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Pathogenesis of Recurrent Aphthous Stomatitis: A Review of Literature

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ABSTRACT

Recurrent aphthous stomatitis represents a very common chronic but poorly understood mucosal disorder, affecting 10% to 20% of the world population. They occur in men and women of all ages, races and geographic regions. It is estimated that at least 1 in 5 individuals has at least once been afflicted with aphthous ulcers. There are 3 clinical subtypes that is minor, major, and herpetiform on the basis of their size and number. Minor aphthous ulcers are the most common subtype, representing 80% to 90% of all recurrent aphthous ulcers. There are four stages of the lesion, these includes premonitory, preulcerative, ulcerative, and healing stage. Clinically, RAS present as extremely painful, shallow ulcerations with an erythematous halo on unattached oral mucosa. Attacks may be precipitated by local trauma, stress, food intake, drugs, hormonal changes and vitamin and trace element deficiencies. Local and systemic conditions and genetic, immunological and microbial factors all may play a role in the pathogenesis of recurrent aphthous stomatitis. The primary differential diagnosis is herpes simplex.

Key words: Recurrent aphthous stomatitis; aetiology; pathogenesis.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is an inflammatory condition of unknown aetiology characterized by painful recurrent, single or multiple ulcerations of oral mucosa. [1]

The Greek word aphthae, which means burning, to set on fire, or to inflame, most probably was first used by Hippocrates (460-370 BC) to represent the clinical symptom of the disease RAS the most common painful, recurrent oral mucosal inflammatory ulcerative condition.[2] RAS affects 5-25% of the general population and in selected groups (students at the time of examinations) reaches a prevalence of more than 50%.[3]

RAS occurs worldwide although it appears most common in the developed countries.[4] Studies have reported that globally 20% of world population is affected by the condition [5, 6] with prevalence as high as 66 % in certain population.[7, 8]The aetiology of RAS is not entirely clear, and aphthae are therefore termed idiopathic. It may be the manifestation of a group of disorders of quite different aetiology, rather than a single entity.[7] Many factors can contribute to the pathogenesis of RAS such as stress [9], immunological factors, [7] local traumas, [10] hormonal states, [7, 5] hereditary [2] and genetic factors,[4] microbial factors,[2] food hypersensitivity [11] drug allergy[12] and hematinic deficiencies.[4]

Despite many studies trying to identify causal microorganisms, RAS dose not appear to be infectious, contagious, or sexually transmitted. [5]

A genetic predisposition, and a positive family history is present in about one-third of patients with RAS. [2]

Typically RAS lesions involve self-limited, painful, clearly defined shallow round or oval 1-3 mm ulcers. [13] The severe pain lasts 3-4 days until there is a thicker fibrinous cover or early epithelialization. Despite extensive investigations, the exact cause for RAS is still unknown. However, most patients who suffer from this disorder are usually healthy individuals. [2]

Classification of Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis is clinically divided into three different variants, according to the classification of Stanley [14](1972), Cooke [15](1969) and Lehner [16](1968)

Minor RAS (MiRAS) which is also known as Mikulicz's aphthae, named for Johann von Mikulicz's-Radecki, who was probably the first to describe it in late 19th Century (1898). MiRAS accounts for 75-85% of all aphthous lesions. [17] Lesions appear in groups, are less than 10 mm which are exquisitely painful, [18] covered with grayish-white to yellow pseudomembrane with bright red erythematous halo[19]. It tend to heal within 10-14 days average 12 days without scarring. Lesions can involve every nonkeratinized mucosa of oral cavity [20] especially in buccal and labial mucosa, floor of mouth and on the ventral or border of tongue [21] and is un common in the keratinized gingiva, palate or dorsum of tongue [21](Scully 2006). The labial mucosa is the most prevalent area. [22] The products of the intensive lymphocytic infiltrate in these ulcers may play a role in the long duration. [23] MiRAS is the most common form of childhood RAS.[24]

Major aphthae (MjRAS) which are called as Periadenitis Mucosa Necrotica Recurrence PMNR[2] are also known as "Sutton's disease, as these lesions were first described by Sutton in 1911 who introduce the term PMNR,[25] occurs in approximately 10% of RAS patients.[23]These lesions are larger than 10 mm in diameter and are single or multiple, and have a tendency to involve the mucosa overlying the minor salivary glands. Lesions usually begin after puberty. [2] They may be round or oval with clearly defined margins, but prodromal symptoms more intense, the ulcers lasting significantly longer, are usually deeper, with raised irregular border, are more painful, have a predilection for lips, soft palate and fauces [24] where they may cause some dysphagia. The ulcerative lesions tend to heal slowly and can last for weeks to several months, leaving a scar after healing. [17]

Herpetiform aphthae (HuRAS) are the third and least form of RAS that afflict 5-10% of all RAS patients.[17] Multiple (5-100) 1-3 mm, rounded, small, grouped lesions which may occur throughout the oral mucosa tend to fuse and produce much larger ulcers, clinically resembling other ulcerative oral diseases. Painful ulcers resemble lesions of intra oral Herpes Simplex hence the name herpetiform derived. Lesions heal without scar formation, the healing time of an individual lesion being 7-10 days. HuRAS occurs more often in women and has a later age of onset. [26]

Another valuable classification of RAS is Simple aphthosis versus Complex aphthosis. Simple aphthosis represents the common presentation of a few lesions that heal in one to two weeks and recur infrequently. Complex aphthosis represents a complicated clinical picture of severe disease, almost constant >3 oral aphthae or recurrent oral and genital aphthae in the absence of Behcet's disease, there is continuous ulceration, with marked pain or disability and associated genital or perianal lesions, [27] which confirm the diagnosis of Behcet's disease, but some patients with complex aphthosis will have occasional genital aphthae never develop Behcet's disease. [17]

Stages of Recurrent Apthtous Stomatitis

The stages of natural evolution of lesions of RAS have been synthesized by Stanley, [14] who divides the natural history into following four stages that is premonitory, pre-ulcerative, ulcerative and healing.

The premonitory stage lasts for upto first 24 hours of development of RAS. Patients suffering from lesion may have burning or tingling sensation at the site of development of RAS. Some patients do not report a pre-monitory stage.[17] Epithelium of the affected site is infiltrated with mononuclear cells, and edema begins to develop. [11] The pre-ulcerative stage occurs during the first 18 to 72 hours (3 days) in the development of a lesion of RAS. Painful sensations vary in intensity during this stage, but are usually moderately severe. Clinically, the aphthae begin as erythematous macules or papules with slight indurated erythematous halo. On the cheeks or lips, lesions are circular, whereas in the buccal or labial sulci or vestibule, oval lesions occur. Lesions overlying fibro muscular bands such as the frenum are exceptionally painful. [17]

The ulcerative stage lasts from 1 to 16 days. Clinically, the papule or macule, which had begun to erode in the second stage, enlarges and ulcerates

but remains a discrete lesion. The maximum size is usually attained 4 to 6 days after the onset. Two or three days later, there is cessation of pain, leaving residual discomfort that correlates clinically with the appearance of the covering fibrino membranous slough. [28] The ulcerative bed is infiltrated mainly by neutrophils, lymphocytes and plasma cells. This stage may last from a few days to 2 or several weeks. [2]

Healing stage occurs during 4 to 35 days. The lesions usually heal without scarring in 10 to 21 days. The ulcer is covered by epithelium, and wound healing occurs, often leaving no scar or trace of the lesion of RAS, [11] with significant lessening of pain. [2] Thus, all lesions of RAS heal and new ones develop. Scarring occurs most commonly with MjRAS and correlates with the depth of necrosis.

Cells of the lesion

Neutrophils are important effector cells participating in the inflammatory events of RAS, although the chemotactic function of neutrophil is normal in RAS, [29] their marked concentration at the ulcer area in the ulcerative phase of the lesion suggests that they may play an active role in the pathogenesis and/or healing of RAS. Oral aphthae are a prominent feature of cyclic neutropenia, [30]and major aphthae in HIV-infected patients have been associated with a depressed absolute neutrophil count. [31] However, the exact role of neutrophils in the pathogenesis or healing of recurrent aphthae is still not known and remains to be identified.

Although macrophages are likely to participate in every stage of the inflammatory process, they have not yet been adequately studied to definitively establish their role in RAS pathogenesis. In a histopathological study of RAS, Schroedere et al [16] found the presence of numerous macrophages loaded with phagolysosomes containing debris of neutrophilic granulocytes, implying that macrophages mainly function to clear the tissue of neutrophil remnants.

Mast cells (MCs) have the ability to provide numerous mediators [32] and have long been regarded as potentially important in the inflammatory events in RAS. In a histopathological study involving Alcian blue/Safranin staining of MiRAU lesions,[33] Dolby AE 1969 found that the MC count in the first 2 days did not differ from that of the normal buccal mucosa, but there was an approximately 50% reduction in MC count in lesions of more than 48 h duration. In contrast, increased numbers of MCs were noted by Lehner T [18] in all three types of RAS (minor, major and Herpeti form) and in oral aphthae associated with Behcet's disease (BD)

Although theγ /δ T-cell population constitutes only about 5% of circulating T-cells, they are much more common in the peripheral blood of patients affected by RAS or Behcet's disease, especially during the active phase of the disease. [34] Interestingly, in a recent study Natah [35] shows that, as in the peripheral blood of patients with RAS and Behcet's disease, γ/δ T-lymphocytes were also increased locally at the sites of RAS lesions.

High plasma levels of IL-2 and a significant increase in its receptor expression by activated peripheral lymphocytes have been found in patients with RAS during the exacerbation stage [36] Gamma/delta T-cells from RAS patients have also been reported to produce IFNγ when induced by mitogenic stimulation. [37] The relevance of TNF α to the pathogenesis of RAS has reduced activity of TNF α in HIV-infected patients and in otherwise healthy persons with RAS. [38] Enhanced release of TNF α by peripheral blood monocytes of patients with RAS has also been demonstrated. [39] Furthermore, a recent study has shown low resting levels of interleukin-10 (IL- 10) mRNA in non-lesional mucosa of RAS patients and high levels of the mRNAs of the pro-inflammatory cytokines IL-2, IFN γ and TNF α in lesional and non-lesional mucosa of patients with RAS compared with controls. [40]

The ulcer area

The superficial tissue exudates consist of clotted fibrin and numerous red blood cells that form hemorrhagic foci. The epithelium is infiltrated with variable numbers of intraepithelial lymphocytes and some neutrophils. [14] Neutrophils are predominating in the immediate ulcerated area, although peripheral areas surrounding the ulcer remain mononuclear in nature.[41]

The area lateral to the ulcer

This is defined as the epithelium-covered area

extending from the edge of the ulcer and sideways to the periphery of the biopsy. There is intense leucocytic infiltration with predominance of lymphocytes in non-ulcer regions, where they outnumber neutrophil. [42] Monocytes/macrophages are also numerous in the tissue adjacent and lateral to the ulcer. The density of MC's is increased in the lamina propria. [16]The lymphocytes in RAS are primarily T lymphocytes, and only 5-12% of all cells in the lesion are B cells [42] A small proportion of plasma cells and eosinophils can be found, more often in older lesions. [43] Dilatation of blood vessels is a constant and prominent feature of RAS lesions, as are foci of perivascular mononuclear cell infiltrate. [43]

Pain and quality of life

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. [44] RAS is a painful phenomenon, characterized by necrotizing ulcers of the oral mucosa that persist, remit, and recur for variable periods of time. Despite the self-limitation of the disease, pain and ulceration may disable patient and prevent them from performing their daily activities. Painful RAS lesions usually affect the movable mucosa, and the frequency of attacks ranges from only once or twice a year to more or less continuous batches of lesions that cause considerable discomfort, often with pain and difficulty in eating and speaking, and a decreased quality of life (QOL)[45]

Quality of life is a relatively new concept in the measurement of health. It broadens the assessment of the impact of disease to include physical, psychological and social functioning. [46] Indeed, the impact of RAS on QOL has not yet been studied, but the clinical impression is that RAS causes much suffering in affected patients due to repeated painful attacks. [47]

Recurrent aphthous stomatitis has been the subject of active investigation along multiple lines of research, including epidemiology, immunology, clinical correlation, and therapy. Numerous review articles have been written since 1960s, to permit the student to assess the large and actively growing literature regarding RAS. Fortunately, most patients with RAS suffer from simple aphthosis, which although aggravating and frustrating, common in young people (20%) dose not substantively interfere with quality of life.

We therefore, concluded that patients suffering from lesion of RAS visit to the physician should be treated according to their aetiological or pathological findings.

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