Stevens- Johnson syndrome: case presentation

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Erythema Multiforme (EM) is a rare mucocutaneous disease with a variety of clinical manifestations. EM it was recognized in the early 1800's, and still the etiology is unknown. It has been recently suggested erythema multiforme (EM) major and Stevens-Johnson Syndrome (SJS) could be separated as two distinct clinical disorders with similar mucosal erosions, but different patterns of cutaneous lesions. In particular SJS should be used for a syndrome characterized by mucous membrane erosions and widespread small blisters that appear on erythematous or purpuric maculae, which are different from classic targets. In SJS mouth, eyes, skin, genitalia and occasionally the esophagus and respiratory track may be affected. Oral lesions may cause severe pain and usually lips may become encrusted. Concerning ocular involvement, if there is conjunctivitis or uveitis this may lead to scarring and blindness. Also, the course of disease and the prognosis are in most cases severe.
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INTRODUCTION

Although the etiology of EM is still often obscure, several factors have been implicated as precipitating or triggering factors. Such factors are several drugs, viral or bacterial infections including herpes simplex virus, allergy.

Almost 25 to 50% of patients report oral manifestations of the disease.[3] Any area of the mouth may be involved, but most frequently lips, buccal mucosa, palate and tongue are involved. The oral manifestation include varying types of aphthous-type lesions to multiple, superficial, widespread ulcers. Rarely the initial presentation is short-lived vesicles or bullae. The treatment is symptomatic.

The case presented in this report concerned a 10-year-old Caucasian boy, attended the Ag. Sofia Hospital, Athens. The initiation of the lesions was acute and the first diagnosis by the pediatrician was a childhood disease. However the condition of the boy aggravated and the next day the boy was hastily transferred to the hospital. The family medical history was clear.

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In the medical history of the boy were referred variola, parotitis, a lot of asthma bronchitis episodes, and allergic purpura. The boy has skin, oral and perioral lesions. There was also genital and eyes involvement. The diagnosis was that the boy suffers from severe SJS.

Erythema multiforme is a rare mucocutaneous disease of unknown etiology, with many different manifestations. EM is a vesiculobullous disease, but vesicles and bullae usually are present for only a limited time.[1-4,7,8] It was recognized in the early 1800s, but until now the etiology is unclear.[1-6,9] According to some evidence the disease may be related to antigen antibody complexes that are targeted for small vessels of the upper dermis or submucosa. In most cases precipitating or triggering factors can be identified.[3,4,6,11,12]

The disease occurs primarily in young adults usually men.[2,3] The onset is sudden and runs a course of 2-6 weeks with common recurrences occurring almost one to five times annually.[2,4,12] Patients may often develop EM recurrences seasonally, in spring or fall.[3] It is a self-limited disease that affects either the skin or mucous membranes or both. The term erythema multiforme (EM) represents the multiple clinical appearance of the cutaneous lesions.[3,11] The typical skin lesion of EM is the target or iris lesion that consists of concentric of erythematous rings separated by rings of color similar to the skin natural color. The skin in the center of the lesions may be erythematous or tanned. The extremities are usually affected, in a symmetric distribution. The other types of skin lesions include: papules, vesicles, bullae and urticarial plaques.[3]

Almost 25 to 50% of patients report oral manifestations of the disease.[3] Any area of the mouth may be involved, but most frequently lips, buccal mucosa,

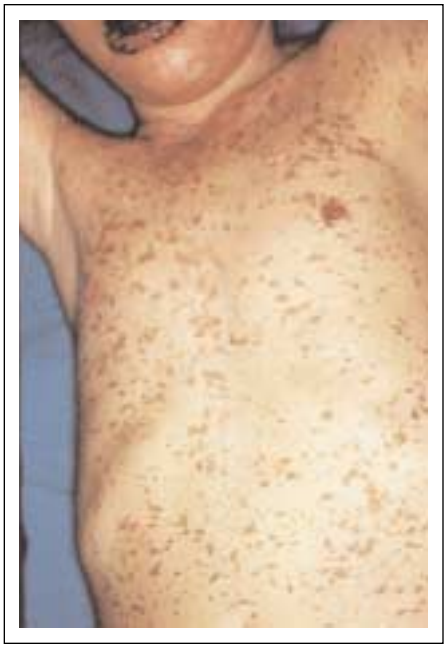

Figure 1. Skin lesions on the upper part of the body.

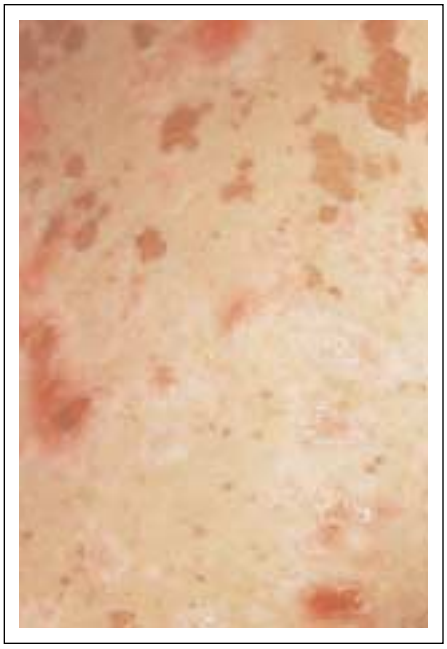

Figure 2. "Target" or "iris" lesions appearance.

palate and tongue are involved. The oral manifestation include varying types of aphthous-type lesions to multiple, superficial, widespread ulcers. Rarely, the initial presentation is short-lived vesicles or bullae.[3] Recurrent oral lesions may appear with the same or less severity of the initial lesions.[3] Symptoms range from mild discomfort to severe pain. It is also possible to occur systematic signs and symptoms such as headache, slightly elevated temperature and lymphadenopathy.[3,12]

As it has been recently suggested erythema multiforme (EM) major and Stevens-Johnson Syndrome (SJS) could be separated as two distinct clinical disorders with similar mucosal erosions, but different patterns of coetaneous lesions.[1] In particular SJS should be used for a syndrome characterized by mucous membrane, erosions and widespread small blisters that appear on erythematous or purpuric maculae, which are different from classic targets.[1] In SJS mouth, eyes, skin, genitalia and occasionally the esophagus and respiratory track may be affected. Oral lesions may cause severe pain and usually lips may become encrusted.[3] Concerning ocular involvement, if there is conjunctivitis or uveitis this may lead to scarring and blindness. Also systemic signs and symptoms may be more severe and the dermal lesions may be more extensive.[3]

CASE PRESENTATION

The case presented in this report concerned a 10-year-old Caucasian boy, attended to the Ag. Sofia Hospital Athens. The initiation of the lesions was acute and the first diagnosis by the pediatrician was a childhood disease.

The condition of the boy aggravated and the next day the boy was hastily transferred to Agia Sofia Pediatric Hospital. The family medical history was clear. In the medical history of the boy were referred variola, parotitis, a lot of asthma bronchitis episodes, and allergic purpura. The dental history was clear.

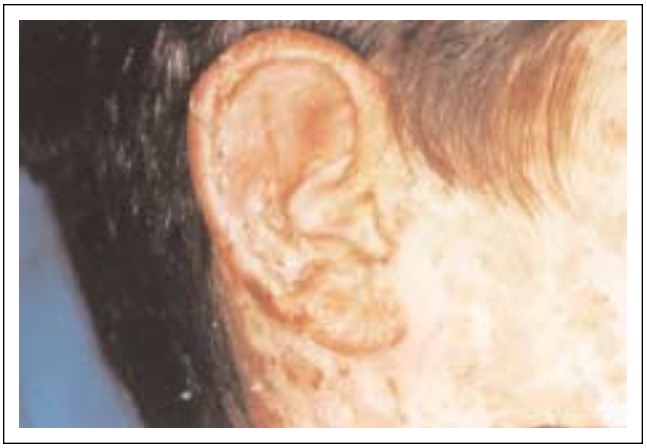

Figure 3. Typical cutaneous lesions on the ear.

When the boy came to the hospital, he had a high temperature, submandibulary lymph nodes of the neck, headache and the typical cutaneous lesions of EM all over his body. In particular there were typical skin lesions all over the upper part of the body, on the upper portion of chest, the extensor and flexor aspects of the arms. (Figure 1) The skin lesions were symmetrical. Initially the appeared as erythematous papules, but finally they had the typical "target" or "iris" appearance, with the erythematous periphery and central zone of necrosis. Bullae and vesicles were also seen (Figure 2). The ears were bilaterally affected as well (Figure 3). Lesions on

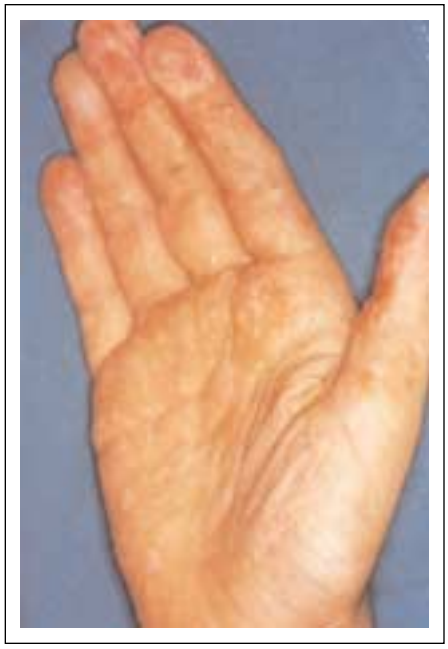

Figure 4. "Targets" lesions on the hands.

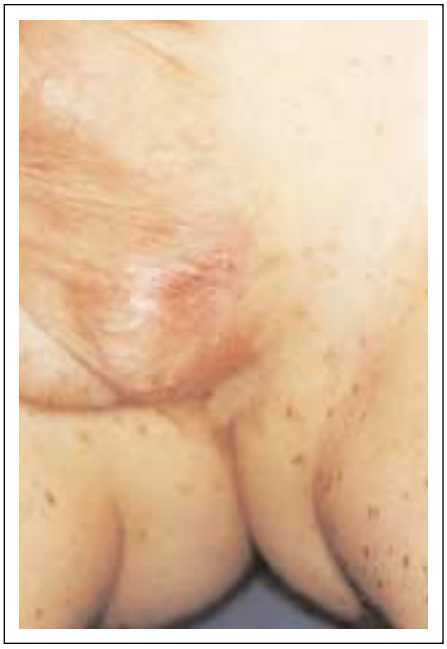

Figure 5. Genital involvement.

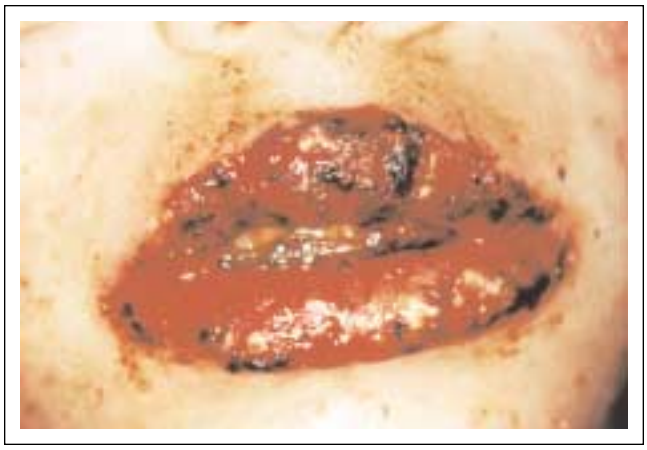

Figure 6. Extensive ulcerative lesions involving the upper and lower lips.

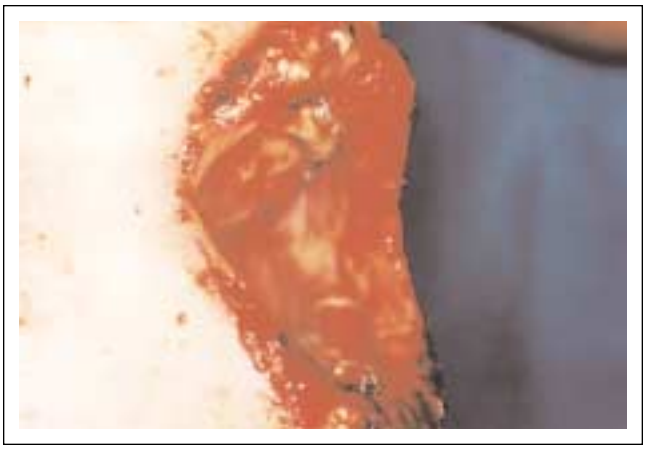

Figure 7. Irregular erosions covered with pseudomembranes had appeared in the hard palate.

the dorsal surfaces of the hands, palms, foots and plantar, could also been detected (Figure 4). In addition to cutaneous and oral mucosa lesions the boy also had genital involvement (Figure 5). The boy had also symptoms from the eyes and mainly photophopia so serious that he could suffer even the daily light inside the room.

The perioral lesions included crusted erosions and ulcers on the upper and lower lips (Figure 6). Intraorally the observed extensive lesions, were erosions and irregular ulcers covered by white or yellow pseudomembranes and surrounded by erythematous area (Figure 7). The lesions were scattered in the entire oral mucosa, but mainly in the buccal mucosa and the tongue and some of them were covered with exudate (Figure 8). The involvement of the oral cavity cause

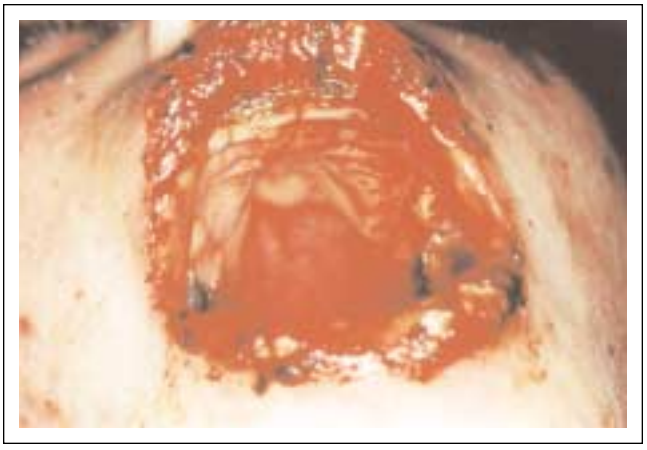

Figure 8. Erosions of the buccal mucosa.

severe pain and extreme discomfort that prevented food and liquid intake. The condition was even worse due to the fact that the boy was under orthodontic treatment and the braces irritating the oral lesions. Of course the braces were removed immediately.

The diagnosis was that the boy suffers from severe SJS. It was impossible to find any triggering factor. No association with herpes simplex or any other infection was identified.

Treatment included systemic corticosteroids Solumedrol, and antibiotics clindamicin Dalacin. After 10 days the condition was improved. Since the boy recovered and left the hospital we did not have further information concerning recurrences or other health problems.

DISCUSSION

There is a little confusion concerning the terminology used for the disease. A recent attempt to clear the terminology has proposed five categories: 1) bullous erythema multiforme when less than 10% total body surface area (TBSA) present typical or atypical target lesions, 2) Stevens Johnson Syndrome (SJS) when less than 10% TBSA blisters plus widespread erythematous or purpuric macules or flat atypical targets are present, 3) overlap SJS-Toxic epidermal necrolysis (TEN) 10% to 30% TBSA blisters plus widespred purpuric macules or flat atypical targets, 4) TEN with spots, greater than 30% TBSA blistres plus widespread purpuric macules or flat atypical targets, 5) TEN without spots, greater than 10% TBSA blisters in large epidermal sheets without any purpuric macules or targets.[9,10,13]

The pathogenesis of the disease is unknown and can be characterized as an enigma.[3,6,7,12] There is some proof that it might relate to hypersensitivity reaction to an antigen antibody complexes that are targeted for small vessels of the upper dermis or submucosa.[3,4,6-12,15] According to the most recent bibliography cutaneous T cells play the main role in this immunologic reaction, but there is also another suggestion that proteins may induce that promote apoptosis in keratinocytes such as FAS antigen (CD95).[9] Also, it has been reported an increased frequency of some HLA such as, HLA-B15(B62), HLA-B35, HLA-A33, HLA-DR53, HLA-DQB10301, antigens in patients with erythema multiforme.[16] There are a lot of precipitating or triggering factors such as infections (due to HSV types I and II), drugs, allergy to food stuffs, malignancy, vaccination, autoimmune disease, alcoholism, acute emotional stress, depression and radiotherapy, that might have a complex interaction.[3,4,6-27] The most commonly implicated drugs are anticonvulsants (diphenhydantoin, carbamazepine,) barbiturates, sulfonamides (mainly sulfmethoxazole), phenylbutazone, digitals, gold salts, hydralzine, iodes, mercurials, antibiotics such as cephalosporins and penicillins, nonsteroidal anti-inflamatory drugs, birth control pills and allopurinol.[7,9,13,19,22,24] We implicate any drug that has been taken within the last 7-21 days. Any drug that has been taken for less that 7 days or more than 2months, is unusual to be involved in the pathogenesis of the disease.[9] The reaction is neither related with the drug dose, nor the mortality.[9] Some diseases have also been associated with EM such as Crohn's disease, ulcerative colitis, leiomyooma, and many infectious diseases.[7]

The most common age at onset of the disease is reported to be the second or third decade and the most common sites affected by the initial attack were the skin or both the skin and oral mucosa.[3,4] In a small number of cases the other mucous membranes as genitals and eyes are also involved as in our case.[3,4] In the recurrences that followed the initial attack most patients had a combination of cutaneous, oral and genital lesions.[4] The incidence and duration of the attacks ranges between 1 to 3 attacks yearly and 1 to 3 weeks respectively.[4] There is a wide individuality concerning the duration of attacks, recurrence time, and pain occurred among patients.[7]

The typical appearance of the skin lesions is the "target" or "iris" that consists of concentric of erythematous rings separated by rings of near- normal color. The skin in the center of the lesions may be erythematous or tanned. In some cases the skin lesions have appeared such as raised atypical targets, flat atypical targets, or purpuric maculae with or without blusters.[1] Usually the extremes are affected, in a symmetric distribution. The other types of skin lesions include merciless, papules, vesicles, bullae and urticarial plaques.[3,4,12]

The severity of mucous membranes involvement is the base for the classification of the disease to EM minor and major. In minor EM usually only the mouth is affected, but in the major EM multiple mucous membranes are involved.[4] Sometimes even if the initial attack is EM minor, the following attacks might be presented as EM major. So both types of EM may occur in the same patient, so the value of clinical distinguishing between the two types could be questioned.[4] The reported incidence of mucosal involvement varies widely. Some authors reported that 25% of the patients had both skin lesions and oral lesions without other mucous involvement on the contrary some other reported that 65% of the patients with skin involvement had lesions in the mouth and 35% also had genital lesions.[4] When referring to patients with primary oral lesions the incidence of skin lesions ranges between 25 and 33%.[4] Also some authors reported the more mucosal sites were involved in drug-related than in herpes-related cases.[1,9] The more extensive the blisters the higher the morbidity and mortality.[9] Even if the intraoral lesions are present there are a lot of different opinions among the researchers concerning the incidence of lips involvement.[4,24]

The incidence of the intraoral lesions according to current bibliography ranged as follows. The entire oral mucosa is affected in 43.8% of the referred cases 9.4% the lips were also involved. The most common sites

involved in the oral cavity is the buccal mucosa, the tongue and labial mucosa. The least commonly affected sites were the floor of the mouth hard and soft palate and gingiva. The discomfort caused by the oral mucosal ulceration could be so severe that the patient might become dehydrated.[4,24]

The ocular symptoms may vary widely. Since the ocular surface epithelium is affected it could be possible to occur conjunctival shrinkage and symblepharon formation, and corneal vascularization, opacity and reduction of vision as well, in both pemphigoid and Stevens-Johnson Syndrome. Some severe cases may result in complete dryness of tears.[5]

The diagnosis of the disease is really a challenge for the clinician. Mainly it is based on clinical criteria and the natural history of the patient.[1,2,6-11] The lesions are symmetrical and initially comprise erythematous papules, but later develop into typical 'target' or 'iris' lesions with the erythematous periphery and central zone of necrosis. Bullae and vesicles may also be seen. If the cutaneous lesions are absent it might be difficult to put the diagnosis although the related history should help confirm the diagnosis.[1,2,6-11] The severity of the symptoms may affect not only the ability of food intake, but the ability of speech or work as well and in some cases the disease might be life- threatening.[1,2,4,6,7,9] The severity of the disease and consequently the mortality is associated with increasing age, the involvement of other organs (renal, hepatic) and neutropenia.[9,27] However the diagnosis based on clinical criteria it is important be confirmed by biopsy when it is possible.[17]

Although irregular epithelial hyperplasia might appeared in some patients histopathology of the disease is not typical.[7] Also damage or edema within the papillary dermis could be observed on the epidermis, and subepidermal blisters.[1,2,6,-7,9,11,14,28] Some authors have reported the EM involves the blood vessels of the superficial plexus, lymphocytes, histkiocytes, erythrosytes, emerges into papillary dermis. The damage into epidermis is reflected by the detection of necrotic keratinocytes, mild spongiosisans basal layer vacuolar alteration. Others have observed complete detachment of the entire dermoepidermal junction, including the hemidesmosomes, basal lamina, and anchoting fibrils. However some authors reported little or no changes in the epithelium.[11,29] Vascular changes were also observed.[11]

In the differential diagnosis conditions such as aphthous ulceration, primary herpetic stomatitis, pemphigus and pemphigoid, allergy, lichen planus, Behcet's syndrome.[1,2,4,6,12-14] Minor aphthous ulceration have a different location and they do not form a confluent area of ulceration and major aphthous ulceration have longer duration and result in scarring.[4] Primary herpetic stomatitis, is not recurrent and typically the gingival and hard palate are involved.[4,6] Some studies report that there is a clear implication between HSV infection and the onset of EM. According to recent studies the HSV may be considered as a precipitating factor and is possible to play a role in the pathogenesis of EM as well.[4,6,25] Pemphigus and pemphigoid may also cause extensive ulceration, but the cutaneous lesions are absent and the characteristic bound autoantibodies put the diagnosis.[4]

The EM is a self-limited disease, so treatment must be supportive.[6,9] Generally the drug dosage, the duration of treatment and side effects vary widely among patients and depend on the severity of the case.[4,6,7,11,13,17] First, recently taken drugs must be discontinued and we must not use any other members of the same drug family.[9] In life threatening conditions patients might need intensive care.[9] The treatment usually includes systemic corticosteroids, but according to some studies could be associated with increased incidence of recurrences and chronicity, topical anesthetics, analgesics and antibiotics i.e. cyclosporine, cyclophosphamide, in order to prevent secondary infection as well and hyperbaric oxygen.[4,6,9] Monthly injections of human immunoglobulin, asyclovir, anti-malaria drugs, azathioprine, are some of the drugs that are referred to be used either with successful results or in some cases with side effects.[4] Treatment for the oral symptoms could only relieve them and include unaesthetic ointments and solutions such as lidocaine, xylokaine, 0.15% benzydmine hydrochloride and 0,2% chlorhexidine gluconate mouthwash.[4,6] In cases of dehydratation the treatment must include hydratation and nutritional supplementation i.e. electrolytes.[6,9]

Diagnosis and proper treatment of the disease is of a major importance because mistreatment of the patient could be possible, due to the variation of clinical manifestations.[7] It is important to notice that no one could predict the onset of the disease nor prevent it through careful use of the drugs.[9] Although the disease demand a total team approach the potential of diagnostic accuracy is very important for the dentist, because usually the oral signs and symptoms of EM are the only manifestations of the disease.[9] Since in some cases EM might be life-threatening for the patient the early diagnosis of erythema multiforme could be crucial for the life of the patient.

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