Review Article

Recurrent aphthous ulcer: Literature review on etiopathogenesis, diagnosis and clinical aspects

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Abstract

Recurrent aphthous stomatitis is a common disease characterized by development of small or large painful, recurring, solitary or multiple ulcerations with circumscribed margin, having yellow or grey floor surrounded by erythematous haloes of the oral mucosa. It clinically presents as recurrent aphthous ulcer minor type, major type and recurrent herpetiform ulcer. Various systemic diseases have an oral manifestation of recurrent aphthous ulcer. This review paper focuses on the etiopathogenesis, clinical features, histopathology, cytology, differential diagnosis and treatment of recurrent aphthous ulcer.

***Keywords*:** Systemic diseases, oral manifestation, histopathology, cytology

Introduction

An ulcer is a loss or break in the continuity of surface epithelium or mucous membrane that extends into lamina propria (Babu et al., 2017). They are secondary lesions associated with systemic conditions and commonly affect the oral mucosa (Muñoz-Corcuera et al., 2009). Oral ulcers can be acute ulcer, chronic ulcer (Sivapathasundharam et al., 2018) and recurrent ulcer (Mortazavi et al., 2016).

Recurrent aphthous stomatitis is a common disease characterized by development of small or large painful, recurring, solitary or multiple ulcerations with circumscribed margin, having yellow or grey floor surrounded by erythematous haloes of the oral mucosa (Tantray et al., 2020). This review paper discusses about the etiopathogenesis, clinical presentation, investigations, differential diagnosis and treatment of recurrent aphthous ulcer.

Epidemiology

A retrospective epidemiological study conducted among 4895 patients by Salomão et al., reveal that 161 (3.3%) had complaints of oral aphthous ulcerations, of which 76 (47.2%) were diagnosed as suffering from recurrent aphthous ulcerations (Queiroz et al., 2018). In another epidemiological study conducted among Indian population by Patil et al. (2014), reveal that 705 patients of the total 3244 patients presented with recurrent aphthous ulcers, giving overall prevalence of 21.7% (Patil et al., 2014). Patients in the third (20.7%) and fourth (26.5%) decade were most commonly affected (Patil et al., 2014). Females (56.3%) were more commonly affected than males (43.7%) (Patil et al., 2014).

Etiology

The etiology of recurrent aphthous ulcer still remains unclear. However, numerous possible etiologic factors have been suggested for recurrent aphthous ulcer (Figure 1).

Bacterial infection- A pleomorphic, transitional L-form of α-hemolytic *Streptococcus*, *Streptococcus sanguis* (this organism has been consistently isolated from lesions of patients with typical aphthous ulcer). Patients when tested with streptococcus vaccine, gives a possible delayed type of hypersensitive skin reaction. Immunologic hypersensitivity reaction to an L-form *Streptococcus* has also been suggested. A T-cell mediated response to *S. sanguis* has also been reported. Patients serum showed elevated gamma globulins against *Streptococcus* 2A and M5 (Sivapathasundharam, 2016). Role of *H. pylori* was implicated in etiopathogenesis of recurrent aphthous ulcer, Porter et al. (1997) concluded the anti-*H. pylori* seropositivity was not significant in patients with recurrent aphthous ulcer (Tantray et al., 2020).

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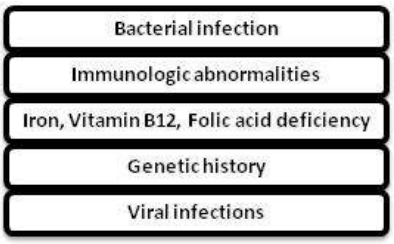

Figure 1. Etiology of recurrent aphthous ulcer

Figure 2. Predisposing factors to recurrent aphthous ulcer

Genetic history- Associated with HLA-B51 gene. The presence of aphthous ulcer in parents significantly increases the risk of RAU development and the course of the disease in their offspring. The risk of the disease occurrence is higher in monozygotic twins than in dizygotic twins. The genetic risk factors which may determine the individual susceptibility to recurrent aphthous stomatitis include various DNA polymorphisms distributed in the human genome. A special attention should be paid to the alterations in the metabolism of cytokines, which include: interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon γ (IFN-γ) and tumour necrosis factor-α (TNF-α), serotonin transporter gene and endothelial nitric oxide synthase gene (Slebioda et al., 2013).

Immunologic abnormalities- Condition of autoimmune response of oral epithelium, evidence of binding of IgG and IgM to epithelial cells of spinous cells of the oral mucosa in patient with recurrent aphthous ulcer.

Cohen suggested a local immune response against an antigenically altered mucosa. He theorizes, the disease is a result of diffusion of bacterial toxin, food, allergens or haptens that initiates an immune response and reacts with epithelial cell surface antigen that results in an adverse inflammatory response. Immune system actively involved in reaction to bacterial and autoimmune antigens and L-form S*treptococci,* might affect intact epithelium of salivary duct and stimulate antibody formation, fix complement and cause cytolysis (Sivapathasundharam, 2016).

Iron, Vitamin B12, Folic acid deficiency- Nutritional deficiencies can be of minor significance in etiology of recurrent aphthous ulcers.

Viral infections- Sun et al. (1998), discovered the existence of Epstein-Barr virus genome in post-ulcerative oral aphthous tissue by polymerase chain reaction in patient with recurrent aphthous ulcer (Sivapathasundharam , 2016).

Predisposing factors

Trauma- Local traumatic incidents that precipitate as aphthous ulcer in most cases can be due to oral surgical procedures, tooth brushing, dental procedures, needle injections, and dental trauma.

Endocrine conditions- A time relationship exists between occurrence of menstrual period and the development of aphthous ulcer. The incidence of aphthae is greatest during the premenstrual period and post ovulation period, which can be related to the blood levels of progesterone. It is also reported that there is remission of their aphthous lesion during pregnancy but show eruptions following parturition (Sivapathasundharam, 2016).

Allergic factors- It is reported that patients with history of hay fever, asthma, drug/ food allergy have high incidence of recurrent aphthous ulcer (Sivapathasundharam, 2016).

Psychic factor- Stress and anxiety and acute psychological problem are a predisposing factor to recurrent aphthous ulcer.

Non smoker- Incidence of RAU is significantly lower in smokers. But the incidence of aphthous ulcers increases when the patient stops smoking (Sivapathasundharam, 2016) (Figure 2).

Pathogenesis

Cell mediated immunity in the pathogenesis of recurrent aphthous ulcer

Unknown antigenic stimulation attacks oral keratinocytes. This results in CD4 T-cell activation and cytokine secretion. Oral keratinocytes undergo vacuolization and localized vasculitis. It clinically presents as a papular swelling that later ulcerates (infiltrated by neutrophils, lymphocytes and plasma cells), followed by healing and regeneration of the epithelium (Figure 3).

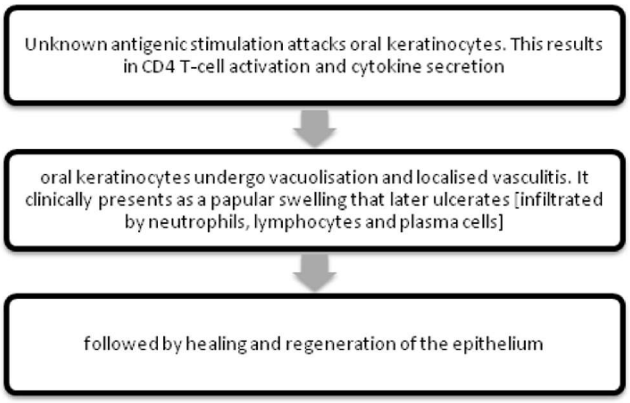

Figure 3. Cell mediated immunity in the pathogenesis of recurrent aphthous ulcer

Classification

Recurrent Aphthous ulcer is classified into recurrent aphthous ulcer minor, recurrent aphthous ulcer major, recurrent herpetiform ulcer and recurrent aphthous ulcer associated with Behcet's syndrome based on their clinical presentation. Altenburg et al. (2014) classified recurrent aphthous ulcer into simple chronic recurrent oral aphthous ulcer and complex chronic recurrent oral aphthous ulcer based on the duration of the lesion (Sivapathasundharam, 2016) (Figure 4).

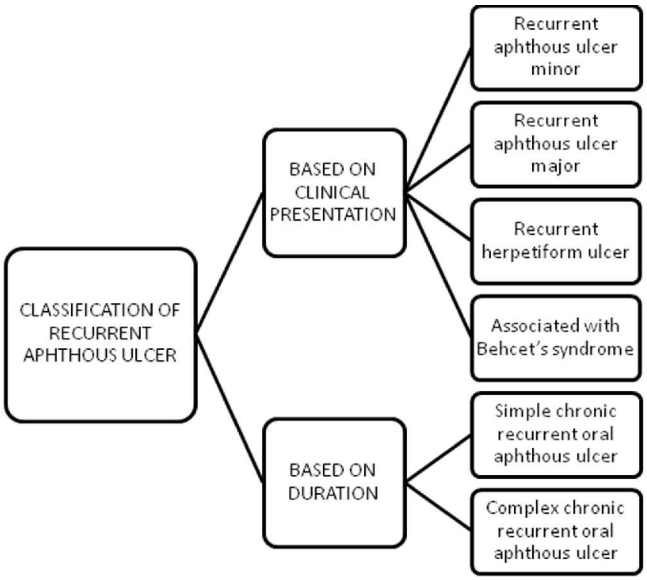

Figure 4. Classification of recurrent aphthous ulcer

Clinical features

Recurrent aphthous ulcer minor

Synonym: Mikulicz aphthae/minor aphthous ulcer

It is a most common type of Recurrent aphthous ulcer. It clinically presents as a shallow ulcer with raised margin surrounded by erythematous halo and covered by grey fibrinous membrane less than 1cm in size, usually lasts for a shorter duration and heals without scarring. Occur frequently on the non-keratinized mucosa (Table 1).

Recurrent aphthous ulcer major

Synonym: Sutton ulcer/ periadenitis mucosa necrotica recurrens

It is a less common type of recurrent aphthous ulcer. It clinically presents as single/ cluster of large crateriform ulcer on the keratinized and non-keratinized mucosa, with an increased depth and more than 1cm in size and lasts for a longer duration and heals with a scar (Table 1).

Recurrent herpetiform ulcer

It is the least common type of Recurrent aphthous ulcer. It clinically presents as dozen to several clusters of small ulcer of 1-2mm in size that coalesces to form larger ulcers. It clinically represents herpetic ulcer. It occurs on the keratinized and non-keratinized mucosa, and lasts for a longer duration up to months. Patient complaints of pain, burning sensation, low grade fever, malaise, difficulty in mastication and speech which is more severe in intensity than minor aphthous ulcer (Table 1).

Table 1. Clinical features of recurrent aphthous ulcer minor, recurrent aphthous ulcer major and recurrent herpetiform ulcer

S. No	Clinical feature	Recurrent aphthous ulcer minor	Recurrent aphthous ulcer major	Recurrent herpetiform ulcer
1	Incidence	Common (80%)	Less common (10%)	Less common (<10%)
2	Sex and age	Female, 10-30 years	Female	Female, late teen
3	Site	Non-keratinized mucosa	Non-keratinized and keratinized mucosa	Non-keratinized and keratinized mucosa
4	Number	Single/ cluster of small ulcer (1-5 ulcers)	Single/ cluster of larger ulcer (1-10 ulcers)	Dozen to several cluster of ulcers (10-100 ulcers)
5	Size	Less than 1cm	More than 1cm	1-2mm small ulcer coalesce to form larger ulcer
6	Clinical presentation	Shallow ulcer with raised margin surrounded by erythematous halo and covered by grey fibrinous membrane	Crateriform ulcer with an increased depth	Resemble herpetic ulcer. Has a wide zone of erythema
7	Duration of ulcer	7-10 Days	Longer duration >10days	Longer duration up to several weeks/months
8	Healing of ulcer	Heal without scar	Heals with scar (longer time up to 6week to heal)	Longer time up to 1 month or more to heal
9	Associated symptoms	1. Pain and burning sensation 2. Low grade fever and malaise 3.Difficulty in mastication and speech	1. More Painful and burning sensation 2. Low grade fever and malaise 3.Difficulty in mastication and speech	1. Extremely painful and burning sensation 2. Low grade fever and malaise 3.Difficulty in mastication and speech
10	Recurrence	Low recurrence	High recurrence	Highest recurrence

Simple chronic recurrent oral aphthous ulcer

Simple chronic recurrent oral aphthous ulcer is limited to oral mucosa. Few self-limiting oral ulcers of shorter duration and occur about 3-6 episodes annually (Altenburg et al., 2014) (Table 2).

Complex chronic recurrent oral aphthous ulcer

Complex aphthosis occurs on almost all mucosal surfaces- oral mucosa, genital mucosa, perigenital area affecting scrotum, vulva, perineum, inguinal region. They present from few to many slow healing ulcers that has a short lesion-free period or they present as repeatedly recurring ulcers (Altenburg et al., 2014) (Table 2).

Systemic diseases which present with recurrent oral ulcerations (Preeti et al., 2011)

Various systemic diseases have an oral manifestation of recurrent aphthous ulcer. They include: Behcet's syndrome, MAGIC syndrome, PFAPA syndrome, Sweet's syndrome, cyclic neutropenia, HIV infection (Table 3).

Investigation parameters

1. Histopathological test
2. Cytological smear
3. Hematological tests- complete blood count, differential leukocyte count, hemoglobin estimation, ESR, CRP.
4. Microbiological test- dark field microscopy, gram staining and acid fast staining, bacterial culture test, PCR
5. Bio-assay- ELISA, Western blot
6. Special investigations- Immuno histochemistry, direct immunoflourescence

Histopathology

Histopathology of recurrent aphthous ulcer reveals an

Table 2. Clinical features of recurrent aphthous ulcer- simple chronic recurrent aphthous ulcer and complex aphthosis

S. No.	Clinical feature	Simple chronic recurrent aphthous ulcer	Complex aphthosis
1	Site	Limited to oral mucosa	Oral mucosa, genital mucosa, perigenital area affecting scrotum, vulva, perineum, inguinal region
2	Number	Few limited ulcers	Few-many ulcers
3	Recurrence	3-6 episodes annually	Frequently appearing ulcer with short lesion-free period or repeatedly recurring ulcers
4	Healing of ulcer	Quickly healing	Slowly healing
5	Associated symptoms	Minimal pain	1. Intense pain 2. Interferences with eating 3. results in inadequate nutrition

Table 3. Systemic diseases which present with recurrent oral ulceration (Preeti et al., 2011)

S. No.	Disease	Clinical presentation
1	Behcet's syndrome	1. Recurrent aphthous ulceration; 2. Ocular- uveitis, conjunctivitis, retinitis; 3. Genital- scrotal or penile ulcer, vaginal or vulval ulcers, perianal ulcers, epididymo-orchitis; 4. Dermatological- papules, pustules, erythema nodosum-like skin lesions, cutaneous pathergy response; 5. Neural- headaches, meningo-encephalitis; 6. Arthralgias
2	MAGIC syndrome	Variant of Behcet's syndrome- major aphthae and inflammed cartilage
3	PFAPA	Periodic fever, aphthae, pharyngitis and cervical adenitis. Seen in young children
4	Sweet's syndrome/acute febrile neutrophilic dermatosis	Fever, increase in PMN in peripheral blood smear; Skin lesions- erythematous plaques, nodules, vesicles, pustules, dense dermal neutrophilic infiltrate
5	Cyclic neutropenia	Cyclic reduction in circulating neutrophils. Oral ulceration, cutaneous abscess, upper respiratory infections, lymphadenopathy
6	HIV	Recurrent aphthous ulcer of oral mucosa

ulcerated epithelium with superficial tissue necrosis covered by a fibro purulent membrane. Superficial colonies of micro organisms are present. Vacuolization and necrosis of individual cells present. Underlying connective tissue has dense neutrophil infiltration. Lymphocytes, plasma cells, macrophages and mast cells can be seen in the deeper part of connective tissue. Perivascular cuffing has been observed. Minor salivary glands mostly appear in areas of aphthae reveal focal periductal and perialveolar fibrosis and chronic inflammation (Tantray et al., 2020).

Cytology

Anitschkow cells: They contain elongated nuclei with linear bar of chromatin with few radiating process extending towards nuclear membrane. Nucleus is seen as a caterpillar pattern in longitudinal section. It is a predominant cell but is not pathgnomonic (Tantray et al., 2020).

Differential diagnosis

1. Herpes simplex and herpes zoster infection

Herpes simplex infection (caused by HSV1 and HSV2) has a histopathology of ballooning degeneration of the infected epithelial cells, presence of intranuclear virus inclusion bodies (lipschutz bodies), multinucleate giant cells and inflammatory cell infiltration in connective tissue. Cytology reveals presence of tzanck cells. Herpes zoster infection has similar findings and can be differentiated from herpes simplex infection by fluorescent antibody staining, viral culture, serological tests (Sivapathasundharam, 2016).

2. Infectious mononucleosis

Viral infection caused by Epstein Barr virus, it presents as dozen to several hundred palatial petechia. Diagnosis is based on history, clinical presentation, serological investigations and positive Paul bunnell test.

3. Hand, foot and mouth disease

Epidemic viral infection caused by Coxsackie virus. It is characterized by appearance of maculopapular, exanthematous and vesicular lesion of skin and numerous multiple vesicular and ulcerative oral lesion. Laboratory investigation demonstrates intracytoplasmic viral inclusions and rise in acute or convalescent serum antibody titer to coxsackie A16.

4. Herpangina

Specific viral infection caused by Coxsackie group A virus. Clinically presents as small vesicles that rupture to form crops of ulcer showing a grey base and an inflamed periphery on anterior faucial pillars, hard and soft palate. Serological tests are used to diagnose the disease.

5. Syphilis

Syphilis is a sexually transmitted disease. It is caused by *Treponema pallidum*. Hence, history taking is an important diagnostic tool. Dark field microscopy is employed in case of

Table 4. Diagnostic criteria for major aphthous ulcer (Natah et al., 2004)

S. No.	Major criteria	Description
1	Clinical appearance	Single or multiple round/oval ulcers, shallow, regular margins, yellow-gray base, surrounded by erythematous margins. Ulcer is never preceded by vesicles. Less than 1cm in diameter
2	Recurrence	At least three attacks of RAS within past 3years, ulcers do not appear in the same focal site
3	Mechanical hyperalgesia	Painful lesion, exacerbated by movement of ulcer affected area
4	Self-limitation of condition	Ulcer heals spontaneously without sequelae with or without treatment

Table 5. Diagnostic criteria for minor aphthous ulcer (Natah et al., 2004)

S. No.	Minor criteria	Description
1	Family history of rau	Positive family history of RAU present
2	Age of onset	First attack of RAU below 40years
3	Location	Non-keratinized oral mucosa
4	Duration	Ulcers lasts from few days to few weeks
5	Pattern of recurrence	Irregular
6	Histopathological examination	Non-specific inflammation
7	Presence of precipitating factor	Attacks triggered by hormonal changes, exposure to certain foods and drugs, intercurrent infections, stress and local trauma
8	Presence of hematinic deficiencies	Hematinic deficiency especially ferritin, folate, iron, vitamin B and zinc
9	Negative association with smoking	RAU patient is a non-smoker or develops ulcer after stopping smoking
10	Therapeutic trial with gluco-corticosteroids	Positive response to treatment with local or systemic steroids

suspicion of primary syphilis. Screening tests- VDRL and RPR is done and confirmatory tests- TP-PA, EIA, FTA-ABS tests can be done to diagnose the disease.

6. Acute Necrotizing Ulcerative Gingivitis

It is a distinct and specific disease characterized by rapidly progressive ulceration typically starting at top of the interdental papilla, spreading along marginal gingiva and going on to acute destruction of periodontal tissue. Clinically presents as a punched out crater like depression at tip of interdental papilla that can extend to the buccal mucosa and is covered by a pseudo membranous slough and patient presents with fetid odor. It can be diagnosed by history, clinical presentation and bacterial culture tests.

7. Pemphigus vulgaris

It is a mucocutaneous disorder associated with immunologic defects. Diagnosis based on a history of vesicle that ruptures to form an ulcer. Nikolsky sign is positive. Cytology study reveals the presence of Tzanck cells. Histopathologically, suprabasilar cleft is seen and presence of tzanck cells. Immunofluorescence test reveals a fish-net or chicken-mesh appearance.

8. Cicatricial pemphigoid

It is a mucocutaneous disorder associated with immunologic defects. Diagnosis based on the presence of definitive ocular symptoms along with a history of a vesicle that ruptured to form an ulcer. Histopathological study reveals a sub epithelial cleft. Ocular lesions- symblepharon, entropion, trichiasis. Nikolsky sign is positive.

9. Erythema multiforme

It is a self limiting hypersensitive disease characterized by target skin or mucosal lesion. Skin lesions have a target or bull's eye clinical presentation. Immunohistochemistry shows connective tissue positive for IgM in the wall of dermal vessel.

Steven Johnson syndrome is associated with an extensive and severe form of erythema multiforme, and involves skin, oral mucosa, respiratory mucosa, genitalia and eye.

10. Oral squamous cell carcinoma

A non-healing ulcer that persists more than three weeks must be subjected to biopsy. The histopathology shows epithelial dysplasia and is graded as well-differentiated, less well-differentiated and poorly differentiated carcinoma depending upon the degree of differentiation.

11. Traumatic eosinophilic ulcer

Eosinophilic ulcer is a rare self-limiting chronic benign lesion of the oral mucosa. Clinically, the ulceration has been most frequently found in tongue and it is characterized by the presence of mildly indurated borders (Bortoluzzi et al., 2012). The histopathology shows an ulcerated area covered with fibrinoid material. A dense polymorphous inflammatory infiltrate was seen and with numerous eosinophils. Immunohistochemistry for CD68 antibody is done. The diagnosis is made by combining histologic findings with the clinical follow-up (Bortoluzzi et al., 2012).

12. Ulcerative colitis

Ulcerative colitis is a chronic, idiopathic inflammatory disease that affects the colon. It rarely affects the oral mucosa. The diagnosis of ulcerative colitis is based on a combination of symptoms, endoscopic findings, histology, and the absence of alternative diagnoses (Ungaro et al., 2019).

13. Chron's disease

It is an inflammatory bowel disease**.** Chronic diarrhea is the most common presenting symptom, abdominal pain and weight loss, blood and/or mucus in the stool may be seen sometimes (Van Assche et al., 2010). Cobblestone appearance of the buccal mucosa is noticed. Chron's disease is a heterogeneous entity comprising a variety of complex phenotypes in terms of age of onset, disease location and disease behavior. The macroscopic diagnostic tools include physical examination, endoscopy, radiology, and examination of an operative specimen (Van Assche et al., 2010). Microscopic features can be only partly assessed on mucosal biopsy (Van Assche et al., 2010).

14. Reiter syndrome

The syndrome is a tetrad of symptoms- conjunctivitis, non-gonoccal urethritis, mucocutaneous lesion and arthritis. Oral manifestation includes painless aphthous like ulcer, pruritic spots and geographic tongue.

15. Sarcoidosis

Multisystem granulomatous disease of unknown origin characterized by formation of uniform, discrete, and compact non-caseating epitheloid granuloma. The oral lesion shows small papules or bleb-like with clear fluid. The investigation results reveal increased CRP, IgG, and ACE. Hypercalcemia and chest x-ray shows hilar lymphadenopathy. Kveim-Siltzback test is a diagnostic test. Biopsy can be taken from the oral lesion which shows a sarcoid granuloma.

16. Contact stomatitis

Reactions in which lesion of skin or mucous membrane occur at localized site after repeated contact with causative agent. Clinically presents as erythema followed by vesicle then erosion that can become extensive. It results occurrence of itching and burning sensation of oral mucosa. Patch test can be performed and the lesion subsides with the withdrawal of the causative agent.

17. Traumatic ulcer

The traumatic ulcer may result from mechanical trauma, chemical, electrical, or thermal stimulus, fractured,

malposed, or malformed teeth (Apriasari et al., 2012). The main therapy of traumatic ulcer is eliminating the etiology factor. The monitoring of the ulcer must be done until 2 weeks after the teeth extraction (Apriasari et al., 2012). If the lesion was persistent, it is suspected as malignancy (Apriasari et al., 2012).

18. Lichen planus

It is a chronic inflammatory mucocutaneous disorder of unknown etiology which is characterized by a clinically persistent red, white or mixed lesion. Diagnosis is based on history and clinical presentation of the lesion and investigation. The histopathology shows presence of saw tooth shaped rete processes, sub epithelial lymphocytic infiltration. Erosive lichen planus has an atrophied epithelium, clinically erythematous with central ulceration and peripheral Wickham's striae covered by a pseudo membrane. It is a premalignant condition (Sivapathasundharam, 2016).

Diagnosis

Diagnosis of Recurrent aphthous ulcer is based on history, clinical presentation, and histopathology. Rule out other causes of recurrent oral ulceration.

Diagnostic criteria for minor Recurrent aphthous ulcer were proposed by *Natah et al.,*(Natah et al., 2004) in 2004 (mentioned below in Table 4 and 5). They proposed that a diagnosis of idiopathic recurrent aphthous ulcer and secondary recurrent aphthous ulcer (associated with systemic disease) is established when four major and one minor criteria are fulfilled (Preeti et al., 2011).

Treatment

There is no absolute curative treatment for recurrent aphthous ulcer. The systemic association with Recurrent aphthous ulcer is ruled out, especially when there is chronic multiple ulcers on the oral mucosa. Minor aphthous ulcers with mild symptoms usually do not require specific treatment (Bilodeau et al., 2019). When the ulcer is bothersome to the patient, treatment aims at symptomatic relief for the patient.

(A) Treatment of mild cases of recurrent aphthous ulcer (Sivapathasundharam et al., 2018):

1. Protective emollient- orabase

2. Topical anesthetic gel for pain relief

(B) Treatment of severe cases of recurrent aphthous ulcer (Sivapathasundharam et al., 2018):

1. High potency steroid preparation- 1.5% cortisone acetate, hydrocortisone acetate, triamcinolone, fluocinlone, clobetasol cream, beclomethasone spray placed directly on the lesion- reduces the size and shorten healing time.

2. Intralesional injection of Triamcinolone acetonide for recurrent aphthous ulcer major.

(C) Treatment of more severe cases of recurrent aphthous ulcer (Sivapathasundharam et al., 2018):

1. Systemic corticosteroids- prednisone 20-40mg/day for a week followed by tapering of the dose.

2. Other systemic corticosteroids- dapsone, colchicines. Thalidomide, pentoxifylline, low-dose

Interferon-α

3. Antihelminthic drug- Levamisole can modulate immune responses, used successfully as monotherapy and as an adjunct to treatment in variety of diseases.

Conclusion

Oral ulcers are common lesions of the oral mucosa. Examination and diagnosis of the ulcerative lesions of the oral mucosa is of much significance. Some ulcers can be self limiting and benign, some ulcers have high potency to transform in malignancy whereas some ulcers are malignant in their presentation. Thorough knowledge about the clinical presentation and differential diagnosis of the ulcerative lesions of the oral cavity is very critical.

Recurrent aphthous ulcer has an uncertain etiology and absolute curative treatment is not yet suggested. But, it becomes important to consider it as an alarming clinical presentation as it can be associated with various systemic diseases. And it is also equally important to consider the differential diagnosis to recurrent aphthous ulcer to arrive at a definitive diagnosis.

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