Systemic corticosteroid therapy was used in 9 cases with EM erythematous-papular form and in 13 cases with erythematous-vesiculobullous EM. The recommended dose was generally 0.5-1 mg/kg/day of prednisone or equivalent dose of methylprednisolone for a short period of time (10 days). Also used were: betamethasone (6 cases), dexamethasone (3 cases) and hydrocortisone hemisuccinate (5 cases). Treatment with acyclovir was administered in 3 cases of recurrent EM of herpetic etiology.

All 43 cases had a favorable outcome, the lesions disappearing after treatment. Of the eight cases of recurrent EM one patient had six episodes of EM over 8 months. In the other cases the episodes occurred about once a year. Adherence to treatment was good, given that the treatment was short-term, and the prognosis was favorable in all cases.

**DISCUSSION**

In the present study EM had some features consistent with literature data (incidence of less than 1%, more frequent in second to fourth decades of life, onset with prodromal symptoms in 20% of cases, favorable, self-limited course).

The 6 cases in children and adolescents under 20 years of age accounted for 15% of the cases, close to the percentage of 20% reported by other authors (3). A significant percentage (32.5%) of patients was diagnosed at an age older than 50 years, although EM is considered rare under the age of 3 and over 50 years.

Regarding the etiology of EM the drug factor was involved in a considerable percentage of cases, 42.50% (most commonly involved being the antibiotics – especially amoxicillin, and NSAIDs). According to several authors the drugs involved in the etiology of this disease are primarily the sulfonamides, followed by anticonvulsants...
and other types of medication (antibiotics, antifungal agents, NSAIDs, and others) (4, 5, 6, 7, 8). In the literature there are numerous case reports of EM due to the use of drugs, but there is no test that can accurately demonstrate the association between a single case and a specific drug. In our study patients various drugs have been administered concomitantly, making it difficult to differentiate the possible etiology of EM in these cases.

HSV infection, another reported etiologic factor associated with EM minor (9, 10) was found in only 7 cases, being associated with only one case of EM minor the erythematous–papular form. Other infectious causes are the infections with streptococcus, mycoplasma, dermatophytes, cytomegalovirus (CMV) and Epstein Barr virus (EBV) (11, 12, 13). Virus–drug interactions have been reported as a trigger factor for the occurrence of EM, including CMV infection and terbinafine treatment (14) and EBV infection and amoxicillin treatment (15). In the present study the presence of beta-hemolytic streptococcal infection (2 cases of streptococcal pharyngitis), candida infection (4 cases of oral candidiasis), dermatophyte infection (tinea pedis 4 cases, 1 case of onychomycosis) was detected.

The clinical manifestations were key to diagnosis, cases of EM erythematous–papular form and erythematous–papulo–vesicular form, recurrent EM and EM during pregnancy being recorded. Physical examination was sufficient to establish the diagnosis in all cases. In EM major the mucous membranes can be also involved: oral mucosa showing bullae that progress to painful erosions, genital mucosa by vulvitis or balanitis, and conjunctival mucosa by conjunctivitis or corneal ulceration. These can lead to complications such as dehydration and fluid and electrolyte imbalances, secondary bacterial infections, ocular complications (corneal ulcers, anterior uveitis, corneal opacities, etc.). Scars (especially on mucosal lesions), and strictures (esophageal, lower respiratory tract, urethral, vaginal, anal) are less common. Oral mucosal involvement was found in 16% of patients and genital mucosal involvement in 7% without complications.

For the diagnosis of EM laboratory tests are not highly specific. However, the results of routine investigations were consistent with the data in the literature, revealing inflammatory syndrome, mild leukocytosis, mild anemia, and hypereosinophilia in most cases.

With regard to the treatment of EM, mainly used was corticoid therapy, both systemic and topical. Although the literature states that its use is controversial being even contraindicated in the mild forms of disease and the most severe may increase the risk of complications without improving the prognosis, in this study the use of corticosteroids did not lead to complications, with favorable outcome in all cases. Treatment with acyclovir was administered in 3 cases of recurrent EM of herpetic etiology.

**CONCLUSIONS**

*Erythema multiforme* is a rare skin condition, easily diagnosed based on the characteristic clinical appearance, but remains a challenge for the physician with respect to establishing the causal agent, in the literature most cases being considered idiopathic. In the present study the drug factor was incriminated in almost half of the cases (42.50%), but we cannot say with certainty that there is a cause–effect relationship.
between administered drug and disease occurrence. The presence of prodromal symptoms in a significant number of cases (20%) and self-medication in these cases before presentation to the doctor make impossible the accurate detection of the trigger factor. The therapeutic goals were EM cure and prophylaxis for the prevention of recurrences. In cases of EM major interdisciplinary collaboration is important as ophthalmology, ENT, gynecology, urology, gastroenterology consultations may be required.

REFERENCES