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Dental conditions in rheumatic diseases.

Afecciones odontológicas en enfermedades reumáticas.

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Abstract

Objectives. Review oral manifestations of rheumatic diseases since these can be a diagnostic challenge.

Procedures. We performed a PubMed search using terms of rheumatic diseases, autoimmune disease and oral manifestations and also reviewed related guidelines and classifications.

Results. We describe the clinical presentations of rheumatic diseases, such as scleroderma, rheumatoid arthritis, Sjögren's syndrome, Systemic lupus erythematosus and others that present specific oral manifestations. We also review the association between periodontal disease and autoimmunity that has been recently described in the literature.

Conclusions. The oral manifestations of rheumatic diseases are diverse and can represent a challenge for medical and dental professionals.

Keywords: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, autoimmune disease, periodontal disease, oral cavity.

Resumen

Objetivos. Revisar las manifestaciones bucales de las enfermedades reumáticas, ya que estas pueden ser un reto diagnóstico.

Procedimientos. Se realizó una búsqueda en PubMed utilizando términos de enfermedades reumáticas, enfermedades autoinmunes y manifestaciones orales y también se revisaron directrices y clasificaciones relacionadas.

Resultados. Describimos las presentaciones clínicas de enfermedades reumáticas, como esclerodermia, artritis reumatoide, síndrome de Sjögren, lupus eritematoso sistémico y otros que presentan manifestaciones orales específicas. También revisamos la asociación entre la enfermedad periodontal y la autoinmunidad que se ha descrito recientemente en la literatura.

Conclusiones. Las manifestaciones orales de las enfermedades reumáticas son diversas y pueden representar un reto para los profesionales médicos y odontológicos.

Palabras clave: escleroderma, lupus eritematoso sistémico, artritis reumatoide, enfermedad autoinmune, enfermedad periodontal, cavidad oral.

INTRODUCTION

Patients with rheumatic diseases present multiple oral manifestations. These diverse disorders primarily involve structures of the musculoskeletal system with varying degrees of disability, from mild limitations to life threatening disease. In this review, we describe some of these manifestations and also review the association between periodontal disease and autoimmunity. The diseases reviewed were chosen because of their diverse oral signs and symptoms, which can be a diagnostic challenge for medical professionals.

Examination of the mouth and gums can represent a challenge for most physicians because of the wide range of local and systemic processes that can be present. Dentists have better training in the recognition of oral lesions but in their daily practice they limit physical examination to the head and oral cavity. Also, they sometimes lack knowledge of autoimmune diseases.

METHODS

We performed a PubMed search using the terms scleroderma, systemic lupus erythematosus, rheu-

matoid arthritis, autoimmune disease and oral manifestations. We also carried out a review of guidelines and classifications related to these rheumatic diseases and their treatment. Clinical manifestations that can occur in the oral cavity because of specific therapies were also taken into consideration.

Oral Conditions in Rheumatic Diseases

Systemic scleroderma (SCD) is characterized by the thickening and tightening of the skin in addition to inflammation of body organs. Its prevalence varies according to different studies in populations, although it most commonly affects women between 30 and 50 years of age. Hardening of the skin of the fingers (sclerodactyly) and edema and/or hardening of the skin of the face, neck, trunk and extremities are common manifestations. In later stages of the disease, skin furrows that radiate from the mouth and thinning of the vermilion are typical. Telangiectasia can also be detected on the face and even on the tongue and cheeks. Patients with SCD have great difficulty opening their mouths wide[1]. (Table 1)

Raynaud's phenomenon is a paroxysmal vasospasm caused by exposure to cold or emotional stress that affects many patients with SCD and systemic lupus erythematosus (SLE). It presents as pallor, cyanosis, and erythema of the fingers. The dentist may notice this sign in patients when air conditioning is on[2].

Rheumatoid arthritis (RA) is a chronic inflammatory, systemic disorder of unknown etiology that predominantly affects diarthrodial joints. Its annual incidence is approximately 12 cases/100,000 population. The disease is frequent in women between the ages of 35 and 50 years with a prevalence of approximately 1% [3].

A typical observation in chronic RA is bilateral limitation or ankylosis of the wrists. Also, bilateral limitation or ankylosis of the temporomandibular joints can be found[4]. Changes of the tongue are frequently observed. Secondary amyloidosis, which causes infiltration of the salivary glands and tongue that produces macroglossia, has been reported. Although this clinical manifestation is rare, it can be seen in patients with longstanding disease[5]. Patients also show an increased incidence of sicca and secondary Sjögren's syndrome[6]. A recent study shows greater loss of periodontal attachment and alveolar bone in early RA suggesting that intensive dental care must be established to limit periodontal damage[7].

Sjögren's syndrome (SS) is a chronic inflammatory disease characterized by decreased tears and saliva. It is classified when two of the following criteria are met: a positive serum anti-SSA/Ro and/or anti-SSB/La (positive rheumatoid factor and ANA titer 1:320), or a labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis and the presence of keratoconjunctivitis sicca[8]. It occurs in a primary

form not associated with other diseases and in a form secondary to rheumatic disease[9]. The most common disease associated with secondary SS is rheumatoid arthritis. The clinical manifestations of SS can be divided into those associated with exocrine gland function and those that are extraglandular[10]. A prospective study of 80 patients with primary SS that were followed for a mean of 7.5 years reported keratoconjunctivitis and/or xerostomia in all patients, with this being the only clinical manifestation in 31%. Extraglandular participation occurred in 25% and non-Hodgkin´s lymphoma occurred in 2.5% [11].

Patients with Sjögren usually have poor oral hygiene. A study of 81 subjects, 21 with primary SS, 29 with secondary SS, and 31 healthy individuals, showed that patients with SS considered their oral health poor and described dryness of the mouth as intense. The most common symptoms were acid sensitivity (68%), difficulty eating dry foods (66%), and sensitivity to spicy foods (58%). Dry lips (76%) and tongue (68%) were also among the most frequent complaints. Cervical and atypical cavities (83%), a fissured and erythematous tongue (70%) and oral candidiasis (74%) were also reported[12].

Another frequent alteration in several rheumatic diseases is ulcers, which have a wide differential diagnosis. One of the rheumatic diseases that may present recurrent ulcers in the oral and pharyngeal mucosa is Behçet's disease, a rare autoimmune illness that should be suspected in patients with recurrent multiple round painful oral ulcers. It should also be suspected if systemic manifestations such as thrombophilia, genital ulcers, eye disease, skin lesions, gastrointestinal involvement, neurological disease, vascular disease, or arthritis are present[13, 14].

Systemic lupus erythematosus is a chronic systemic inflammatory autoimmune disease that results from an alteration of immunoregulation mechanisms caused by an interaction of multiple genetic, environmental, and hormonal factors. The prevalence of SLE is currently estimated at 2.9/100,000 to 400/100,000. It is more common in women with a female:male ratio of 9 to 1, but in childhood or after menopause the ratio is narrower (2:1). SLE seems to be more common in certain racial groups, mainly Afro-Americans, Hispanics, and possibly Chinese and other Asian populations[15]. It can occur at any age but is most common between 20 and 40 years of age. There are a variety of manifestations with arthralgia, arthritis, and myalgia, but skin manifestations are the most common. Of these, the most typical and frequent is a "butterfly" rash and lesions caused by photosensitivity[16].

Typically the disease affects several organs but not all systems and can proceed with periods of exacerbations and remissions over several years. Antinuclear antibodies have been helpful in its diagnosis, since 98% of patients are positive.

SLE patients present a variety of oral health manifestations: poor oral hygiene, third-grade caries, and

painless superficial ulcers that frequently affect the oral mucosa, lips, and palate[17]. Also, the SLE patient can present sicca complex characterized by reduced tear and saliva production[18].

Ulcerations of the palate have been reported in patients with Wegener's granulomatosis, an autoimmune disorder characterized by small vessel vasculitis that is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA). Its incidence is undetermined but in some countries ranges between 3–10 cases per 100,000 individuals. Hallmarks of this condition are systemic necrotizing vasculitis, necrotizing granulomatous inflammation, and necrotizing glomerulonephritis. The etiology of granulomatosis with polyangitis is linked to environmental and infectious triggers that incite the onset of disease in genetically predisposed individuals[19].

Gingival involvement in Wegener's granulomatosis is a common manifestation that is characterized by a reddish-purple hyperplasia of the gingiva with petechial hemorrhages, a manifestation described as “strawberry gingivitis” [20]. Oral ulcers can occur in areas of the oral and nasal cavity in early stages. Less commonly nasal septum perforation or destruction of the nose cartilage resulting in a "saddle nose” can occur. Oral ulcers can be painful or painless. Patients usually report recurrent episodes of sinusitis or chronic sinusitis that do not respond to antibiotics. Chronic sinusitis is the presenting symptom in 50% of cases and in 80% during the course of the disease[21].

Chronic inflammation of the nasal mucosa is detected in 70% of patients, manifested by a bloody or purulent nasal discharge and epistaxis. In the pharyngeal mucosa, chronic inflammation causes obstruction of the ear canal resulting in chronic serous otitis media or acute suppurative otitis media. In the tracheal or laryngeal mucosa subglottic stenosis may occur, which in severe cases, can cause stridor and respiratory failure. The previous data alone or combined with nodular pulmonary infiltrates in a seriously ill patient, with abnormal urinary sediment in the absence of urinary infection, and the presence of symptoms such as fatigue, malaise, multisystem disease, peripheral neuropathy without diabetes and/or the appearance of skin lesions such as petechiae, palpable purpura, livedo reticularis and ulcers lead to the diagnosis of vasculitis[22].

ANCA, which produce a pattern called cytoplasmic or c-ANCA with indirect immunofluorescence, have been particularly helpful in the diagnosis of certain vasculitis, such as those associated with Wegener's Granulomatous[23]. Since the dentist is one of the first health care professional to recognize Wegener's granulomatosis manifestations, it is important to train clinicians to facilitate early diagnosis.

Painless superficial ulcers in the oral mucosa and tongue are mucocutaneous manifestations associated with reactive arthritis. Reactive arthritis is a spondyloarthropathy that shares features with undifferen-

tiated spondyloarthritis, ankylosing spondylitis, psoriatic arthritis and spondylitis associated with inflammatory bowel disease. Members of this family share certain clinical similarities, especially the presence of HLA-B27, which occurs in up to 90% of patients with reactive arthritis[24]. Reactive arthritis usually occurs 2-4 weeks after an infectious event and has been associated with certain sexually transmitted microorganisms such as *Chlamydia trachomatis*, and bacterial gastrointestinal dysenteric infections such as *Salmonella*, *Shigella*, *Yersinia* or *Campylobacter*. The classic triad is nongonococcal urethritis, conjunctivitis and arthritis but incomplete forms may occur. Oral lesions can occur anywhere in the oral cavity and present as aphthous-like ulcerations, plaques, and erythematous lesions or depapillation of the tongue[25].

Kawasaki disease or syndrome usually occurs in children with febrile syndrome with 85% of cases presenting in children less than 5 years of age with a mortality of 1% to 2.6%. Its incidence is low, approximately 70-80 cases/100,000, although in epidemics, this frequency can increase. The appearance of diffuse erythema of the oral and pharyngeal mucosa, red lips, and a "raspberry tongue" are data that should orient to the diagnosis. In addition to these symptoms, erythema of the palms and soles, indurated edema in the acute phase, and finally, desquamation, can occur. This disease, also known as mucocutaneous lymph node syndrome, is one of the most common vasculitis of childhood[26] and rarely occurs in adults. It is usually self-limited with fever and manifestations of acute inflammation that last an average of 11 days without treatment. However, complications such as coronary artery aneurysms, depressed myocardial contractility, heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and result in significant morbidity and mortality[27].

Another group of autoimmune diseases that share characteristics with those previously described are autoinflammatory syndromes, also known as familial periodic fever syndromes (FPFS), which are characterized by attacks of inflammation, apparently without cause, without the presence of autoantibodies or autoreactive T cells[28]. These genetic syndromes result from defects in proteins of the innate immune system. More than ten inherited autoinflammatory syndromes caused by more than 770 different mutations have been identified, although 30% to 70% have not been associated with known diagnostic mutations[29]. The most common condition of this type is periodic fever, aphthous stomatitis, pharyngitis, and adenitis. Another syndrome included in this group is cyclic hematopoiesis, which has very similar clinical features; however, PFAPA is a syndrome that occurs sporadically. In children with PFAPA syndrome, periodic fever usually begins between the ages of two and five years with a slight male predominance and no ethnic or racial preference. Familial cases are rare. In most patients attacks stop occurring before 10 years of age[30]. Appearance of periodic oral ulcers in association with periodic fever and other symptoms could suggest PFAPA syndrome. That is why the pediatric dentist may be the first healthcare worker to evaluate a child with clinical signs compatible with PFAPA syndrome. Additonally,

children diagnosed with this condition require systematic oral follow-up to monitor for signs of ulceration[31].

Temporomandibular Joint Disorders

It is rare to find this joint inflamed. When affected, the patient usually complains of pain when eating because of limitation of mouth opening secondary to pain. Mild inflammation is difficult to detect when exploring this joint unless it occurs asymmetrically. The joint can be felt by placing a finger in front of the ear canal and asking the patient to open and close his/her mouth and to move the jaw to look for evidence of inflammation and tenderness. In some patients, crepitation can be heard and felt, even when arthritis is not severe.

Disorders of the temporomandibular joint (TMJ) can be classified as intracapsular or extracapsular. Extracapsular disorders are more common and are collectively known as myofascial pain syndrome of the masticatory muscles. A common name for this disorder is TMJ syndrome. TMJ syndrome is characterized by acute or chronic musculoskeletal pain, with dysfunction of the masticatory system. It is aggravated by jaw movement, but is distinct from dental disease. Myofascial pain of the masticatory muscles presumably occurs because of persistent, unconscious, repetitive use of the muscles involved [32]. Regarding intracapsular causes, the diseases that most often affect the TMJ are RA[33], degenerative osteoarthritis[34], ankylosing spondylitis[35], and juvenile rheumatoid arthritis (JRA)[36]. If inflammation persists without proper treatment, decreased bone growth, which results in severe micrognathia, can occur.

Functional disorders of the TMJ are the most common cause of temporomandibular joint pain[37]. Bruxism is another little-known cause[38]. These and other conditions of the temporomandibular joint involve orofacial pain and reduced mandibular function, which are common conditions in the general population. Factors such as bruxism, aggravated by stress or trauma, can accelerate the emergence of joint disorders[32].

Jaw claudication, manifested by fatigue of the mastication muscles, has been described in temporal arteritis, also called giant cell arteritis, a large vessel vasculitis that frequently occurs in elderly Caucasians. This disease may develop with headache, fever, fatigue and malaise. Its incidence is 6.7/100,000/year but in individuals over 50 years it is 18.3/100,000. It has been associated with HLA-DR4 and CW3[39]. Patients with headache, jaw claudication when eating, talking or chewing, with or without tongue claudication, masticatory muscle pain and reduction of jaw opening, should be referred to a rheumatologist for a complete evaluation. In this condition, there is a high erythrocyte sedimentation rate of 70 to 100

mm/hour, anemia, and a high C-reactive protein level[40].

Drugs that can cause dental disorders

In addition to the autoimmune processes or the symptoms of rheumatic diseases, the use of drugs aimed at controlling an underlying disease and its symptoms (NSAIDs, glucocorticoids, disease modifying antirheumatic drugs [DMARDs] and immunosuppressants) may produce adverse effects such as ulcers, mucositis, gingivitis, stomatitis, and gingival bleeding.

Methotrexate, for example, at high doses, may cause mucositis[41]. The use of penicillamine can cause taste disturbances or even ageusia[42]. The use of gold salts is associated with the presence of cheilitis. Steroids at high doses as well as DMARDs predispose to infection by opportunistic pathogens such as *Candida albicans*. Gingival hyperplasia has been observed in patients treated with cyclosporin A[43]. Relapses or outbreaks of herpes sores may be more frequent with the use of corticosteroids or immunosuppressants.

Osteonecrosis of the jaw (ONJ) has been associated with the use of bisphosphonates[44], medications that are used in the treatment of osteoporosis secondary to corticosteroid use and that of postmenopausal origin and in the treatment of various conditions such as the hypercalcemia of cancer and Paget's disease. Recently, the medical community has been warned of this adverse event, which although rare, is devastating[45].

Bisphosphonates are drugs that affect bones by altering the function of osteoclasts. A review of ninety-nine cases of ONJ among patients who were prescribed a bisphosphonate for an indication other than cancer included 85 patients with osteoporosis, 10 patients with Paget's disease, two patients with RA, a patient with diabetes, and one with fibrous dysplasia of the maxilla. Mean age was 69.4 years, 87.3% were women and 83.3% were receiving an oral bisphosphonate. A dental procedure was performed in 88.9% before the onset of osteonecrosis of the jaw. Seventy-one percent were taking at least one medication that affects bone turnover, in addition to bisphosphonates, and 81.3% reported other underlying health conditions. Thus, multiple factors likely influence its pathogenesis[46]; however, a previous history of tooth extraction is an important factor.

In another study, the frequency of ONJ in patients with osteoporosis, especially with weekly oral alendronate was 1 in 2,260 to 8,470 (0.01% to 0.04%) patients. If extractions were carried out, the calculated frequency increased significantly to 1 in 296 to 1,130 cases (0.09% to 0.34%). The total dose of oral

alendronate in the presence of ONJ was 9,060 mg. The frequency of ONJ in cases of Paget's disease was 0.26% to 1.8%. If extractions were carried out, the calculated frequency of ONJ increased from 2.1% to 13.5%. The frequency of ONJ in cases of bone malignancy with intravenous pamidronate or zoledronate treatment was 0.88% to 1.15%. If extractions were carried out, the calculated frequency of ONJ was 6.67% to 9.1%. The total dose of pamidronate was 3,285 mg (± 2,530) and 62 mg of zoledronate (± 54.28) at the onset of ONJ. The median time to onset of ONJ was 12 months for zoledronate, and 24 months for pamidronate and alendronate[47]. It may be advisable to perform dental procedures before prescribing bisphosphonates.

Periodontitis and Autoimmune Disease

An association between rheumatic disorders and inflammatory mechanisms is suggested by their physiopathological resemblance. In recent years, new evidence supports the concept that oral and intestine microbiome can play an active role in triggering rheumatic diseases[48]. Periodontitis is an inflammatory condition associated with localized infection that directly affects the teeth and supporting structures. Multiple studies have demonstrated the involvement of autoimmune processes in periodontal disease. The presence of auto-antibodies directed against modified type I and III collagen, and anti-cyclic citrullinated peptide (aCCP) antibodies or autorreactive T lymphocytes in patients with aggressive periodontitis has been reported[49]. An association between RA and periodontitis has been reported by multiple groups[50, 51] with infection often being caused by *Porphyromona gingivalis*, which is credited with protein citrullination[52], generating auto-antigens derived from extracellular soluble protein such as fibrinogen, alpha-enolase, collagens or vimentin and promoting an autoimmune response in RA[53]. Recent studies have evidenced the presence of *P. gingivalis* DNA in blood and synovial tissue[54] or that periodontal treatment decrease aCCP antibodies in RA patients[55]. Although it has been observed that RA patients often present with periodontal disease, its presence has not been associated with disease activity or severity[56]. Surprisingly, in a recent pilot study conducted at the Universidad Autónoma de Nuevo León in Monterrey, México (unpublished data), it was found that 40% of patients with RA were molecular test positive for *B. forsythus* (*Tannerella forsythensis*), a bacterium of the red complex of periodontal pathogens. This preliminary result indicates a strong relation between periodontal disease and RA. In a similar context, recent efforts have been done to associate periodontal microbioma with aCCP and RA pathology[57].

Other diseases have been associated with periodontal disease: JRA, where a higher prevalence of periodontal disease has been reported in comparison with a control population[58]; also, an association between JRA, chronic periodontitis, and HLA-DRB3 has been reported[59]. In systemic sclerosis (SS),

characterized by excess collagen production and intense fibrosis of the skin, an increase in the periodontal space (with the most affected areas being the molar and premolar areas in comparison with the incisor area), tooth loss, difficulty swallowing and other oral sequelae-including microstomia, oral mucosal/gingival fibrosis and xerostomia, have been observed[60].

CONCLUSION

Systemic autoimmune diseases present many oral manifestations that can be difficult to identify and manage depending on the characteristics of the disease. Medical professionals should carefully evaluate these patients to provide the best available treatment but they should also consider effects caused by the drugs they use to treat these illnesses since these can also cause lesions in the oral cavity or mucosa.

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Table 1. Association between rheumatic diseases and oral manifestations.

Disease	Rheumatic manifestations	Oral manifestations
Ankylosing spondylitis	Arthritis	Intracapsular TMJ inflammation
Behçet's disease	Thrombophilia, papulopustular lesions, Joint arthritis, increased γλT cell.	Multiple round painful oral ulcers, pharyngeal mucosa ulcers
Giant cell arteritis	Large vessel vasculitis, concomitant polymyalgia rheumatica	Jaw claudication, masticatory muscle pain, reduction of jaw opening
Kawasaki disease	Childhood vasculitis, Fever, Acute inflammation	Diffuse erythema of the oral and pharyngeal mucosa, red lips, "Raspberry tongue"
PFAPA syndrome	Familial periodic fever syndromes, Aphthous stomatitis, Adenitis	Pharyngitis, periodic oral ulcers
Reactive arthritis	Undifferentiated spondyloarthritis, Ankylosing spondylitis, Psoriatic arthritis	Ulcers in the oral mucosa and tongue, diverse oral lesions
Rheumatoid arthritis	Chronic joint inflamation, Swollen joint count, Elevated levels of autoantibodies, Elevated levels of autorreactive cells, Elevated levels of citrullinated synovial proteins	Periodontitis, infection by P. gingivalis, gingival overgrowth, disease-associated periodontitis, macroglossia in long onset patient, intracapsular TMJ inflammation, ulcerations, sicca symptoms
Scleroderma	Sclerodactyly, edema, hardening of the skin of the face, telangiectases	Difficulty in opening the mouth wide, face skin edema, telangiectases in skin face and tongue, thinning and stiffness of the face
Sjögren's syndrome	Sicca syndrome, elevated levels of autoantibodies, increased concentration of serum IgG	Sicca syndrome (keratoconjunctivitis and xerostomía), poor oral higiene, acid sensitivity, difficulty eating dry foods, sensitivity to spicy foods, dry lips and tongue, cervical and atypical cavities, oral Candidiasis
Systemic Sclerosis	Excessive collagen production, high skin fibrosis	Increase in the periodontal space, tooth loss, difficulty swallowing, microstomia, oral mucosal/gingival fibrosis, xerostomia

Systemic Lupus Erythematosus	Arthralgia, arthritis, myalgia, skin manifestations (“butterfly" rash), Raynaud phenomenon, elevated levels of autoantibodies, multiple organ damage	Periodontitis and gingivitis, poor oral hygiene, third-degree caries, oral mucosal lesions, TMJ dysfunction, sicca symptoms, painless superficial ulcers, pallor, cyanosis and erythema of the fingers
Wegener's granulomatosis	Small vessels vasculitis, elevated levels of ANCA, systemic necrotising vasculitis, granulomatous inflammation, glomerulonephritis, skin lesions (petechiae, palpable purpura, livedo reticularis)	Oral and nasal ulcerations, sinusitis, chronic inflammation of the nasal mucosa, otitis, mucosa subglottic stenosis
TMJ disorders	Extracapsular TMJ inflammation, acute or chronic musculoskeletal pain, myofascial pain of the masticatory muscles	Masticatory system dysfunction, temporomandibular joint inflammation