

## Is it herpes or aphthae lesions?

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### ABSTRACT

Recurrent intraoral herpetic (RIH) and recurrent aphthous stomatitis (RAS) are common oral disorders and these diagnosis are often mistaken for one another. The confusion associated with developing an accurate diagnosis is somewhat understandable since these two very different lesions share some common characteristics. Misdiagnosis may result in effective treatment, thereby worsening the lesion. We reported 4 cases to evaluate these similarities and differences, includes the patients history, information regarding initiating factors, frequency of lesions, relieving factors, aggravating factors, the physical examination, and the results of any indicated tests, which are important data to the diagnostic process of these two lesions. By considering these data, an accurate diagnosis of theses two common oral disorders can be developed. It's concluded that RIH and RAS have some similarities and differences, which are very important to developing an accurate diagnosis and the treatment plan, therefore the dental and oral health professional must be knowledgeable in defferentiating between RIH and RAS.

**Key words:** Recurrent intraoral herpetic, recurrent aphthous stomatitis, diagnosis

### INTRODUCTION

The success of oral soft tissue abnormality management relates to an accurate diagnosis. The presence of various signs and symptoms often become a problem in the diagnosis making process.<sup>1</sup> Recurrent intraoral herpes (RIH) and recurrent aphtous stomatitis (RAS) is a frequent abnormal finding in the oral cavity.<sup>2-4</sup> There are often difficulties in making the diagnosis for the two abnormalities since the two different lesions have several similar characteristics.<sup>3,5</sup> An accurate diagnosis for RIH and RAS is very important in deciding on the treatment plan because the treatment approach used for the two lessions is very different. The mistake in making the

diagnosis will lead to ineffective treatment and worsen the lesion,<sup>5</sup> e.g. treating RIH with topical steroid (which is appropriate for RAS) may cause more severe abnormality.<sup>3</sup>

The high prevalence and lesions that are often painful and disturbing become the patients' reason to seek for treatment to the dentist. Therefore, the oral and dental practitioners should be able to differentiate the two abnormalities. We have tried to discuss the difference of RIH and RAS in several cases in the Oral Medicine Clinic of Cipto Mangunkusumo Public Central Hospital. It is expected that the results of this discussion will provide information for practitioners in the oral and dental field in making appropriate diagnosis and choose the appropriate management.

## CASE REPORTS

### Case 1

A 35-year-old male, 55 kilograms weight and 167 cm tall, complained of small ulcers that initially occurred on the tongue end since a week before. The ulcers were painful that the patient had a difficulty to eat and drink and had been difficult to talk since the night before. Around 2 months ago, this patient visited a GP because he experienced fever and similar oral ulcers and the GP gave him mefenamic acid and ciprofloxacin for 3 days. About one month ago, this patient visited the ENT doctor who told him that he experienced tonsillitis and oral fungus. He was given 3 kinds of medicine (including antibiotics) but the ulcers did not go away. The patient then visited an oral surgery dentist who said that his complaint was originated from stress and this dentist did not give him any medicine. The patient then bought Betadine mouth wash and albothyl but there was no improvement on the ulcers. Before this, patient rarely experiences oral ulcers and has never experienced severe oral ulcers. He also denied a familial oral ulcer history. This patient has a chronic gastritis that is rarely symptomatic. Starting one month ago, the patient felt that he was very tired, did not have enough to eat and did not sleep well. He also experienced stress because he has to pay hospital bill for his wife, whom he married 3 months ago, who was admitted to the hospital due to typhoid. The general condition was good, no extra oral lesion. The intra oral examination showed several whitish and shallow ulcers that was surrounded by erythema. The shape was oval and irregular with a diameter of 1-5 mm. The ulcers were found in the labial mucosa (Fig. 1a and b), ventral and lateral areas of the tongue (Fig. 1c and d), buccal mucosa (Fig. 1e and f). The oral hygiene was bad. Based on the subjective and objective examinations, a diagnosis of RIH suspect compared to herpetiformis RAS was made. The hematological test showed an LED of 83.0 mm, Hb level of 13.4 g/dl, Ht of 40.5%, erythrocyte count of 4.87 millions/ml, MCV of 87 fl, MCH of 30 pg, MCHC of 34 g/dl, thrombocyte of 288,000 ml, leucocyte of 8,700 ml. The immunology examination showed a positive anti HSV-I IgG (OD=2.30), a positive anti HSV-I IgM (OD=1.30), a

negative HSV-II IgG (OD=0.20) and a negative HSV-II IgM (OD=0.90) which gave an impression of the presence of herpes simplex type 1 infection.

### Case 2

A 35-year-old female, 43 kg weight (decreased from 46 kg during the last 2 weeks) and 150 cm tall, complained of a very painful and disturbing oral ulcers. About two months before, the patient experienced fever with a swollen gland at the right part of her neck and a week after that there was an outbreak of small ulcers on the inner lips and tongue. The patient went to a GP and she was told that there was the possibility of lung infection and was given medication including Betadine mouth wash. The neck was not swollen anymore and there was small improvement on the ulcers but they were never totally cured. In 1998, patient has experienced ulcers in the inner upper lip. At that time, the patient visited a GP and was told that she had malnutrition and she received multivitamin and Enkasari. However, the ulcers became more and more but finally resolved on their own after the patient often drank honey. Before that, she rarely had mouth ulcers and she denied a familial mouth ulcer history. This patient has a chronic gastritis that is rarely symptomatic. She had had problems with her boyfriend since several months before. In the extra oral examination, no abnormality was found. The intra oral examination showed several whitish, shallow ulcers surrounded by erythema area with an oval and irregular shape, 1-6 mm diameter, in the labial mucosa labial (Fig. 2a and b), dorsum of the tongue (Fig. 2c), buccal mucosa (Fig. 2d and e), palatum durum and molle (Fig. 2f). The oral hygiene was fair. At that moment an RIH suspect diagnosis was made with a comparative diagnosis of RAS herpetiformis. The hematological and immunological tests showed an LED of 110.0 mm, Hb of 11.8 g/dl, Ht of 35.9%, erythrocyte count of 4.49 millions/ml, MCV 80 fl, MCH 26.3 pg, MCHC 32.9 g/dl, leucocyte 8,800 ml, thrombocyte 388,000 ml, positive anti HSV-I IgG (OD=3.00), positive anti HSV-I IgM (OD=1.00), negative anti HSV-II IgG (OD=0.70) and positive anti HSV-II IgM (OD=1.50). Those test results show an impression of the presence of herpes simplex type 1 and type 2 infections.

### Case 3

A 34-year-old female, 34 kg weight and 156 cm tall (stable), came with mouth ulcers complaint that started 3 days ago in the inner lips, tongue, gum and palate. The ulcers were very painful that the patient had a difficulty to eat. The patient had used Betadine mouthwash and VCO (coconut oil) but the problem was not solved. Patient did not feel any fever before the ulcer outbreak. For the last several days, the patient felt very tired in her work. She had many previous mouth ulcer histories and she had experienced severe mouth ulcers before when she was still in the Senior High School. The outbreak was accompanied by fever. In addition, she always develops mouth ulcer if she hurts her mouth accidentally by toothbrush. Mouth ulcer history is also found in the parent (mother). The patient denied systemic disease history. The clinical examination showed no extraoral abnormality. In the intra oral examination, vesicles in the left lower labial mucosa (Fig. 3a) and dorsal part of the tongue (Fig. 3b) were found. The ulcers were white, shallow and surrounded by erythema area. The shape were oval and irregular with a diameter of 1-4 mm in the labial mucosa (Fig. 3c), lateral part of the tongue (Fig. 3e), mouth base (Fig. 3f), buccal mucosa (Fig. 3g) and gingiva (Fig. 3g) while erythematous spots are found in the palatum durum (Fig. 3i). Her oral hygiene was poor. A diagnosis of RIH suspect was made with a comparative diagnostic of RAS herpetiformis. The hematological and immunological tests show an LED of 17 mm/hour, Hb of 13 g/dl, Ht of 43.7%, erythrocyte of 5.09 millions/ $\mu$ l, leucocyte of 9,600  $\mu$ l, trombocyte of 253,000  $\mu$ l, positive anti HSV-I IgG (OD=2.53), positive anti HSV-I IgM (OD=1.5), negative anti HSV-II IgG (OD=0.20) and negative anti HSV-II IgM (OD=0.20). Those results support the diagnosis of RIH.

### Case 4

A 62-year-old male, 88 kg weight (decreased from 92 kg before he got ill) and 174 cm tall, came with a main complaint of mouth ulcers since 2 ½ before. There was a pain and burning pain on his tongue. Two days before he came, the patient experienced difficulty in speaking but he did not experience any fever before. The location of ulcers were not fixed, one healed another came out in a different place. Initially, the patient

treated himself using herbs, Enkasari, Vitamin C, Chinese herbs and also tried ice compress with no improvement. The patient then visited a GP with a complaint of difficulty in eating and drinking. He was given antibiotic, pain killer, and vitamin. Because he was not cured, he visited an oral medicine specialist and he was given Kenalog in orabase with Bactidol mouthwash. The pain was reduced but the ulcers were not totally cured. He rarely has mouth ulcers and he does not know about the familial ulcer history for sure. The patient has had asthma since he was a child and rarely experiences attacks. There was no abnormality found in the extraoral examination. The intra oral examination showed a thick yellowish white coated tongue at the dorsum area of the tongue (Fig. 4a) with several white and shallow ulcers surrounded by an erythematous area. The shape was oval and irregular with a diameter of 1-6 mm at the ventral and lateral part of the tongue (Fig. 4b and c) and buccal mucosa (Fig. 4d and e). The oral hygiene looked poor with calculus near the ulcers in the left buccal mucosa (Fig. 4f). At first, the diagnosis made was RIH with a comparative diagnosis of RAS herpetiformis. The hematological tests showed an LED 1 hour of 14 mm/hour, Hb of 12.4 g/dl, Ht of 36%, erythrocyte count of 4,29 millions/ $\mu$ l, MCV of 82 fl, MCH of 28 pg, MCHC 34 g/dl, leucocyte count of 8,700  $\mu$ l, trombocyte count of 341.000  $\mu$ l, negative anti HSV-I IgG (OD=0.02), negative anti HSV-I IgM (OD=0.25), negative anti HSV-II IgG (OD=0.15) and negative anti HSV-II IgM (OD=0.20). This examination results do not support RIH diagnosis and lead to RAS herpetiformis.

### DISCUSSION

All cases above show a comparative diagnosis between recurrent intra oral herpes (RIH) and recurrent aphtous stomatitis (RAS) herpetiformis. To compare the two diagnosis we use herpes lesion and aphtous lesion. The Greek scientists, especially Hippocrates, used "herpes" term that means creep or crawl to describe spreading lesion.<sup>6</sup> Meanwhile, the term aphtous also started at the Hippocrates time in 460-370 BC to describe oral disorder. In the general usage, the aphtous refers to undefined ulcers in the mouth.<sup>3,7</sup> Aphtous stomatitis is described as oral ulcers in the oral cavity mucosa or as a component from

the vesicle-ulcerative abnormality that involves various organ system. It is difficult to make an accurate diagnosis for RIH and RAS herpetiformis if we only look at the clinical description directly because those two ulcers have similar appearance. An accurate diagnosis is important to determine the treatment as the treatment for the two ulcers is different. Therefore, besides looking at the clinical description, it is important also to know the patient and her/his family history and to get indicated laboratory test results. Information on the frequency of lesion, factors that make the disease less severe (medication used) and factors that make the disease more severe is also important and can be gained from the history taking of the patient and the family member who comes with the patient.<sup>3</sup>

The subjective examination in the form of accurate and complete history taking is important. The first thing to be asked is the patient's chief complaint. Both herpetic and aphtous lesions often presence with prodromal symptoms that can provide important clues to make the diagnosis.<sup>3</sup> Literatures state that the prodromal symptoms for herpetic infection may be confusing and patient may not realize that the fever symptom is a prodromal symptom. However, for patients who often experience herpetic lesion, this symptom can be easily identified. The first indication of recurrent herpetic lesion is perhaps an uncomfortable sensation in the involved tissue and can be felt as reduced sensoric sensation and burning sensation.<sup>3</sup> In the three cases with RIH diagnosis above, through the history taking, it is apparent that the patients were complaining of a pain that disturb eating, drinking and even speaking activities. Fever was experienced by the two first patients while the third patient did not experience any fever before the oral lesion came out. Recurrent herpetic lesion does not always start with a prodromal symptom such as fever and it even can happen without the patient realizing it.

The prodromal symptom of RAS also includes localized pain or burning sensation for 24-48 hours before the ulcer.<sup>13</sup> The degree of pain is various starting from mild pain to severe pain and is often considered as exceeding the lesion size.<sup>3</sup> The patient usually starts to be aware of the RAS when there is a local discomfort felt in the lesion area.

In Case four, the patient with RAS diagnosis stated a pain and burning sensation on the tongue without any fever. This symptom is similar to the other three cases so it is apparent that by looking at the clinical symptoms only, it is difficult to determine which diagnosis is appropriate for the abnormality without considering other clinical parameters.

Another important information that should be revealed in the history taking process to differentiate RIH from RAS is the etiological and predisposition factors. It is already known that RIH is caused by herpes simplex virus type 1 (HSV-1). However, it is also possible that herpes simplex virus type 2 (HSV-2) causes the problem. The virus re-activation may be triggered by fever (e.g. due to upper respiratory tract infection), sunlight (fever blister), trauma, stress, or immunosuppression condition that lead to recurrent or secondary infection.<sup>5,11,14</sup> In RAS, there is no certain etiological factors,<sup>3,15</sup> but it is suspected that the main cause of RAS is the hereditary factor.<sup>16</sup> Various factors may trigger RAS in susceptible patients including oral trauma, stress, hematinic deficiency (lack of iron, vitamin B or folic acid), sensitivity towards food (preservatives such as benzoic acid), gastrointestinal abnormality, immune deficiency and disproportional hormone balance related to menstrual cycle.<sup>4,12,13,17,18</sup> In the three patients with RIH, it is evident that the abnormality is caused by HSV infection which is apparent from the immunological tests. The triggering factors are psychological and physical factors. In one patient with RAS, the trigger may be predicted as the hematinic abnormality which is evident from the hematological test results. However, this patient needs further examination to search for any other possible systemic abnormality. Therefore, the patient was referred to the Internal Medicine Department. In a literature, it is stated that the term RAS is used for recurrent lesion found in the oral cavity with no systemic disease history. However, the lesion with a clinical appearance that is similar to RAS can be found in systemic disorders such as Behcet's syndrom, gastrointestinal disorders, immunodeficiency syndrome such as HIV infection and cyclic neutropenia. If someone does not have any lesion history with a clinical appearance of aphtous lesion in his/her childhood, the ulcer is then called aphtous-like ulcers.<sup>4</sup>

The clinical appearance is a very important parameter in making the diagnosis of RIH dan RAS herpetiformis. Therefore, after the clinical symptoms are learned, a more thorough clinical examination is important. The literatures stated that after the prodromal stage, herpetic lesions will manifest in the form of a cluster of small grayish ulcers that are then ruptured and create small ulcers with a diameter of 1 mm or less. These ulcers may integrate to create a bigger ulcer that is up to 1.5 cm. In the 3 cases of herpetic infections above, in the first and second ulcers, there was no vesicle lesion while in the third patient there were vesicle lesions in the lower labial mucosa and the dorsal part of the tongue. The big irregular ulcers are the results from the unification of the smaller ulcers seen the three cases.

Aphtous lesion usually has a clear border, shallow with a rounded or oval form and shallow necrosis area in the middle that is covered by a yellowish gray pseudomembrane. The lesion is usually surrounded with a reddish area (erythematous halo).<sup>4,13</sup> It is already known that RAS has 3 types, i.e. mayor, minor, and herpetiformis.<sup>3,4,13-16</sup> The aphtous lesion that is similar to the herpetic lesion is the RAS herpetiformis type. However, this aphtous lesion does not go through the specific stages such as those in the herpetic lesion. The lesion can increase the size starting from undetected up to maturation.<sup>3</sup> In Case 4, white and shallow ulcers with clear erythematous halo are found in the buccal mucosa. There is no vesicle lesion found and this fact can become one factor that is against the possibility of herpetic infection.

The location of the initial lesion can also give a clue on the existing condition. A herpetic lesion generally starts in the keratinous tissue such as in the vermillion border, hard palate and fixed gingiva while recurrent aphtous stomatitis is usually found in the non keratinous tissue or near a gland. The typical locations are labial mucosa, buccal part of the mouth base, oropharynx, vestibulum and the lateral part of the tongue.<sup>3</sup> In the three cases of herpetic infection, the lesion location is seen in the keratinous and non keratinous mucosa while in case 4 the lesions are seen only in the non keratinous mucosa. The findings on the lesion location also support the diagnosis of RAS herpetiformis.

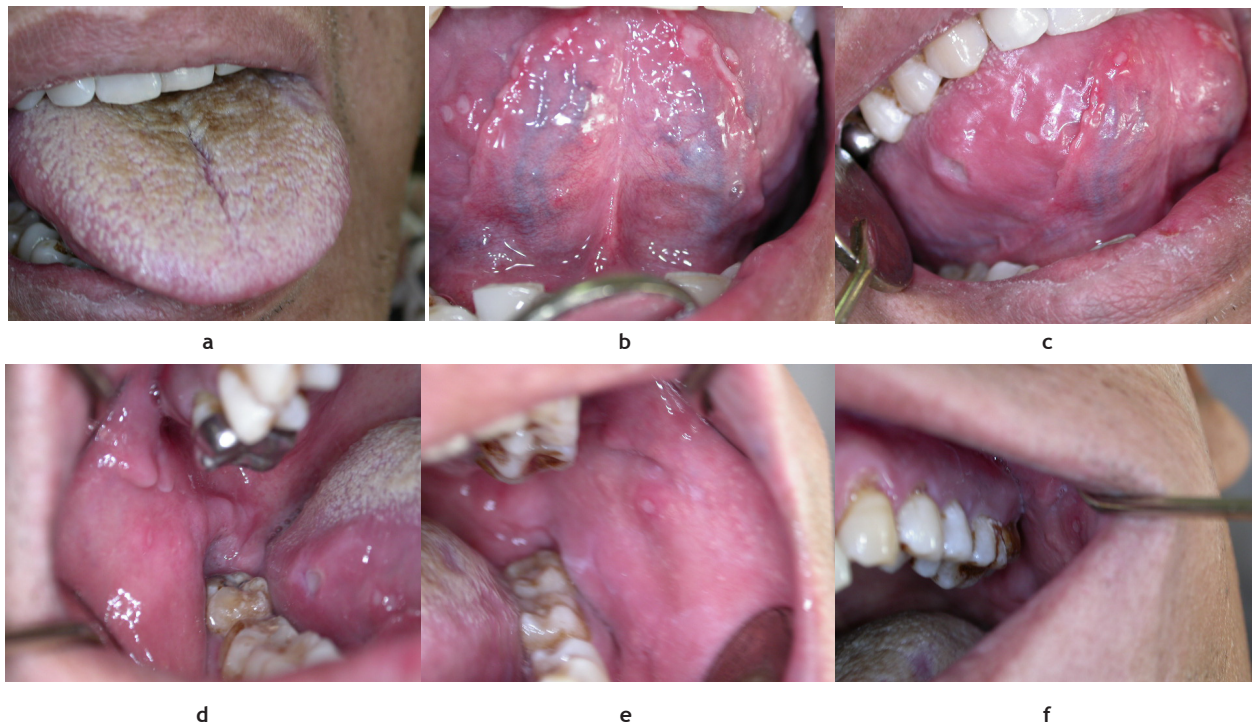
Supporting examination is also very important to make the diagnosis of the two abnormalities including the hematological and immunological examination in the form of anti HSV IgG and IgM. The examination results in the three RIH cases show that there is a positive anti HSV-I IgG and IgM result in two patients and a positive HSV-II IgM in a patient hile case 4 shows a negative anti HSV-I and II result. This finding supports the RIH diagnosis in the first three cases and leading the diagnosis to RAS herpetiformis in case 4. The supporting examination is a very important tool in making the diagnosis especially when the lesion appearance and patient's history is not clear enough.<sup>19</sup> Literatures stated that herpes virus may be found frequently in the environment leading to frequent exposure, both symptomatic and asymptomatic. Many healthy people have antibody towards various types of herpes virus. Herpes infection can be suspected when there is a significant increase in the antibody titer during illness or after. The increased antibody titer amount in this herpes infection is still controversial. A study has reported that at the time an examination is performed to a subject with herpetic lesion shows a higher antibody titer compared to subject without lesion.<sup>20</sup> Another literature shows that to make a primary herpes infection diagnosis, the antibody titer is at least 4 times. If not, the lesion is a recurrent (secondary).<sup>21</sup> A significant increase of anti HSV level may not be found at the same time of the lesion in the oral cavity of the patient. In the three RIH cases, various decreases in antibody titers is found. However, from this anti-HSV examination results, it is seen that there is a chronic and active herpes virus infection. Besides the serological examination, the herpes virus can usually be isolated from the primary lesion and cultured. However, this examination was not performed due to limited fund.

Based on the evaluation of the four cases above, the two lesions obviously have similarities and differences. Therefore, to know for sure, an thorough clinical parameters, patient's history, extra oral examination and indicated laboratory test results are important in making the diagnosis so that further treatment can be planned correctly and irrational prescription related to the wrong diagnosis can be avoided. This can be seen in the first case where patient received an antibiotic





**Figure 1. Case 1: Multiple white and shallow ulcers with erythematous area surrounding the lesion. The shape is oval and irregular with a diameter of 1-5 mm in labial mucosa (a,b), ventral and lateral area of the tongue (c,d), and buccal mucosa (f).**



**Figure 2. Case 2: Multiple white and shallow ulcers with erythematous area surrounding the lesion. The shape is oval and irregular with a diameter of 1-6 mm in the labial mucosa (a,b), dorsum part of the tongue (c), buccal mucosa (d,e), palatum durum and molle (f).**





Figure 3. Case 3: Vesicles in lower labial mucosa (3a) and dorsum part of the tongue (b), multiple white and shallow ulcers with erythematous area surrounding the ulcers. The shape is oval and irregular with a diameter of 1-4 mm in the labial mucosa (c,d), lateral part of tongue (e), the mouth base (f), buccal mucosa (g), gingiva (h), and palatum durum (i).

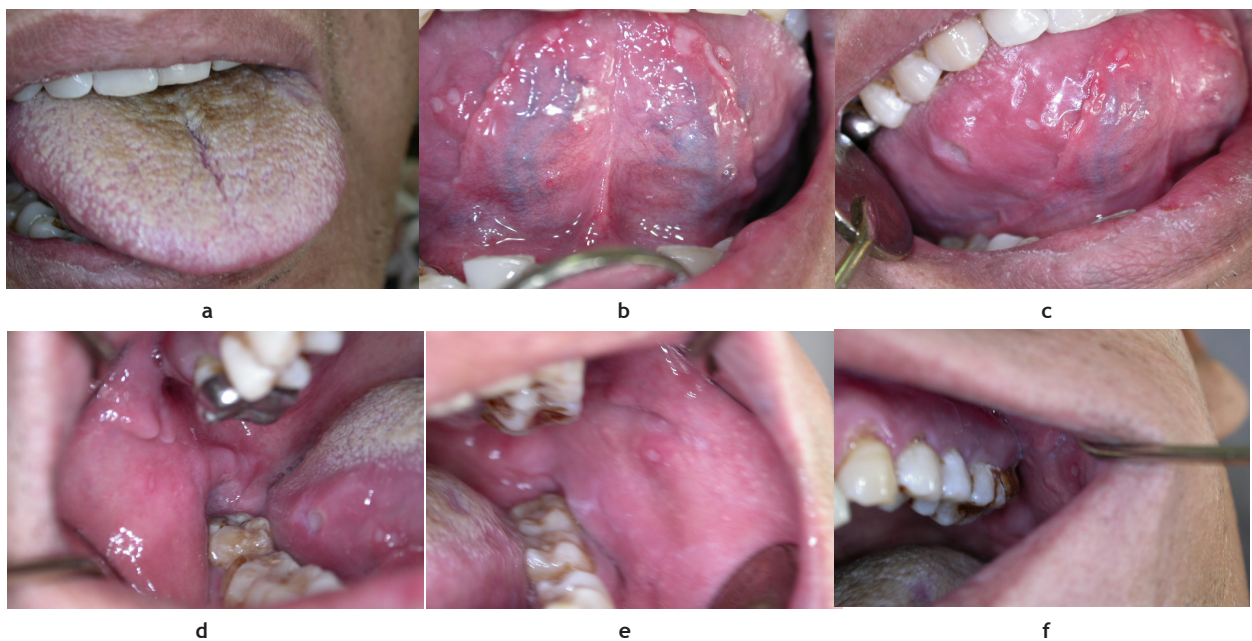


Figure 4. Case 4: Thick coated tongue (4a). multiple white and shallow ulcers with erythematous area surrounding the ulcers. The shape is oval, irregular and extended with a diameter of 1-6 mm in the ventral and lateral part of the tongue (b,c), (c,d), buccal mucosa (d,e) and poor oral hygiene appearance with calculus near the ulcer location in the left buccal mucosa (f).

therapy that is actually inappropriate.

Finally, when the general practitioners experience problems when finding herpes lesion or aphtous, the decision to refer to a specialist needs to be done if the diagnosis is not so clear or if there is a possibility of a serious disease and a systemic disease, complex treatment, unclear prognosis and based on the patient's willingness.<sup>12</sup> This is to avoid irrational treatment and to prevent more severe disease from happening.

## CONCLUSION

Recurrent intraoral herpetic (RIH) and RAS herpetiformis are oral cavity abnormalities that have similarities and differences in several parameters. An accurate diagnosis in both abnormalities is very important because the mistake in making the diagnosis may lead to an ineffective treatment. Therefore, the oral and dental professionals should have quite vast knowledge to differentiate the two oral abnormalities that lead to the treatment success.

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