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ORAL ERYTHEMA MULTIFORME –CASE REPORTS, DIAGNOSTIC AND TREATMENT DILEMMA

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Abstract

Erythema multiforme is acute mucocutaneous condition that is considered to be immune-mediated hypersensitivity reaction to medicine or an infection. There are described three forms of erythema multiforme: "minor form", "major form" and oral erythema multiforme. It presents a diagnostic dilemma due to varied possible manifestations. Diagnosis is often made based on history and clinical examination.

In this article we report 5 cases of different forms of erythema multiforme following drug administration.

Keywords: erythema multiforme, drug induced.

Introduction

Erythema multiforme is condition caused by immune-mediated hypersensitivity reaction and usually involves skin with or without mucosal lesions. Erythema multiforme is an acute inflammatory and sometimes self-limiting disease, but there may be marked stages of remission and exacerbation. There is a slight predominance at men and young people between the ages of 20 and 40 are more affected. A number of possible etiological factors are listed, so it can be said that the disease has a multicausal etiology or idiopathic, because approximately fifty percent of the cases are with no identifiable cause. As etiological factors of erythema multiforme have been reported: viral, bacterial and fungal infections, drugs, contact exposure, radiation therapy, flavorings and preservatives, mmunologic disorders, physical or mechanical factors, foods, malignancy, pregnancy and hormonal disturbances. Postvaccination causes are mentioned as reasons that may contribute to development of erythema multiforme as well.

Also erythema multiforme involves broad spectrum of clinical symptoms. There are two variants of this condition, one with mucosal involvement termed erythema multiforme major and one without mucosal involvement, known as erythema multiforme minor [1].

Erythema multiforme minor is usually mild form of a polymorphous, symmetrical skin eruption of macules, papules, and characteristic "target" lesions. Predilection sites are the dorsal and volar side of the arm and leg, extensor aspects of the extremities and genitals. The lesions usually begin as annular erythema easily elevated above the level of the skin with a purple center and pink halo also called as "iris" lesion. At erythema multiforme major, at least two mucous membranes will be included.

Oral erythema multiforme (EM) is considered as a third category of EM other than EM minor and major. Patients present with oral and lip ulcerations typical of EM but without any skin target lesions [2].

Oral involvement is symptomatic and often shows characteristic crusting ulceration of the lips and ulcerations often involving buccal mucosa or other mucosal surfaces [3].

The main clinical feature is the polymorphism of the changes with a predominance of erythema, vesicles, bullae and papules.There are no specific diagnostic tests for EM and the diagnosis is mostly based on medical signs and symptoms, rather than diagnostic tests.

Objectives

This article presents five cases of erythema multiforme of which three are oral erythema multiforme and two can be recorded as major form.

Case Presentation

Case 1

Twenty-six-year-old female patient, after a previous referral and recommendation from a general dentist, referred to our clinic with complaints of painful lesions in the oral cavity. The patient described that the vesicles first appeared on the hard palate and soon began to spread throughout the oral cavity. She noted that soon vesicles ruptured and only painful areas remained. History revealed that six days ago she starts therapy with ciprofloxacin due to recurrent urinary tract infection and the next day she experienced sudden onset of fever and fatigue. The same day the first vesicle appears on the palate, and subsequently the vesicles expand. She goes to a general practitioner and a general dentist. Without explaining the cause of the condition in the oral cavity, the medical practitioner prescribes her as therapy aloe vera gel for local use and sage1 tea to rinse the mouth with. While the general dentist recommends nystatin oral drops and borderlne product in form of mouth spray, that is intended to relieve the symptoms of canker sores, gingivitis, stomatitis and erosions of non-infectious and infectious etiology. Active ingredients in the mouth spray were: 25% propolis extract in a 100 ml diluted alcohol, benzocaine as well as ped sage, peppermint leaf, aniseed and menthol.

The lesions were unresponsive after that local treatment and continued to progress in severity and extent. The patient was worried because even after 5 days of therapy there was no improvement in the condition of the oral cavity but on the contrary worsening and in the meantime occurre painful erosions accompanied with itching in the perivaginal region. Due to that concern and the discomfort, the patient addresses to our clinic on friday.Intraoral examination revealed oral erosions with an erythematous periphery and a pale erythematous center on the buccal mucosa, lips, hard palate, dorsum of the tongue and floor of the mouth.

The patient was instructed to discontinue ciprofloxacine therapy and to consult the general doctor for different type of medication as threatment option for the urinary tract infection. Topical therapy was given as application of 1% methylene blue solution, 3% borax glycerin, solcoseryl ointment, nystatin and ointment containing gentamicin sulfate and betamethasone dipriprionate and an oral antihistamine was prescribed.

Two days after the given therapy the patient felt a reduction of the pain and withdrawal of the changes. Already after 4 days, particularly the fifth day when the patient came for a control examination, the changes were completely withdrawn.

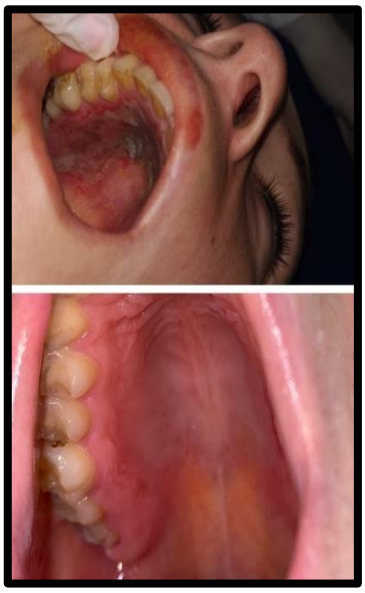

Figure 1. Diffuse erosions and ulcerations covered with pseudomembrane.

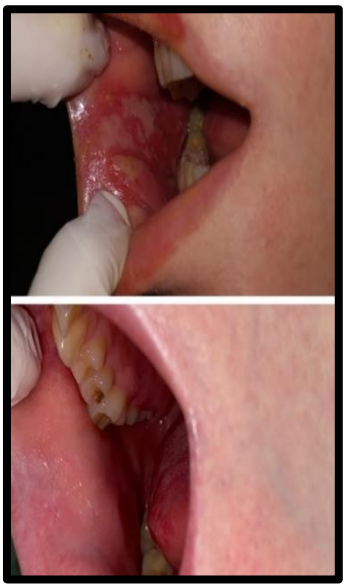

Figure 2. Diffuse ulcerations on bucal mucosa (before and after the treatment).

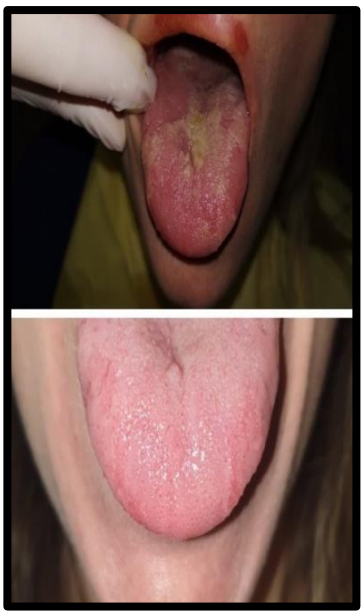

Figure 3. Yelowish plaques and iregular erythematous lesions on dorsum of the tongue (before and after the treatment)**.**

Figure 4. Erythematous lesions on upper lip.

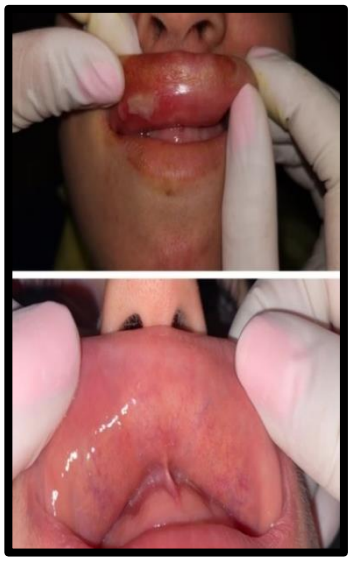

Figure 5. Irregular ulceration and diffuse erythema on lip mucosa.

Case 2

A 65-year-old female patient reported to our clinic with compliant of enlarged lower lip, redness and pain of the labial mucosa. This patient also reported that she was taking ciprofloxacin due to a urinary tract infection and that she noticed swelling of the lip the very next day.

The patient was also at our clinic a few months ago due to geographic tongue and dry mouth which caused her significant impairment of quality of life. Then at our request, she performed laboratory tests and was confirmed that she had prediabetes. We further referred the patient to a general practitioner for control and advice on controlling the prediabetes condition.

As therapy to the patient we recommended one tablet oral antihistamine daily and corticosteroid ointment for topical use on the affected areas. After 3 days the patient came to control examination and the swelling and redness were completely gone. She also mentioned that the next day after treatment she felt pain relief.

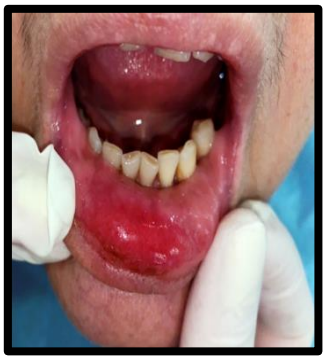

Figure 6. Swollen lip accompained with crusts and erythema on labial mucosa**.**

Figure 7. Condition three days after treatment.


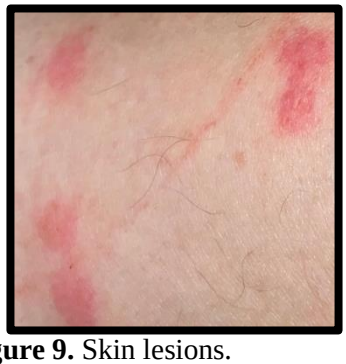

Figure 8 and Figure 9. Skin lesions.

Case 3

We are describing a case of acute low lip enlargement and superficial red lesions at the level of the right side of the buccal oral mucosa and the mucosa of the lower lip in a 25-year-old woman. The erythematosus lesions were clearly delimited by the surrounding healthy mucosa and the lip enlargement was diffuse.

We learned from the patient's anamnestic statement that 3 weeks ago she received a second dose of Covid-19 vaccine and three days later she had a sore throat. Therefore, without consulting a doctor she had taken pastilles to relieve the symptoms. The pastilles she used contain tyrothricin, chlorhexidine and lidocaine. She exceeds the stated dose of eight pastilles in a 24-hour period and after the second day of use felt dryness on the labial mucosa of the lower lip and right buccal mucosa.

According to her declaration, first appeared vesicle on the right buccal mucosa and lower lip, after which the next day swelling and redness occur in the same places. She did not complain of burning sensations or pain.

Antihistaminic once a day, ointment with betamethasone and gentamicin twice a day and borax glycerin three times a day were prescribed to use. A follow-up examination was scheduled for two days.

Figure 10. Swollen enlarged lip;

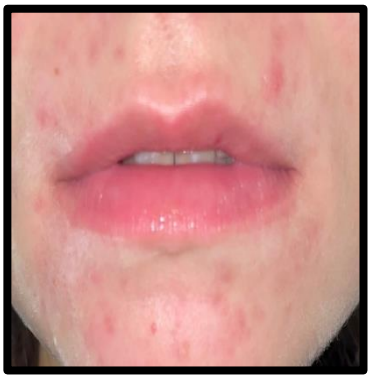

Figure 11. Condition two days after treatment;

Figure 12. Diffuse erythema limited by the surrounding buccal mucosa;

Figure 13. Condition two days after treatment.

Case 4

A 20-year-old female patient attend our clinic with compliant of gum pain that started sudden four days ago. Initially, she did not consult a dentist, believing that using chamomile and sage-based gum gel at home would reduce her pain. On the contrary, her initial attempts to address this were unsuccessful and the pain intensified in the following days.

For the next two days, the pain spreads to the throat and almost the entire oral cavity, the hard palate, the labial mucosa, and the soft tissue around both mandibular third molars. The patient complained that she could not eat or drink, nor maintain oral hygiene.

The anamnesis reveals that the beginning of the changes was preceded by a high temperature of 38.5. The day before, she started treatment with 875 mg amoxicillin combined with 125 mg clavulanic acid due to a urinary tract infection, according to antibiogram results.

She gave a history of multiple vesicles of the oral mucosa which ruptured to form painful ulcerations. She especially complained of intense painful and tender to touch attached gingiva of mandibular incisors. The tongue was coated and with mouth sores. Examination also indicated enlarged red tonsils with irregular white patches. The patient was surprised when she was told about the changes in her throat because even though she complained of pain generally in the entire oral cavity and inability to eat and function in everyday life, she did not feel any sore throat.

As a local and symptomatic therapy was suggested use of borax glycerin, gel with 10% benzocaine, ointment with betamethasone and gentamicin as active ingredients and to rinse twice a day with combination of 0.12 % chlorhexidine gluconate and 3% hydrogen peroxide.

The patient was advised to discontinue the use of antibiotic she was taking and to take oral antihistamine once a day. Low-level laser therapy was also included.

Subsequently after the initial improvement of the changes, the patient notices two new vesicles on the labial mucosa which are already erosive surfaces the next day.

Two days after the initial examination, the patient was additionally suggested to include topical application of paste that contains a haemodialysate from calves' blood to promote healing and polidocanol to quickly and lastingly relieve pain and decortin 5 mg 3 per day in therapy. The paste also forms a dressing and protects the oral lesions from irritation while eating and drinking. And prednisolone of 5 mg was added to the therapy twice daily for three days and once a day the following two days.

Eleven days after the start of treatment, the changes completely subsided.

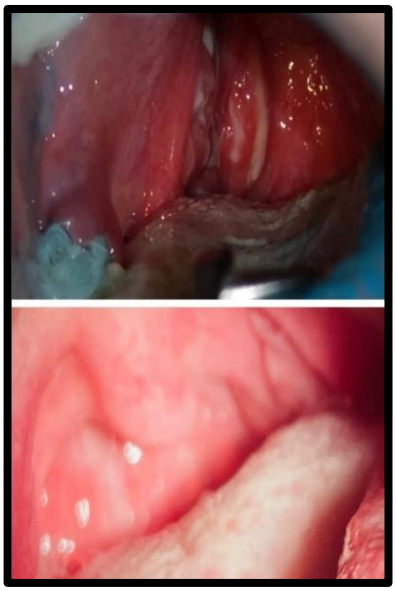

Figure 14. Enlarged red tonsils with irregular white patches (before and after treatment).

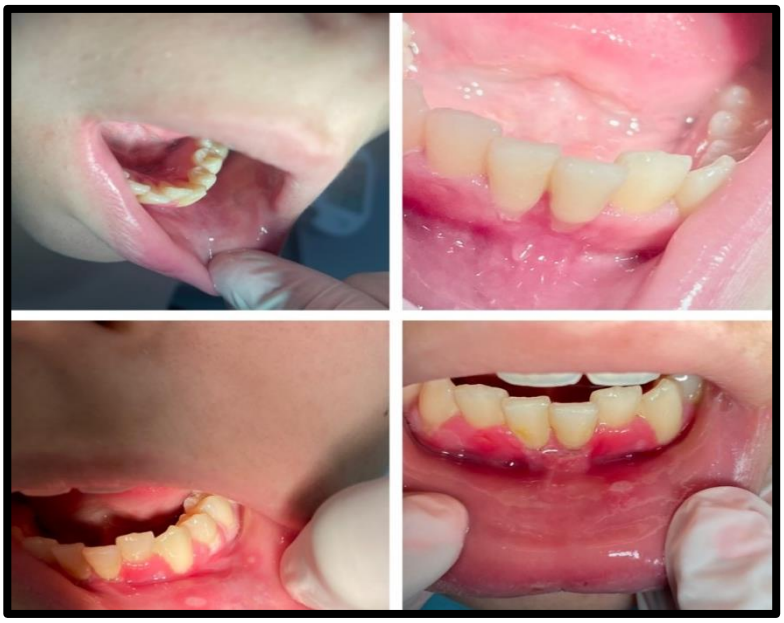

Figure 15. Swollen red gingiva and mouth sores.

Figure 16. Inflamed tissue around third molar and erosion beneath.

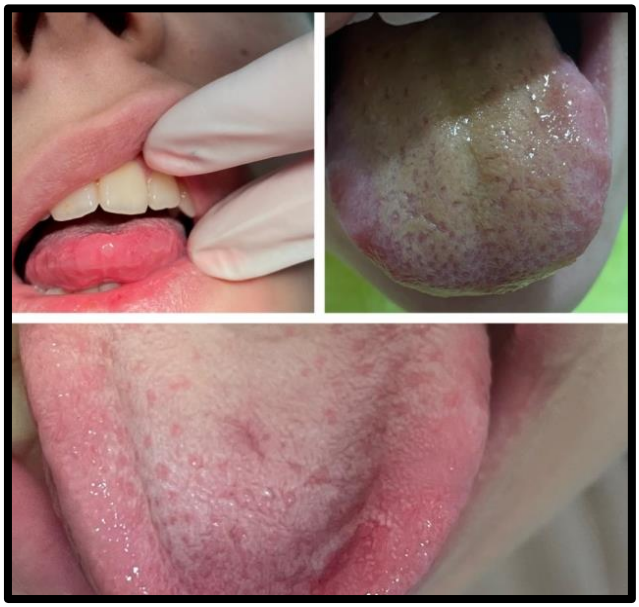

Figure 17. Coated tongue and mouth sore on it.

Case 5

A 16-year-old female patient came to our clinic because of pain in the oral cavity. She complained of pain in the gums, soft tissue around lower third molars, throat and lips.

We find out from the anamnesis that the patient has a sore throat for two weeks. She started therapy with sore throat lozenges but there was no improvement. Two days ago by recommendation of general practitioner although without a blood test or throat swab, she started antimicrobial therapy. Since the patient was allergic to penicillin, she was receiving erythromycin every 12 hours.

The same day she started taking the antibiotic, in the evening she had a fever of 38.5° C and felt lethargic and exhausted.

Examination revealed redness of the throat and tonsils with a whitish surround. There were erosive lesions on the vermilion of the lower lip, covered with scabs and scales. Gums were swollen and painful. The gum tissue around both right and left lower wisdom teeth was also swollen and inflamed.

There were irregular erosive lesions covered with fibrinous membrane, both above and below the operculum.As a topical therapy, the patient is recommended to use 3% borax glycerin and gel that contains ozonized extra virgin olive oil and Arnica Montana extract, known for its reconstructive action. Extra virgin olive oil, thanks to its high content of essential fatty acids and the effect of ozone, in contact with the tissue has anesthetic, anti-inflammatory and anti-edematous action.

Arnica is a plant that has anti-inflammatory, anti-edematous, antiseptic analgesic and immunostimulatory properties.

The next day, the patient underwent laser treatment in several sessions, and after the initial improvement and reduction of the pain, sub gingival curettage, debridement was performed and sub gingival application of chlorhexidine gel**.**

On the seventh day after treatment, the patient no longer felt any pain. However, although there was no sore throat, the patient was suggested to have a throat swab and re-examination and consultation with the family doctor.

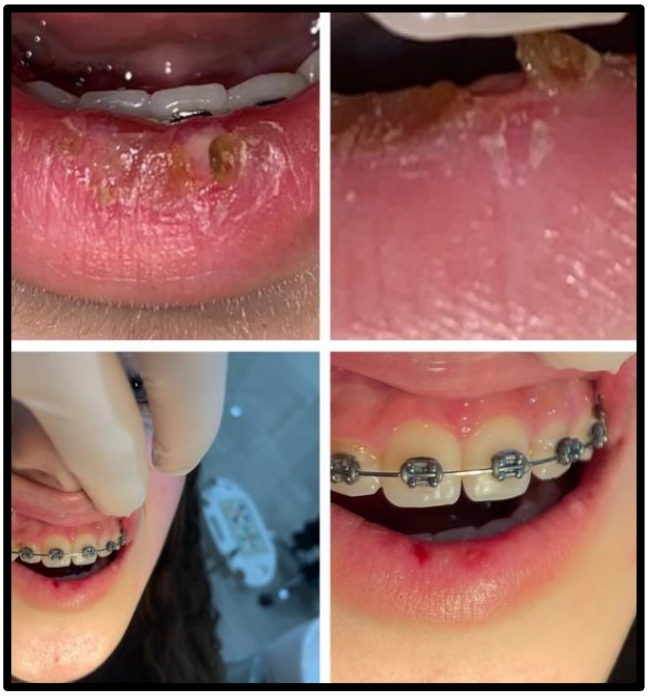

Figure 18. Erosive lesions on the lower lip, covered with scabs and scales.

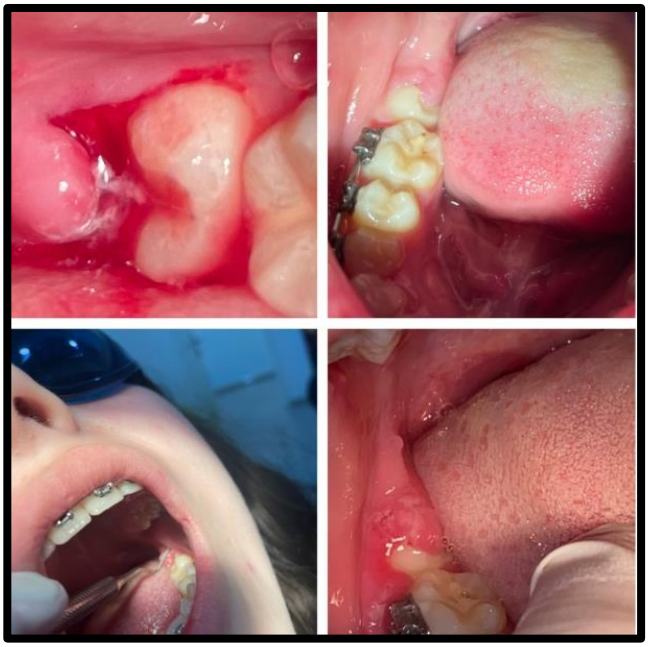

Figure 19. Inflamed tissue around third molar and erosion beneath the operculum.

Figure 20. Redness of the throat and tonsils.

Discussion

Erythema multiforme is considered as acute cutaneous or muccutaneous condition and type IV hypersensitivity reaction associated with certain infections, medications, and other various triggers [4].

It is regarded that infection represents as a triggering agent in approximately 90% of cases, and the most common infectious agent responsible are viruses especially herpes simplex virus type 1[5].

The list of medications which may trigger erythema multiforme include: antibiotic, non-steroidal anti-inflammatory drugs and anticonvulsants. Causative antibiotics include penicillin, ampicillin, tetracyclines, amoxicillin, cefotaxime, cefaclor, cephalexin, ciprofloxacin, erythromycin, minocycline, sulfonamides, trimethoprim-sulfamethoxazole, and vancomycin [6,7].

Aproximately 60% of cases of erythema multiforme major are related to medication use, but no test reliably proves the link between a single case and a specific drug.Although that is a fact that EM

can be provoked by hundreds of factors, only a limited number are reasonably well documented as possible precipitating agents [8].

Despite the fact that almost every literature data cite medications as a less common cause of the disease and place Herpes simplex or Mycoplasma pneumonia as most frequent etiological triggers, there are also quite a few cases caused exactly by medication [5,6,9,10].

Even though drug related erythema multiforme typically affect oral mucosa and lips drug induced oral erythema multiforme is a rare and less described variant [6].

In all our presented cases, manifestation of the lesions appeared after the initial intake of drug. In case 1, 2 and 4 that was after initial use of ciprofloxacin prescribed to treat urinal bacterial infection. In case 3, symptoms appeared after use of pastilles with tyrothricin, chlorhexidine and lidocaine in its composition. In case 5, symptoms appeared after use of erythromycin prescribed for sore throat. All of them denied previous history of herpes viral infection and the patient from case 5 reported penicillin allergy. Almost all our patients had mild prodromal symptoms hours or one day before the clinical manifestation and most of them were around 20 years old, which is consistent with the fact that EM usually affects younger individuals between the ages of 20 and 40 with absent or accompanied with mild prodromal symptoms.

The patient from case 1 complained that despites oral lesions she had painful and itching lesions in the perianal and perivaginal area, while at the patient from case 2 there were irregular round shape well-demarcated erythematous changes on lower legs that itched.

If it takes into account skin involvement, it can be stated that the patients in case 1 and case 2 had mild form of erythema multiforme major and patients in case 3, 4 and 5 had oral erythema multiforme.

Erythema multiforme is a diagnostic and therapeutic dilemma due to its wide range of manifestations and etiology.

The presence of characteristic “iris” skin lesion is usually diagnostic. However, heterogeneous nature of the disease, especially when the skin involvement is minimal, atypical, or as in our first presented case due to the specific location of the lesions and inability to record clinically, brings difficulty in diagnosis.

The mucosal changes can be different shapes and sizes, hence the Latin name: erythema (redness), multi (many) and forme (shapes).

There are no specific diagnostic tests for EM, and diagnosis is usually made by careful clinical examination. A well taken history is also a key factor in making a diagnosis, paying particular attention to recent symptoms of herpes simplex virus infection or mycoplasma pneumonia infection, as well as recent use of certain medications.

Most cases of erythema multiforme do not require further diagnostic tests. Other tests, such as punch biopsy [11]**,**can be used to confirm the diagnosis of Erythema multiforme.

In patients who have target skin lesions, diagnosis is easy to make and skin biopsy is not necessary. Differential diagnosis includes: herpes zoster, urticaria, lupus erythematous, Stevens-Johnson syndrome and autoimmune bullous diseases.

When the clinical manifestation is explicit, biopsy is rarely necessary because biopsy findings are not specific for erythema multiforme. The classic lesion will reveal vacuolar interface dermatitis with marked lymphocytes infiltration (predominance of CD 8 T) along the dermal-epidermal junction. However, skin biopsy results vary depending on the clinical morphology and the duration of the lesions’ existence as well as the area of the lesion from which the specimen is obtained [12].

The differential diagnosis for oral erythema multiforme must distinguish conditions like: aphthous stomatitis, bullous lichen planus, acute necrotizing ulcerative gingivitis and contact stomatitis that may present similar clinical features.

Lesions associated with erythema multiforme minor resolve within one to two weeks, but when mucous membranes are included may take up to six weeks to resolve. While skin lesions are no painful, mucosal lesions are mostly in the mouth and are frequently painful [11].

Mucosal erosions may be extremely painful; therefore, clinicians should assess the patient's ability to maintain oral intake [13]. Patients that are presented in these cases were also anxious and impatient to reduce their pain and regain their ability to eat. When this fact was taken into account, and the urgent need for treatment, the demand for timely diagnosis imposed.

In our cases, diagnostics included the information that antibiotic such as amoxicillin and ciprofloxacin are associate with the onset of erythema multiforme, plus that topical therapies may produce erythema multiforme-like eruptions [5,6,9,10]. As for example in case 3, the acute low lip enlargement and superficial red lesions occurred after topic use of pastilles.

Red lesions caused by hypersensitivity to a systemic or topical drug can arise anywhere in the oral cavity. The topical allergic lesions have been broadly subdivided into two types, erythema multiforme and lichenoid, because of their resemblance to the lesions seen in erythema multiforme and lichen planus [14].

Mucosal lesions in oral erythema multiforme usually affect lips which become swollen and non-keratinized mucosa as it was also in our cases. Although oral mucosal lesions are characteristically seen on the anterior part of the oral cavity, in our cases pharyngeal mucosa was involved. That is consistent and with literature data that other mucosal sites such as ocular, nasal, pharyngeal, laryngeal, lower respiratory, and anogenital mucosa may be involved [5]. The mere fact that the symptoms of a sore throat reced after the prescribed therapy confirmed that it was not a bacterial infection of the throat.

In two of our cases also and the tissue around third molars was affected with erosions surfaced by white pseudo membrane. Pericoronitis was excluded due to the presence of other accompanying changes in oral cavity, precise clinical examination, and also due to the information given to us by the patients on the previous presence of a blister at that spots. The fact that bilateral pericoronitis is rare and rarely seen before 20 and after 40, helped to distinguish the diagnosis [15]. The patients from case 5, among other things, complained of gum pain. It is known that orthodontic appliances are prone to evoke gingivitis and although the patient wore fixed orthodontic braces, she said she had no previous problems with swollen or sore gums.

Since the clinical appearance of the oral mucosal lesions can be in different forms, which also depens on the time of occurrence, besides detail clinical evaluation and thorough medical/dental history is required.

Based on the prodromal symptoms, patient's complaints, clinical manifestation, type of the lesions at the day of the clinical examination and their development according to the patient's description, skin involvement (in case 1 and 2), the sudden onset, the positive drug histories associated with the occurrence of the lesions lead us to provisional diagnosis – erythema multiforme major and oral erythema multiforme.

Failure to diagnose oral erythema multiforme early in the course may result with deterioration in patient's condition.

Following and analyzing the recent updates in the treatment of erythema multiforme it can be concluded that it has not fixed pattern. The treatment will depend of the cause of the disease, involvement of mucosa or skin and whether there is an acute or chronic course.

For example, if the drug is found to be the cause, then it should be discontinued, or if erythema multiforme is associated with herpes simplex virus infection, should be treated with antiviral therapy.

Treatment for acute EM is focused on relieving symptoms with topical steroids or antihistamines as well as antiseptic or anesthetic solutions for mucosal involvement.

In our cases treatment was mainly with topical steroids, local antiseptics and analgesics, antihistamines and discontinuation of medication for which there was a reasonable suspicion that it was the causative agent. In one of the cases (case 4) we also used systemic steroids because the patient complained of appearance of new vesicles and due to the prolonged non-working days and the inability to examine the patient in those days. The dose of corticosteroids was adjusted according to the age and weight of the patient.

In two of the cases (case 4 and case 5) as adjuvant treatment we use and low level laser therapy to promote healing and pain relief. Accordingly, and Amanda de Paula Magallanes et al. [16] report a favorable result from the use of low-level laser therapy to treat oral erythema multiforme and it recommends as adjuvant to other treatment modalities due to its benefits such as easy application, non-invasiveness and no adverse effects.

Treatment for recurrent EM is most successful when tailored to individual patients [17].

As second-line treatment for patients with refractory and recurrent erythema multiforme are suggest immunosuppressive agents, antibiotics, anthelmintics, and antimalarials. Even so further research and more evidence to support these treatments are encouraged [13,17].

However, there has to be logical and individual approach to the treatment because is not methodized, and different drugs with very different mechanisms of action are used.

Conclusion

The sudden onset of oral EM and the need for rapid resolution of subjective oral dysfunctions and disability leaves little room for delay in diagnosis and treatment. Treatment of this complex disease could and should involve different approaches depend of its causative agent.

Also careful medication history can be very helpful in development of diagnosis and doctors who prescribe medication need to be more careful and review drug adverse reactions.

Erythema multiforme should be recognized, recorded and its causality identified in order to minimize the risk of its recurrence and optimize outcomes from therapy. Early diagnosis and early treatment is the key to prevent further complications and recurrences.

Further publication of numerous case reports may contribute to the development of clearer diagnostic criteria, etiology, proper treatment and easier distinction of various clinical subgroups in the spectrum of Erythema multiforme.

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