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Erythema Multiforme: A Retrospective Study of the Clinical Manifestations of Patients Attending an Oral Medicine Clinic in Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author AMO designed the study and wrote the protocol. Author AAA performed the statistical analysis and wrote the draft of the manuscript. Authors EOO and FJO managed the analyses of the study and revised the manuscript. Author IKM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Erythema multiforme (EM) manifests on the skin and mucosa surfaces such as the oral mucosa and the genitals as ulcerative lesions. The spectrum of clinical presentation underscores the importance of describing the clinical features observed in patients presenting in an oral medicine clinic for treatment.
Aim: To describe the epidemiology and the clinical features of patients presenting with erythema multiforme in the oral medicine clinic of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC).
Methodology: A retrospective study of cases diagnosed as EM in the Oral Medicine clinic of OAUTHC between August 2009 and August 2019. Patients' hospital records were retrieved and

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reviewed. Information extracted included biodata, clinical findings, presence of co morbidity and treatment received. Diagnosis of EM was mostly clinical; some patients also had histopathologic and/or Direct Immunofluorescence (DIF) investigations. Data was analyzed using STATA 13 statistical software.

Results: Out of the total number of 923 patients seen in the clinic during the study period, 19 (2.08%) patients had EM. Nine males and 10 females were affected. The age ranged from 9 years to 73 years with mean age of 35.53± 16.20 years. EM minor was diagnosed in 17(89.47%) while EM major was diagnosed in 2(10.53%). The affected oral sites were upper and lower lips 16(84.21%), buccal mucosa 9(47.3%), hard and soft palate had 3(15.79%) and tongue 2(10.52%). Seven patients (36.84%) presented with target skin lesions. Seventeen patients (89.47%) had recurrence. Sixteen (84.47%) patients had no identifiable causative factor while one patient each presented with ciprotab® (5.26%), septrin® (5.26%) and sulphonamide (5.26%) as the implicating triggers. Two (10.53%) of the patients presented with oral and genital ulcers. The 2 patients had histopathology and Direct Immunofluorescence investigation. Patients were treated with steroids and other supportive therapy.

Conclusion: Erythema Multiforme appears to be an uncommon presentation in the oral medicine clinic, but may be associated with recurrent lesion in and around the oral tissue. The lips were the most common site of oral presentation. Drug reactions were identifiable etiological factor. Topical or systemic steroids were effective in patient management.

Keywords: Erythema multiforme; oral ulcers; target lesions; drug reaction.

1. INTRODUCTION

Erythema multiforme (EM) is an acute, self-limiting, hypersensitivity, inflammatory, mucocutaneous disease that manifests on the skin and often oral mucosa while other mucosal surfaces, such as the genitalia, may also be embroiled [1]. The term EM was coined by Ferdinand Von Hebra in 1866 [2]. He described the clinical presentation on the skin as EM however, Kenneth in 1968 described the oral component of EM [3]. Bastuji-Garin et al defined EM as detachment of the skin that affects less than 10% body surface area with localized typical and or raised atypical target [4]. Typical targets are defined as lesions less than 3cm in diameter and characterized by three different concentric zones. Raised atypical targets on the other hand contain only two zones [4].

Epidemiological data on EM showed that the reported prevalence is less than 1% worldwide [5]. It typically affects young adults 20-40years with a male to female ratio of 1.5:1 [6,7]. The prevalence of Oral lesion in EM vary from 35% to 65% among those with cutaneous lesion [8].

EM is characterized as an immune complex, antigen-antibody reaction that target small blood vessel in the mucosa and skin. The common cause has been linked to herpes simplex virus in about 70-80% of cases. HSV-1 have a predominant role in the recurrence of EM clinically diagnosed as herpes associated EM (HAEM) [5]. However, the Mayo Clinic study of recurrent EM described the etiologic findings as idiopathic in about 60% of the 48 patients under review [9]. Despite this designation, it is pertinent that a subclinical HSV infection may have been present in some of these cases. Sulfonamides, non-steroidal anti-inflammatory drugs (NSAID), penicillin and anticonvulsants are some of the medications that have also been implicated [5,7] (Table 1).

EM was contemplated to epitomize a range of conditions, including EM major, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis. However, a consensus clinical classification postulated signal that recommends that EM major and SJS are independent, distinct disorders which manifest with similar mucosal erosions but distinctive cutaneous lesions [10]. EM has been generally classified as EM Minor if there is less than 10% skin involvement and EM major if there is more than 10% skin involvement [11]. Furthermore, EM is subdivided into EM minor (involvement of 1 mucosal site) and EM major (involvement of 2 or more mucosal site) by some authors [12]. However, there are lesion that affect the oral mucosa alone with no skin involvement. The view of pure oral EM is contentious and not entirely recognized because some dermatologists still bask in the idea that the distinguishing appearance and distribution of target skin lesions are the prerequisite for the diagnosis of EM [11] (Figs.1,2).

Table 1. Etiological factors for developing erythema multiforme

Infections Approximately in 90% of cases.	Viral	Herpes viruses; HSV-1 and HSV-2, Epstein-Barr virus, cytomegalovirus, varicella- zoster virus, Adenoviruses
	Bacterial	*Myoplasma pneumoniae, Chlamydia pneumoniae, Corynebacterium diphtheriae, Hemolytic streptococci, Legionella pneumophila, Salmonella*
Drugs (less than 10% of cases)	Highly suspected	Sulfonamides(trimethoprim,sulfamethoxazole) Nonsteroidal anti-inflammatory drugs Penicillins Anticonvulsants Valporic acid Antifungal (Terbinafine)
Immune condition	Immune disease	Graft versus host disease Inflammatory bowel disease Polyarteritis nodosa Sarcoidosis
	Immunization	Hepatitis B, Bacille Calmette-Guerin
Others	Food additives Chemicals	Benzoate, Nitrobenzene Terpenes, Perfume

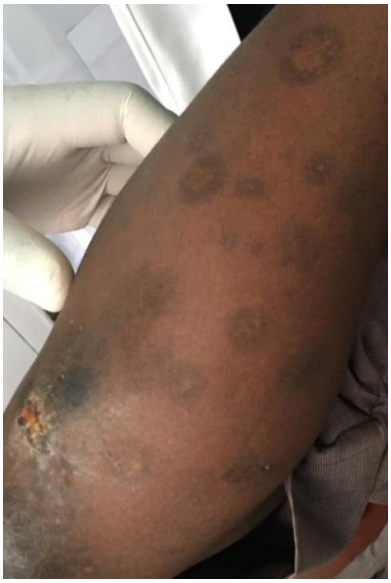

Fig. 1. Target skin lesions of EM on the extensor surface of the arm in a 38 year old man with recurrent idiopathic EM

Its presentation in dental setting and the acute nature of the lesion makes it an important condition that need prompt diagnosis and care. It usually presents as blistering, ulcerative, mucocutaneous lesion that is characterized by target or iris lesion distributed symmetrically on the extremities and trunk [13]. The oral component present clinically as a painful, erythematous erosive or ulcerative lesion with pseudomembranous necrotic surface on non-keratinize mucosa or erosions over a protracted period of time interfering with speech, mastication, and swallowing producing considerable morbidity [14]. Commonly, buccal mucosa, labial mucosa, vermillion lips, and non-attached gingivae are involved in presentation of EM [11,13]. Crusting and bleeding of the lips are common, but not always present [11] (Fig. 3).

The diagnosis of oral EM is a challenging task especially when the disease is restricted primarily to the oral mucosa. It exhibits

enormous variable characteristics that can imitate other diseases [15,16]. Many of such diseases include, pemphigus, paraneoplastic pemphigus, mucous membrane pemphigoid, and oral lichen planus, which also present with chronic erosions of the oral cavity and many times can be confused with recurrent oral EM [14]. The major value of biopsy is to exclude other inflammatory and vesiculobullous and dysplastic diseases. Immunofluorescent testing of mucosa and serum is important to exclude pemphigus, paraneoplastic pemphigus, mucous membrane pemphigoid, and lichen planus [14,17] (Table 2).

Treatment of EM depend on the severity of the lesion and no single treatment has been found ideal. An untreated EM will heal within 2 to 3 weeks. Identification of the trigger remain the best way to either treat or prevent recurrence of the lesion [17].

EM may display a wide spectrum of clinical disease. On the mild end of the spectrum, isolated oral ulcerations develop. In the severe form, sloughing and ulceration of the skin and other mucosa may be seen in addition to oral ulcers. This characteristic nature of the disease necessitates the need to describe the epidemiology and clinical features of EM from an oral physician's perspective. This will further add to the existing knowledge of medical specialties that manage EM in our environment and perhaps improve clinical diagnosis.

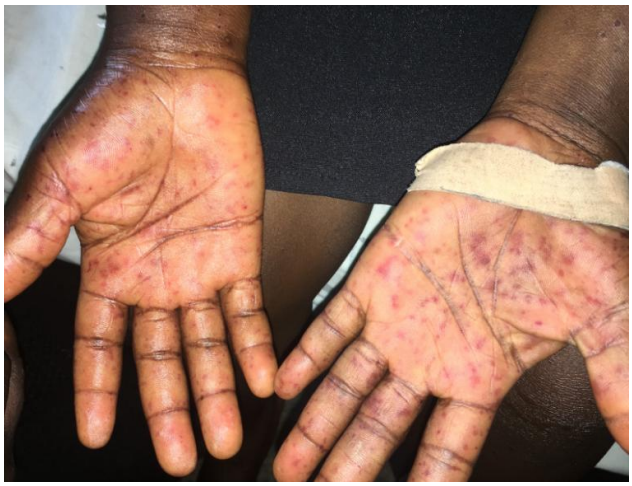

Fig. 2.Target skin lesions on the palms of a 23 year old woman with Sulphonamide induced EM

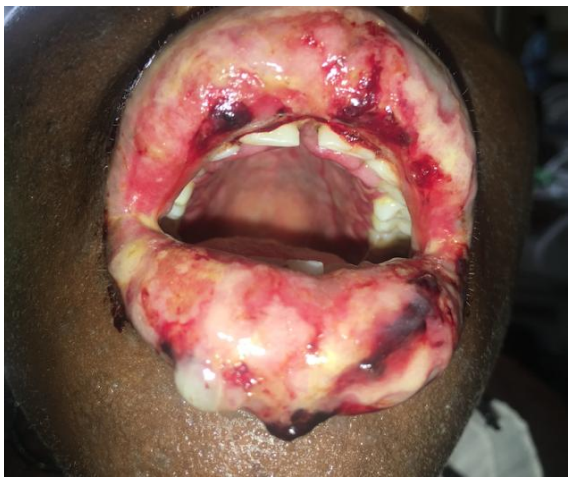

Fig. 3. Hemorrhagic crust on the lips and palatal mucosa ulceration in a 23 year old woman with sulphonamide induced EM

Table 2. Differential diagnosis of erythema multiforme (EM)

Stevens-Johnson Syndrome
Pemphigus Vulgaris
Mucous membrane pemphigoid
Herpetic gingivostomatitis
Bullous pemphigoid
Fixed drug eruption
Paraneoplastic pemphigus
Erosive Lichen Planus

2. METHODOLOGY

2.1 Study Design

The study was designed as a retrospective study of all cases of EM presenting in the clinic between August 2009 and August 2019.

The study was done at the oral medicine clinic of the Obafemi Awolowo University Teaching Hospital Ile-Ife, Osun State, southwestern Nigeria.

Participants were patients who presented in the clinic and diagnosed with Erythema multiforme under the period of review of ten years.

2.2 Method

Medical records of patients that presented and managed for erythema multiforme in the clinic were retrieved and reviewed. Information extracted included biodata, clinical findings, presence of co morbidity and treatment received. The clinical diagnosis of EM is routinely made in our clinic based on clinical criteria for diagnosis as reported by Schofield et al. [13] and Samim et al. [5]. Nikolsky's signs were negative for the patients. Some patients also had histopathologic and/or Direct Immunofluorescence (DIF) investigations.

2.3 Data Analysis

Data analysis was done using Stata 13 statistical software (Statacorp, Texas USA). For descriptive continuous variables mean, minimum value and maximum value were determined. For descriptive variables that are categorical, simple frequency and percentages were determined.

3. RESULTS

A total of 923 patients were seen in the clinic during the study period. Nineteen cases (9 males and 10 females) were EM, giving an incidence of 2.08%. The mean age was 35.53± 16.20 years, with range from 9 years to 73 years (Table 3).

Upper and lower lips 16(84.21%) were the most affected oral site, followed by the buccal mucosa 9(47.3%). The hard and soft palate had 3(15.79%) occurrence and the least affected site was the tongue 2(10.52%).

EM minor was diagnosed in 17 (89.47%) while EM major was diagnosed in 2 (10.53%). Seventeen patients (89.47%) had recurrence while 2(10.53%) had a single episode. Two (10.53%) of the patients presented with oral and genital ulcers. They had histopathology and DIF and were diagnosed as EM major. Two (10.53%) had ocular involvement while 7(36.84%) had skin involvement as target or Iris lesion (Table 4).

Sixteen (84.21%) patients had no identifiable causative factor while one patient each presented with Ciprotab® (5.26%), Septrin® (5.26%) and Sulfonamide (5.26%) as implicating triggers (Table 5).

Table 3. Demographic characteristics

Variables	Frequency (N)	Percentage (%)
Gender		
Male	9	47.37
Female	10	52.63
Age (Years)		
Mean=35.53±16.20		
<20	2	10.52
21-30	5	26.32
31-40	5	26.32
41-50	4	21.05
51-60	1	5.26
>60	2	10.53

Table 4. Clinical characteristics of EM

	Frequency (N)	Percentage (%)
Site		
Upper and Lower lips	16	84.21%
Buccal mucosa	9	47.37%
Hard and soft palate	3	15.79%
Tongue	2	10.52%
Class		
Minor	17	89.47
Major	2	10.53
Extra oral and oral Involvement		
Genital	2	10.53
Eye	2	10.53
Skin (Target lesion)	7	36.84
Oral only	8	42.10
Episodes		
Recurrent	17	89.47
Single	2	10.53

Table 5. Implicated aetiology of EM

Variable	Frequency (N)	Percentage (%)
None	16	84.21
Septrin®	1	5.26
Sulphonamide	1	5.26
Ciprotab®	1	5.26

Fifteen (78.95%) had no known co morbid condition while 2(10.53%) patients presented with hypertension (HPT), 1 (5.26%) patient with peptic ulcer and 1(5.26%) with diabetes mellitus (DM) (Table 6). The 2 patients who had histopathology and DIF showed typical perivascular invasion of blood vessels by inflammatory cells and demonstration of IgM and C3 antigen in the basement membrane. All patients had full blood counts which were within normal range.

Table 6. Underlying systemic conditions

Variables	Frequency (n)	Percentage (%)
Hypertension	2	10.53
Peptic ulcer disease	1	5.26
HPT/DM	1	5.26
None	15	78.95

4. DISCUSSION

EM is a constellation of reactions which are acute and self-limiting. Their multiple presentation and symptoms coupled with no specific laboratory marker makes diagnosis challenging [11]. The typical target or Iris lesion is a characteristic cutaneous lesion that distinguish it from its counterparts [2] but may be absent in purely mucosa lesions. The severe forms may develop with constitutional symptoms which include malaise, headache, fever as early as a week before onset of bullae or ulceration.

The average age of presentation in this study was 35.53±16.20 years. The observed age in our patients and female preponderance (52.63%) were similar to those reported in previous stuidies [7,9,13,17].The incidence of EM in this study was 2.06%, this is in agreement with other reported studies of annual incidence of less than 1% [14,18].The current study report annual incidence of 0.21% and is consistent with the reported annual incidence of EM ;less than 1% but not less than 0.01% in all population studied by Clark *et al.* [7].They also observed that EM incidence could be seasonal with no firm pattern of occurrence.

There is considerable variability in the oral presentation of EM in many patients. Oral disease had a debilitating outcome, preventing patients from normal activity of eating or drinking, meddling with sleep, triggering weight loss, and even promoting clinical depression that may require treatment. The present study showed the most common site of occurrence was the upper and lower lip with 16(84.21%) cases. Lorzarda-Nur et al. [15], reported involvement of the lip vermilion as the most affected site and cutaneous involvement typical for EM minor may

be seen in 25% of patients while extraoral lesions may be present. The sites of the lesions are also variable giving it the name multiforme. However, Schofield et al. [13] reported the buccal mucosa as the most affected site.

In some patients, EM lesions are limited mainly to the oral cavity. Lesions may be persistently present or may be self-limiting and reappear periodically. The clinical appearance of the lesions is also variable and may present as, ulceration with or without a pseudomembrane, diffuse areas of mucosal erythema bullae and erosions, or nonspecific hyperkeratotic plaques interspersed with erythematous changes [14]. In the present study, 2(10.53%) patients had orogenital involvement, 2(10.53%) had ocular involvement while target lesion on the skin was found in 7(36.84%) of patients studied. Schofield et al. [13], found that 25% had genital lesions and 17% had ocular involvement in EM. Pope and Krafchik [19] also described a case of herpes-induced recurrent EM involving 3 mucous membranes (ocular, oral and genital).

The target lesion was found on the extremities with a symmetric distribution in a centrifugal fashion healing without scaring. The oral alone presentation was found in 8(42.11%) of patients that presented in the clinic. This is in agreement with study by Lozada-Nur et al. [15] who found 43% of patient out of 95 having oral lesion alone but Wetter *et al* found 10% of patient presenting in Mayo clinic having only mucosal lesion [9]. Though EM was initially thought not to involve the oral cavity alone, it has now been established that EM can present with only oral lesion with no or mild skin involvement [5]. The prevalence rates of oral EM lesions vary from 35% to 65% among patients with cutaneous lesions, while oral EM occur in 70% of cutaneous EM [5].

EM minor was found in 17(89.47%) of patient that presented in our clinic within the period of study, while EM major was seen in 2(10.53%) of the study population. The observed reason for the low cases of EM major in our clinic is that most patients with extensive skin lesions present at the dermatology clinic. Referrals are sent to the oral medicine clinic for cases with oral mucosa involvement.

Recurrence of the ulcer is a common feature seen in EM. The present study showed a higher recurrence rate of 89.47% compared to other studies. The recurrence was noted to be three per year and this is consistent with report by Burket et al. [11]. However, Schofield *et al.* [13] and Wetter et al. [9] reported a recurrence episode of up to 6 times per year. Recurrence has been linked mostly to infection and the presence of HSV infection. EM typically follow a lesion of recurrent HSV1 by about 1-3weeks, averagely 10 days [5]. Herpes-associated EM occurs primarily in young adults and the EM associated herpes lesions, is commonly recurrent [5]. Both type 1 and type 2 herpes infections have been associated with EM [20]. The characteristics of herpes-associated EM are typically those of EM minor with cutaneous or cutaneous and limited mucosal, which is usually oral involvement [5].

Oral erythema multiforme is thought to be an immune complex disease where 7–10 days after a herpes simplex infection, IgG antibodies are formed and bind to remaining residual tissue-located herpes antigen giving rise to localized inflammation and ulceration [11].

The implicated aetiological factor in these patients showed that Sulphonamide, Ciprotab® and Septrin® had 1(5.26%) patient each presenting with EM. The majority of patient 16(84.21%) had no identifiable trigger which suggest they may be associated with herpes simplex virus considering the recurrence rate and prodromal symptoms they exhibited before presentation. The most common trigger for the development of EM is the herpes simplex virus (HSV-1 and HSV-2) [18,21].This connection is buttressed by the discovery of HSV DNA in 60% of patients clinically diagnosed with recurrent herpes-associated EM (HAEM) and in 50% of patients with recurrent idiopathic EM using polymerase chain reaction of skin biopsy specimens [5]. In general, cutaneous EM, HSV-1 prominent in the prevalence of HSV-1 in 66.7% of cases, HSV-2 in 27.8% of cases, and with both HSV types in 5.6% of cases [22].

The investigation done for the patients include histopathology (hematoxylin and eosin) and immunohistochemistry which revealed typical perivascular invasion of blood vessels by inflammatory cells and demonstration of IgM and C3 antigen in the basement membrane. Full blood count was within normal range for all the patients.

Most patients in this study were treated with systemic corticosteroid. Patients with features of recurrent EM and associated prodromal symptoms were placed on acyclovir. Other

supportive treatment given with varying degree of success included warm saline mouth bath, xylocaine gel, 0.2% Chlorhexidine mouth rinse, and petroleum jelly and they showed marked clinical improvement within a week. Medications which were causative were withdrawn and patient counselled on the danger of administration of those medications.

As the diagnosis of EM in patients included in this study was mostly clinical, investigation with histopathology and or DIF for all the patients would have confirmed the diagnosis as well as rule out autoimmune mucocutaneous diseases. Nevertheless, histopathologic assessment of perilesional mucosa in EM reveals a pattern that is characteristic yet not pathognomonic.

5. CONCLUSION

Erythema Multiforme appears to be an uncommon presentation in the oral medicine clinic, but may be associated with recurrent lesion in and around the oral tissue. Successful treatment outcome was achieved with both topical and systemic steroids and other supportive treatments.

CONSENT AND ETHICAL APPROVAL

As per international standard, patient's consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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