

Review Article**Syndromes associated with aphthous ulcers**

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ABSTRACT

Recurrent Aphthous Stomatitis (RAS) is a common oral condition which is characterized by formation of recurrent, multiple, small, round or oval ulcers over the oral mucosa. The etiopathogenesis of RAS is still unclear. The diagnosis of this condition is very easy but many times, these ulcers are a part of an underlying disease or syndrome. The main aim of this article is to make the clinicians aware of the underlying syndromes associated with RAS so that appropriate patient care and further management with proper referrals can be arranged. A brief review of the syndromes associated with RAS is described.

Key words: Aphthous syndromes, Aphthous ulcers, Stomatitis

INTRODUCTION

Recurrent Aphthous Stomatitis (RAS), also known as canker sores is a common oral condition characterized by formation of recurrent, multiple, small, round or oval ulcers over the oral mucosa. These ulcers have circumscribed margins, erythematous haloes and yellow or grey floors. These ulcers appear first in childhood or adolescence [1, 2].

RAS can be described under three clinical variants – Minor aphthae, Major aphthae and Herpetiform aphthae. Minor aphthae are multiple small round or ovoid ulcers 2 – 4mm in diameter with yellowish grey floor and are surrounded by erythematous halo. They are found mainly on the non-keratinized mobile mucosa of the lips, cheeks, floor of the mouth, sulci or ventrum of the tongue. They heal within 7 to 10 days without any scar formation. The major form has large painful ulcers more than 1 cm in size, which remain for a week to month and generally heal with scar formation. Herpetiform ulcers are rare and occur as small ulcers usually about 50 to 100 in number which may coalesce to form large ulcers. Their clinical course is similar to minor RAS [2, 3]

The etiology is still unclear but many predisposing factors are suggested. These include genetics, trauma, stress, tobacco, certain drugs, haematinic deficiency, gluten sensitive enteropathy, inflammatory bowel disease, sodium lauryl sulphate containing toothpaste, hormonal changes, bacteria like oral Streptococci and Helicobacter pylori and viruses like Cytomegalo virus and Epstein Barr virus. Tumor necrosis factor alpha (TNF – α) has

also been implied in the development of aphthous ulcers [3, 4, 5]

The diagnosis is mainly based on history and clinical examination. However, in some cases, RAS is associated with some underlying systemic disease or syndrome which should be considered in differential diagnosis. These include Behcet's syndrome, MAGIC syndrome, cyclic neutropenia, PFAPA syndrome, Sweets syndrome and AIDS [1-5]. A short review of each of these conditions is described.

Behcet's Syndrome :

Behcet's syndrome (BS) is a chronic multisystem inflammatory disorder of unknown cause. The characteristic features include recurrent aphthous stomatitis, genital ulcerations, ocular lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, papulopustular lesions or acneiform nodules) or a positive pathergy test. It was first described by Hulusi Behcet in 1937 as a triad of oral and genital aphthous ulceration and iridocyclitis[6]. It is seen mainly in the Mediterranean basin, Middle East and the Far East. Turkey has the highest prevalence, while the frequency is lower in western countries[7,8]

This disease is caused by immunocomplexes that lead to vasculitis of small and medium sized blood vessels and inflammation of epithelium caused by immunocompetent T lymphocytes and plasma cells. Majority of patients with this syndrome are sporadic, a familial aggregation of such patients has been noted. Studies have supported the direct role of HLA-B5, and particularly with its split B5 in the pathogenesis of BS [8, 9].

Two forms of this syndrome are recognized, which include child onset which affects children mainly between the age of 9 and 10 years and adult onset [6]. Most common site of involvement of Behçet's syndrome is oral mucosa. In 90% of the patients, the ulcers resemble the RAS. The lesions can occur anywhere on the oral mucosa as well as pharyngeal mucosa and mimic the minor or major variety of RAS. The second most common site is the genital area which involves ulcers of the scrotum and penis in males and ulcers of the labia in females. The eye lesions consists of uveitis, retinal infiltrates, edema and vascular occlusion, optic atrophy, conjunctivitis and keratitis [8, 10, 11]

Arthritis can occur in more than 50% of patients and most frequently affects the knees and ankles. Some patients have central nervous system involvement which includes brainstem syndrome, involvement of cranial nerves, or neurologic degeneration resembling multiple sclerosis. Other signs of BS include thrombophlebitis, intestinal ulceration, venous thrombosis and renal and pulmonary disease. Involvement of large vessels is life threatening because of the risk of arterial occlusion or aneurysm [8, 10]

A set of diagnostic criteria for BS has been given by an International Study group for BS that includes recurrent oral ulceration occurring at least three times in one 12 month period plus two of the following four manifestations [10].

- Recurrent genital ulceration
- Eye lesions including uveitis or retinal vasculitis
- Skin lesions including erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules in post-adolescent patients not receiving corticosteroids
- A positive pathergy test.

The management of BS depends on the severity and the site of involvement. The drugs used are corticosteroids, azathioprine, pentoxifylline, cyclosporine, colchicine and thalidomide. However corticosteroids remain the mainstay of treatment particularly to control the disease rapidly. Plasmapheresis is also an emergency treatment modality [11].

MAGIC SYNDROME

This term was given by Firestein et al in 1985 [12]. Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome is a very infrequent disease which includes clinical manifestations of Behçet disease and relapsing polychondritis (RP). RP is characterized by recurrent episodes of inflammation of the cartilaginous structures, resulting in tissue

damage and tissue destruction. All types of cartilage may be involved such as: the elastic cartilage of the ears and nose, the hyaline cartilage of peripheral joints, the fibrocartilage of the axial skeleton and the cartilage of the tracheobronchial tree. It can progress in a fluctuating manner and without treatment, can result in permanent destruction of the affected body part [12, 13].

Pathogenesis of RP is unknown; it is generally believed to be an autoimmune disease resulting from circulating antibodies against type II collagen in cartilage. It is also associated with HLA DR4 suggesting an immune mediated pathology [13].

Clinical features of MAGIC syndrome are similar to Behçet's syndrome along with relapsing polychondritis which mainly affects the external ear causing pain, redness, swelling or tenderness of one or both ears. The episodes remain for few days or weeks and then the patient recovers with or without treatment. After recurrent or persistent inflammation, there is destruction of cartilaginous structures and there may be hearing loss. Patients generally also suffer from joint pain with or without arthritis. This arthritis mimics rheumatoid arthritis but tests for RA factor are negative. Involvement of nasal cartilage causes swelling and pain initially but destruction of the cartilage can cause saddle nose deformity [13, 14].

Inflammation of the laryngeal, tracheal and bronchial cartilages causes hoarseness, non productive cough, dyspnea, wheezing and inspiratory stridor. The skin, ocular and genital manifestations are similar to Behçet's syndrome [13, 14].

Laboratory findings during the symptomatic phases show increased ESR, C – reactive protein, anemia, leukocytosis and thrombocytosis. Serum antibodies to collagen II have been found in nearly half of the patients. Biopsy from ear cartilage or other inflamed sites help to confirm the diagnosis [15, 16].

Management includes control of inflammation using non steroidal anti inflammatory drugs and oral prednisolone initially. In severe cases, large doses of prednisolone (1mg/kg/day) is required until there is control of symptoms and then tapered. Other drugs like azathioprine, cyclosporine, methotrexate, dapsone, D – penicillamine, colchicine and cyclophosphamide with or without steroids are used with varying results [15, 16].

CYCLIC NEUTROPENIA (CN)

Cyclic Neutropenia is a rare disorder occurs secondary to a periodic failure of the stem cells in

the bone marrow. It is characterized by transient severe neutropenia that occurs approximately every 21 days due to oscillations in production of neutrophils by bonemarrow [17].

Cyclic neutropenia is inherited as an autosomal dominant disorder with full penetrance but varying severity of clinical manifestations. Gene studies have revealed that the families affected with CN had mutations in the gene for neutrophil elastase (ELA2). Cellular studies have demonstrated that accelerated apoptosis of neutrophil precursors is the proximate cause of the reduced neutrophil production [17, 18].

Clinical features include fever, malaise, aphthous stomatitis, mucus membrane infections and lymphadenopathy. Manifestations of this disease usually begin in childhood but some patients suffer from the adult onset form. Between these periods of recurrent fever, mouth ulcers, and infections, patients are usually without symptoms and have normal physical examination [19].

Management of CN includes proper care of patient during the period of decreased neutrophil count. Antibiotics and antipyretics are administered to control the symptoms. Splenectomy, androgens, glucocorticosteroids, and lithium were used, but are not much effective. The availability of recombinant human G-CSF has greatly changed the management of cyclic neutropenia. G-CSF has shown to shorten the period of neutropenia as well as the length of the neutropenic cycle. This treatment is known to be effective at least as early as the age of six months to one year. For affected individuals with a well matched donor, haematopoietic stem cell transplantation may be the preferred treatment option[17,18,19].

PERIODIC FEVER, APHTHOUS STOMATITIS, PHARANGYTIS AND CERVICAL ADENITIS (PFAPA) SYNDROME

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome was first described by Marshall in 1987[20]. It is a pediatric periodic disease characterized by recurrent febrile episodes associated with head and neck symptoms. The etiology of this syndrome is unknown but infectious and immunological mechanisms have been implicated [20].

The clinical characteristic features of PFAPA syndrome is high fevers (usually 40.0°C to 40.6°C) recurring at fixed intervals every 2 to 8 weeks. The fevers last for about 4 days then resolve spontaneously. Other symptoms associated with fever are aphthous stomatitis, pharyngitis and

cervical adenitis. It is not familial and begins before the age of 5 years. The episodes of PFAPA may last for years and the patient is well between episodes [21].

This syndrome is defined clinically and diagnosis is made by exclusion. One of the diagnostic criteria include complete resolution of febrile attacks by single oral administration of corticosteroids[22].

The most widely accepted treatment of PFAPA syndrome is corticosteroids, oral prednisolone (1mg/kg/day, 3 to 5 days). It has been observed that one or two doses of prednisolone dramatically shorten the duration of fever without reducing the number of attacks. Other proposed treatments include cimetidine and tonsillectomy. It has been reported that there is complete resolution of symptoms in about two thirds of patients after tonsillectomy [23].

SWEET SYNDROME

Sweet syndrome (SS) was first described by Robert Sweet in 1964 as acute febrile neutrophilic dermatosis. It is characterized by a constellation of clinical symptoms, physical features, and pathologic findings which include fever, neutrophilia, tender erythematous skin lesions (papules, nodules, and plaques), and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis [24, 25].

Sweet syndrome is classified in three main types: Classical, paraneoplastic and drug induced. Classical type is more common in women between the ages of 30 to 50 years, is often preceded by upper respiratory tract infection and may be associated with inflammatory bowel disease and pregnancy. The paraneoplastic type is associated commonly with haematogenous malignancy mainly acute myelogenous leukemia. The commonly associated solid tumors are those of genitourinary organs, breast and of gastrointestinal tract. Drug-induced Sweet syndrome most commonly occurs in patients who have been treated with granulocyte-colony stimulating factor, however, other medications may also be associated [25, 26].

The exact pathogenesis of Sweet Syndrome is not known. However, altered immunological reactivity may be in the form of hypersensitivity to bacterial, viral, and tumour antigens, or circulating auto anti body and immunocomplex reaction or cytokine deregulation are proposed factors [25,26].

Fever is the most common symptom which may be accompanied by general malaise, myalgia and

arthralgia. Cutaneous manifestations consist of erythematous papules, nodules with pseudo vesicular appearance, sometimes coalescing to form plaques which can be studded with pustules, or giving targetoid appearance. Face, neck, upper limb and trunk are the commonly involved sites. Oral manifestations include recurrent aphthous stomatitis and their presence should alarm the association with haematological disorders [25, 26].

Management includes topical and intralesional corticosteroids initially however systemic corticosteroids remain the mainstay of treatment. Other first line systemic drugs include potassium iodide and colchicines. Second line treatment includes indomethacin, clofazimine, cyclosporin, and dapsone. In malignancy associated type, the treatment of the underlying malignancy has showed resolution and in drug associated type, stoppage of the suspected medication has showed good results [26,27].

HIV / AIDS

Recurrent aphthous stomatitis (RAS) is one of the common oral manifestations of HIV / AIDS. In this condition, the ulcers are similar to those of non – infected group but are long lasting and are less responsive to routine medications. In many patients, major aphthae are found and are associated with advanced HIV infection (CD_4^+ counts less than $50 / mm^3$) which suggests that immune compromise is a factor predisposing to aphthous stomatitis [28,29].

Topical and systemic steroids are the treatment of choice according to severity of ulceration. Immune suppressants and immune modulatory drugs have shown to be effective in majority of cases but they do not prevent recurrence and their use is limited by its toxicity. At present the treatment of choice remains anti retroviral therapy as immune recovery is a determining factor in resolution of ulcers [29,30].

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