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Title: An unusual presentation of Erythema Multiforme in a paediatric patient.

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Abstract:

Background

Erythema multiforme (EM) is an acute, vesiculobullous disease of skin and mucous membranes with symptoms ranging from mild to severe. A complex interaction of different factors has been implicated to cause the condition; majority with a preceding herpes simplex infection. This report describes an unusual presentation of erythema multiforme affecting the lips and oral mucosa of a healthy 7-year-old boy in the form of lip adherence.

Case report

Two weeks following eruption of oral ulcerations, a 7-year-old healthy boy patient developed severe erosive ulceration of both lips, causing complete lip adherence. This was accompanied by marked bilateral submandibular and cervical lymphadenopathy, tremor and sweating. Clinical and laboratory investigations led to a diagnosis of erythema multiforme. The patient was treated initially with gentle application of Vaseline between the lips using cotton buds in an attempt to release lip adhesion, followed by surgical release of the lips under general anaesthesia. Analgesics and topical steroid mouthwash were provided.

Follow-up

Seven months later, the patient presented with a flare up of his EM which included target lesions on the skin. Patient was treated with antivirals, topical and systematic steroids to supress the recurrent attacks of EM. Eighteen months following initial presentation the patient and parent reported considerable decrease in the frequency, severity and duration of the occurrence of intra-oral ulcers with no major episode of target lesions on the skin.

Conclusion

Erythema multiforme is rare in children, however should be considered in the differential diagnosis of recurrent erosive oral ulcerative lesions especially when the oral lesions resemble those of primary herpetic gingivostomatitis.

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Background

Erythema multiforme (EM) is an acute, vesiculobullous disease of skin and mucous membranes described first by Hebra in 1866 [Léauté-Labrèze et al., 2000; Ayangco et al., 2001]. The condition predominately affects young adults with an incidence of approximately 0.01%–1% per year and a peak age of 20–40 year [Jawetz et al 2007]. However, 20% of the cases occur in children with a higher incidence in males compared to females [Atzori et al., 2003; Field and Longman, 2003; Jawetz et al., 2007; Scully and Bagan, 2008]. EM can be precipitated by range of factors; the most of which is with a preceding herpes simplex infection. Other important stimulating factors include infections, drugs (such as sulphonamides, cephalosporins and anticonvulsants), neoplastic and autoimmune diseases. Yet, less than half of EM cases occur without a trigger [Atzori et al., 2003; Field and Longman, 2003].

Depending on the clinical presentation of the condition, EM is classified into EM minor, EM major and Stevens–Johnson syndrome. In the minor form, the symptoms are usually mild, self-limiting and mainly confined to the oral cavity whereas in EM major, the clinical picture is more severe and involves at least two different mucosal sites including the oral mucosa. Stevens–Johnson syndrome is a more progressive, fulminating, severe variant of EM that is characterised by widespread lesions involving the skin and other mucous membranes such as the oral cavity, eyes, pharynx, larynx, oesophagus, and genitals. The condition is potentially life-threatening and in some cases is associated with flu-like symptoms, fever, sore throat, headache, arthralgias, myalgias, pneumonia, nephritis, or myocarditis condition [Al-Johani et al., 2007; Scully and Bagan, 2008].

The characteristic appearance of EM includes symmetrically distributed skin lesions located predominantly on the exterior skin of the extremities and less frequently on the palms and soles, with a tendency to reoccur usually in a time period ranging from few weeks to almost a year [Léauté-Labrèze et al., 2000]. The classic skin presentation is that of target or iris-like lesions defined as “ individual lesions less than 3 cm diameter with a regular round shape, a well-defined border, and two concentric palpable oedematous rings, paler than the centre disc ” [Scully and Bagan, 2008].

Oral mucosa is involved in 70% of the cases, characteristically affecting the lips (especially the lower lip). Intraoral lesions typically appear on the non-keratinised mucosa and mostly seen in the anterior parts of the mouth. Lips tend to swell, crack, bleed and crust.

Lachrimation and photophobia can be observed in patients presented with EM involving the ocular area, whereas genital lesions (if present) are usually painful and may result in urinary retention [Ayangco et al., 2001; Field and Longman, 2003; Scully and Bagan, 2008].

The initial diagnosis of EM is entirely clinical as there are no specific diagnostic tests for EM. Perilesional tissue biopsy is usually performed to support the diagnosis of EM which usually has a non-specific histological appearance with degenerative changes in the epithelium and subepithelial bulla formation. Immunofluorescence studies are needed to exclude other immunobullous diseases such as pemphigus and pemphigoid [Field and Longman, 2003; Scully and Bagan, 2008].

Depending on the severity of the condition, EM is treated using local and/or systematic steroids. Long-term prophylactic acyclovir is required in patients with recurrent episodes of EM. In severe forms, hospital admission is required particularly if the patient become dehydrated [Field and Longman, 2003].

The aim of this report is to describe an unusual presentation of erythema multiforme affecting the lips and oral mucosa of a healthy 7-year-old boy and resulting in adherence of the lips.

Case report

History and examination:

A 7-year-old boy was urgently referred to the paediatric department at the Leeds Dental Institute (LDI) by his general dental practitioner for evaluation and treatment of painful oral ulceration that resulted in adhesion of the lips preventing the child from opening his mouth.

On examination (Figure 1), the patient presented with severe erosive ulceration of both lips causing lip adherence. The erosive lesions were yellow-grey in colour with erythematous borders. The patient reported experiencing oral ulcerations two to three weeks prior to his examination. Ulcers affecting the lips appeared five days earlier, and resulted in adherence of the lips the day before. The patient was unable to eat or drink for the last 20 hours; however, was responsive, oriented in time, place and person and showed no signs of dehydration.

There were no extra-oral lesions however the patient had marked bilateral submandibular and cervical lymphadenopathy.

The patient had a history of recurrent severe oral ulceration affecting the mouth and lips, occurring 5-6 times over the past 18 months. There was no pattern of recurrence associated with these ulcers. Erosive ulcers appeared mainly on the lips, eyes and nose over a course of 2-3 weeks at a time. These ulcers were accompanied by tremor and sweating with no development of pyrexia. In addition, the patient reported recurrent cold sores which previously preceded the oral ulceration on some occasions. The patient was otherwise healthy with no relevant past medical history.

Management:

Initial management:

The initial management involved gentle application of Vaseline (petroleum gel) between the lips using cotton buds in an attempt to release lip adhesion. This technique helped release most of the adherent lesions except for a small (~1cm) area on the right side (Figure 1) allowing the patient to eat and drink. After discussing the case with maxillofacial colleagues, the patient was allowed to go home that evening with a review appointment with one of the maxillofacial surgeons the next morning. The patient was prescribed Difflam mouth rinse, (Benzydamine hydrochloride), chlorhexidine 0.2% mouthwash and advised to keep applying Vaseline on the lips to prevent recurrent adhesion.

Further management and investigations:

Unfortunately, the patient presented the next morning with fused lips despite using Difflam and Vaseline. The patient was, therefore, admitted under the maxillofacial department for intravenous (I.V) fluids, surgical release of his lips, incisional biopsy and blood tests under general anaesthesia.

The biopsy showed non-specific ulceration with neither intraepithelial sub-basal clefting nor dysplastic features. Direct immunofluorescence revealed negative autoantibodies (IgG, IgA, IgM, C3c and fibrinogen) and no abnormalities were detected in the haematological investigations (negative antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) screen).

A diagnosis of erythema multiforme was, therefore, made and the patient was prescribed betamethasone (betnesol) mouthwash 0.5 mg four times a day for two weeks.

Review and follow-up:

One week later, the symptoms had subsided considerably, however, the patient presented with ulcerations associated with pseudomembranous slough on the lower lip, posterior surface of the tongue, and the mucosal surface of both right and left sides of the oral commissures.

The lesions completely healed three weeks later and therefore, it was decided to keep the patient under observation. Should the lesions recur, the patient was instructed to use a 3-4 days course of prednisolone with a starting dose of 15 mg.

Seven months later, the patient had a flare up of his EM that included extra-oral lesions (Figure 2 a-f). Ulcers appeared on the lips and eyes accompanied by target lesions on the skin. Mild cervical lymphadenopathy and facial swelling were noted as well. The patient was prescribed systemic prednisolone and topical steroid mouthwash. In addition, the patient was prescribed oral acyclovir as prophylactic measure to supress the recurrent attacks of EM.

Eighteen months follow up appointment revealed the presence of an intra-oral ulcer on the left mucosa of the lower lip which had been present for the last two days (Figure 3 a-h). No other intra-oral lesions were identified. Mildly enlarged tonsils were noticed which was not associated with any pyrexia or lymphadenopathy. The patient reported experiencing intra-oral ulcers approximately every 4 months in the last 12 months with no major episode of target skin lesions. Each episode of intra-oral ulceration lasted for about 3 days before healing. These lesions mostly affected the lower lip mucosa, cheeks and palate.

The patient was advised to use prednisolone and chlorhexidine 0.2% mouthwash at flare ups of intra-oral ulcers. He was also advised to start systemic steroid in the case of significant progression of oral ulcers, recurrence of target lesions on the body and should the patient feel unwell.

Discussion

Erythema multiforme is an acute, self-limiting, mucocutaneous disorder, with many patients experiencing more than one attack [Schofield et al., 1993] and where the main cause remains unknown. However, it is believed that a complex interaction of different factors has to play a role in the initiation of the signs and symptoms of the condition. Recurrent herpes simplex virus infection is considered to be the most common cause of recurrent EM [Ayangco et al., 2001].

Although the initial diagnosis of EM is based entirely on the clinical presentation of the condition, the diagnosis can be challenging particularly when there are no extra-oral lesions [Ayangco et al., 2001]. These patients can present with many variable features which can mimic other conditions; therefore, a biopsy of the oral lesions and immunofluorescence studies must be carried out to exclude other potential conditions. The differential diagnosis of early erythema multiforme includes pemphigus and pemphigoid, ulcerative conditions such as primary herpetic gingivostomatitis, drug eruption, Behçets disease, urticaria, and other hypersensitivity reactions [Lamoreux et al., 2006].

The oral mucosal ulcerations of primary herpetic gingivostomatitis are often similar to those of EM [Farthing et al., 1995]. However, ulcerative lesions of primary herpetic gingivostomatitis usually affect the gingiva and hard palate, and do not tend to reoccur [Farthing et al., 1995].

Pemphigus and pemphigoid are a group of immunobullous disorders that are characterised by widespread formation of bullae on the skin and mucous membranes. Where skin lesions are absent, extensive oral ulceration can be confused with EM [Farthing et al., 1995]. In the case presented, vesicles or bullae did not precede the lesions; therefore, a diagnosis of pemphigus or pemphigoid was unlikely. In addition, ANA and ANCA screens were negative for autoantibodies such as IgG and C3 present in patients affected by pemphigus and pemphigoid.

Urticaria is another differential diagnosis of EM especially at the onset of eruption of the lesions [Lamoreux et al., 2006]. In EM, the characteristic skin lesions tend to last at least one week whereas urticarial lesions present usually in patients for less than 24 hours.

The patient presented here suffered recurrent severe oral ulcerations affecting the lips with subsequent development of target lesions on the skin. Investigations including biopsy of the oral mucosa and direct immunofluorescence were negative for other potential conditions.

It has been cited in the literature that the involvement of the lips is a strong indication of the diagnosis of EM and the presence of target lesion of the skin is almost a pathognomonic feature for the diagnosis of EM (Steven's Johnson Syndrome) [Ayangco et al., 2001; Field and Longman, 2003; Scully and Bagan, 2008].

This case also shows an unusual presentation of erythema multiforme in a child, which resulted in complete adherence of the lips requiring surgical intervention. Management of erythema multiforme is largely dependent on the severity of the condition [Farthing et al., 1995; Ayangco et al., 2001; Lamoreux et al., 2006].

The presence of an inducing factor should be investigated when possible with suspected infectious diseases treated in the first instance and causal drugs withdrawn.

Several reports have shown that recurrent EM attacks can be suppressed effectively by oral acyclovir even if herpes simplex virus (HSV) is not an obvious triggering factor [Schofield et al., 1993; Ayangco et al., 2001; Habif, 2004]. HSV DNA has been detected using the polymerase chain reaction in the cutaneous lesions of EM patients with clinically non-HSV-associated disease emphasising the primary role of HSV reactivation in the initiation of EM signs and symptoms [Brice et al., 1989; Darregh et al., 1991]. However, it should be noted that not all episodes of EM are precipitated by HSV infection, and not all HSV infection precipitates EM in individual patients.

This patient reported a history of recurrent cold sores that might precede an EM attack but did not always lead to EM. Therefore, it was suggested that the patient`s recurrent episodes of EM were mainly secondary to HSV reactivation.

Symptomatic treatment including systemic or topical analgesics, soothing mouth rinses and antibiotic treatment for secondary infection should be provided to patients presenting with mild variants of EM. On the other hand, hospitalisation is required for those with more severe forms, particularly when the skin or oral lesions are severely affected or when the eyes are involved. There is no sufficient evidence in the literature to support the use of systematic steroids in mild forms of the disease; however, systemic steroids could be beneficial in the severe cases of the condition to prevent further progression of the disease [Ayangco et al., 2001].

This case has been managed initially by releasing the lip adherence by gentle application of Vaseline using cotton buds on the day of the patient presentation followed by surgical release of fused lips under general anaesthesia.

Benzydamine hydrochloride, chlorhexidine mouthwash and a topical steroid rinse were initially prescribed. Whereas the final management involved local and systemic steroids due to the recurrent existence of severe ulceration on the lips, mouth and skin. Acyclovir was also added to the regimen as a prophylactic measure in order to suppress any likely future EM attacks. The patient showed good response to the above treatment regime and is currently under regular review.

Conclusion

Erythema multiforme is rare in children, however; should be considered in the differential diagnosis of recurrent erosive oral ulcerative lesions especially when the oral lesions resemble those of primary herpetic gingivostomatitis. Referral to an oral medicine or maxillofacial department is crucial for the investigation and management of these cases.

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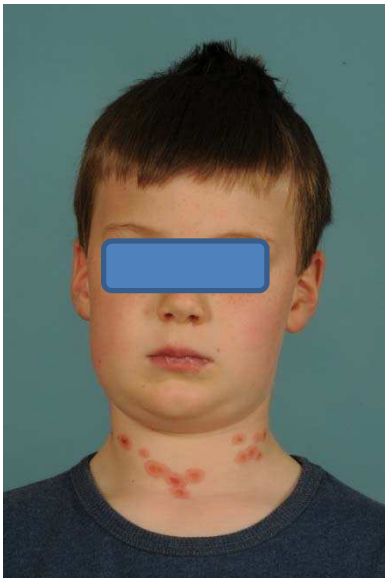
Figures:

Figure 1: Photograph showing ulcerated fused upper and lower lips after releasing the adherence using a cotton bud covered with Vaseline.



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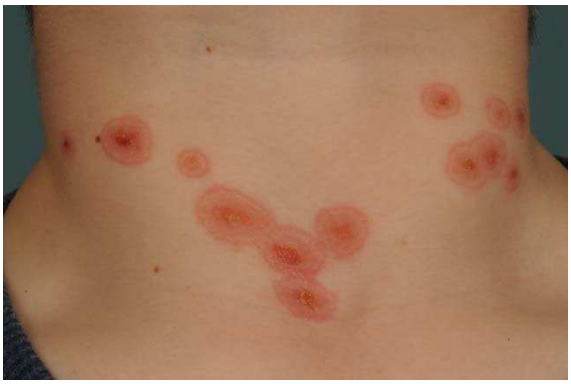

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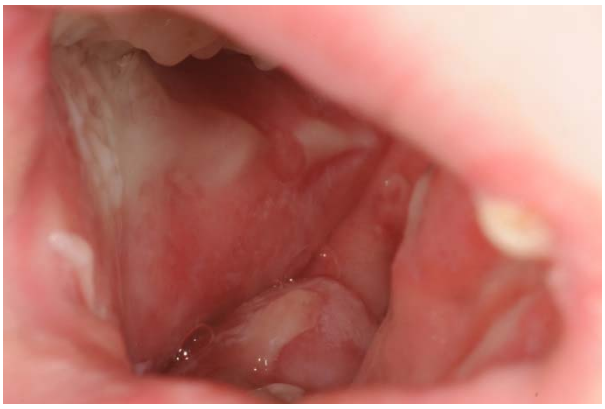

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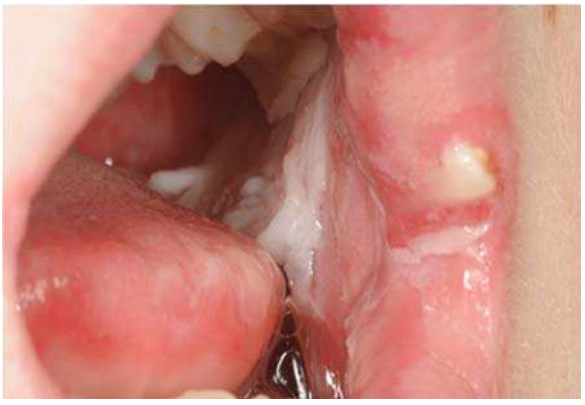

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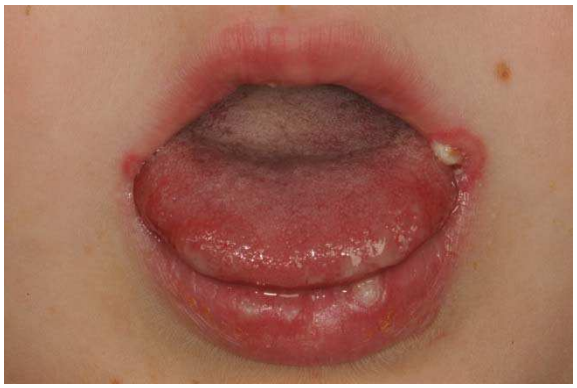

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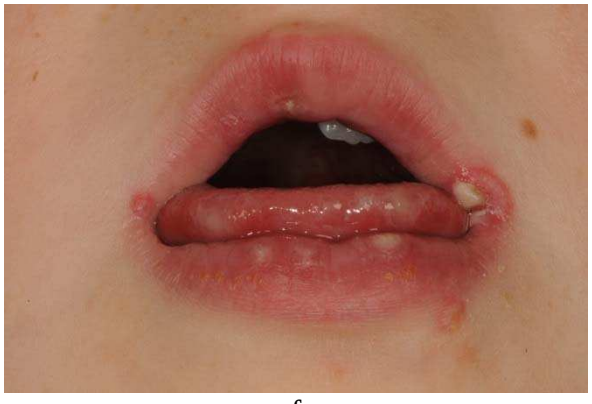

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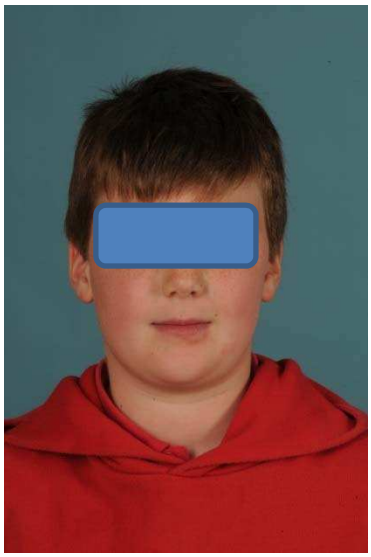
Figure 2: Photographs showing intra- and extra-oral lesions 7 months following initial presentation with (a, b) target lesions on the skin of the neck, (c,d) white plaques with a spongy, corrugated surface affecting the buccal mucosa on both sides, (e,f) grey-yellow ulceration of the lips with erythematous borders involving the vermillion border, left commissure of the mouth and the skin peri-orally (e also shows ulceration of the anterior region of the tongue mostly affecting the dorsal surface).



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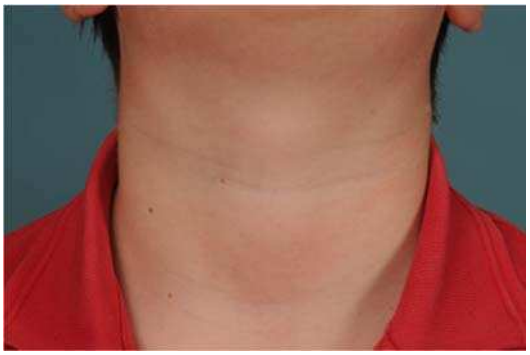

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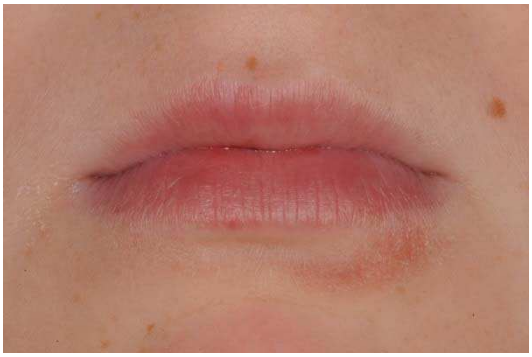

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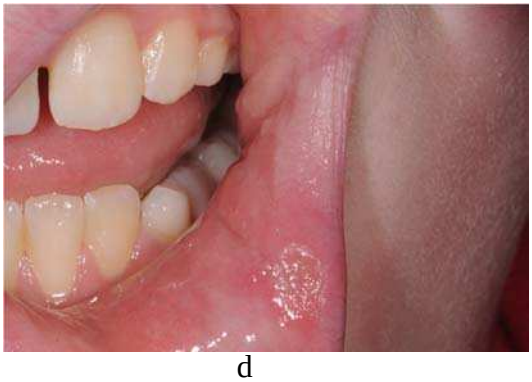

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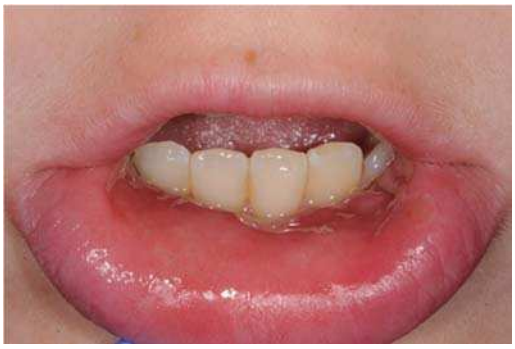

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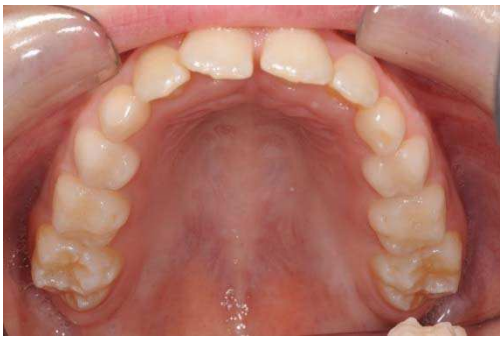

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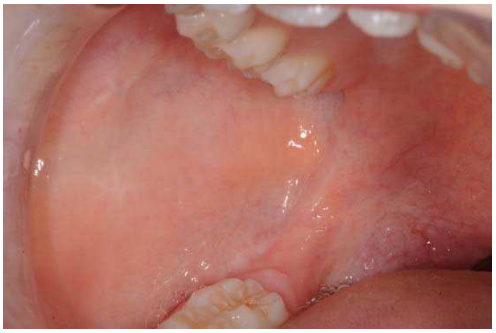

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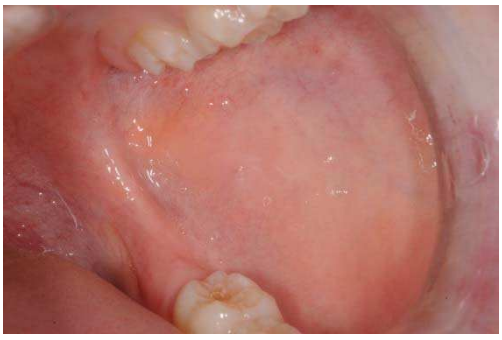

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Figure 3: Photographs at 18 months follow-up appointment showing (a, b) healing of the extra- oral skin lesions, (c,d,e) healing of most of the lip lesions and a 2-3 mm intra-oral ulcer on the mucosa of lower lip, (f,g,h) healing of intra-oral soft tissue lesions on the lips and buccal mucosa.