Topical Review—Connective Tissue Diseases: Orofacial Manifestations Including Pain

Gary D. Klasser, DMD
Assistant Professor
College of Dentistry
Department of Oral Medicine and Diagnostic Sciences
University of Illinois at Chicago
Chicago, Illinois

Ramesh Balasubramaniam, BDSc
Resident
Department of Oral Medicine
Robert Schattner Center
University of Pennsylvania
School of Dental Medicine
Philadelphia, Pennsylvania

Joel Epstein, DMD, MSD
Professor and Head
Department of Oral Medicine and Diagnostic Sciences
College of Dentistry
University of Illinois at Chicago
and
Director
Interdisciplinary Program in Oral Cancer
College of Medicine
Chicago Cancer Center
Chicago, Illinois

Correspondence to:
Dr Gary D. Klasser
University of Illinois at Chicago
College of Dentistry
Department of Oral Medicine and Diagnostic Sciences
801 South Paulina Street, Room 556 (M/C 838)
Chicago, IL 60612-7213
Fax: +312 355 2688
E-mail: gklasser@uic.edu

This topical review presents an overview of orofacial manifestations associated with the more common connective tissue diseases affecting multiple organs. The orofacial manifestations associated with these autoimmune disorders include oral mucosa alterations, salivary gland pathosis, sensory neuropathies, headaches, and temporomandibular disorders. Since many of these orofacial manifestations may be painful, the practitioner managing pain patients should be familiar with them. An understanding of the orofacial manifestations associated with these systemic diseases will enable the pain practitioner to establish an appropriate diagnosis within the context of the underlying systemic disease. This will allow the practitioner the opportunity to contribute and collaborate as a member of a multidisciplinary health-care team in the management of these systemic autoimmune diseases. J OROFAC PAIN 2007; 21:171–184

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Connective tissue diseases represent a spectrum of disorders, from those affecting a single organ to those affecting multiple organ systems due to systemic autoimmune dysfunction or dysregulation. Patients with these disorders may present with overlapping and mixed clinical and laboratory findings. Pain in patients with connective tissue diseases may be due to alterations of oral mucosa, salivary gland pathosis, sensory neuropathies, headaches, and temporomandibular disorders (TMD). It is important for the practitioner managing pain patients to recognize and understand the orofacial manifestations associated with these systemic diseases. This appreciation will allow the pain practitioner to establish an appropriate diagnosis of the orofacial presentations within the context of the underlying systemic disease and contribute to the management of its orofacial symptomatology. This article reviews the orofacial manifestations associated with the more common connective tissue diseases affecting multiple organs.

Systemic Lupus Erythematosus

Overview

Systemic lupus erythematosus (SLE) is a chronic multisystem connective tissue disease related to autoimmune dysfunction characterized by the production of autoantibodies and multisystem inflam-

mation. SLE predominately affects females of childbearing age, with a 7 to 10:1 female-to-male ratio; it has an incidence of 1 in 700 among all women between the ages of 20 and 60 years and about 1 in 250 among African-American women.[1] Children and the elderly may also be affected. Females exposed to estrogen-containing oral contraceptives or hormone replacements have approximately a 2-fold increased risk of developing SLE.[2]

The cause of the disease is unknown but interactions between genetic, hormonal, and environmental factors (exposure to ultraviolet light and infections) have been implicated in its pathogenesis. The hallmark of SLE is abnormal autoantibody production resulting in immune complex deposition leading to inflammation and vasculopathy, which represent the basic abnormality.[3] The antigen-antibody complexes are deposited in a wide variety of tissues and organs, including the kidneys, skin, blood vessels, muscles and joints, heart, lungs, brain, gastrointestinal tract, lymphatics, and eyes.[4,5] The severity of SLE varies from mild to severe, with periods of exacerbations and quiescence; however, complete remission is rare. The American College of Rheumatology has developed criteria for the classification of SLE (Table 1).

Localized forms of lupus, termed discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus, may present with oral mucosal changes. Only 5% of the patients with DLE skin lesions develop the systemic form of the disease, yet 20% of individuals with SLE have the discoid form.[2]

Drug-induced lupus is a syndrome of positive antinuclear antibodies associated with symptoms such as fever, malaise, arthritis or intense arthralgia/myalgia, serositis, and/or rash. This syndrome appears during therapy with certain medications and biologic agents; the most common precipitants are minocycline, hydralazine, and procainamide.[6] It is predominant in Caucasians, has less female predilection than SLE, rarely involves the kidneys or brain, and usually resolves over several weeks after discontinuing the offending medication.[2]

Orofacial Manifestations

The primary oral involvement with SLE is erythema/inflammation associated with vasculitis, which may progress to ulceration of the lips and mucous membrane.[7] The lesions have been described as nonspecific and may be erythematous, with white plaques or radiating peripheral lines. Without careful evaluation, ulcerations may be mistaken for lichen planus or leukoplakia.[8] The prevalence of ulceration (the most commonly reported oral manifestation) varies between 7% and 41%.[9–12] Other studies have reported a high prevalence of various oral mucosal lesions, including erythema, ulcers, angular cheilitis, and glossitis, in addition to subjective complaints of glossodynia, dysgeusia, dysphagia, and xerostomia. These studies also reported a high rate of dental caries and periodontitis and concluded that salivary gland dysfunction was a major contributor to these oral manifestations.[7,13] Some studies have shown an association between mucosal ulceration and SLE disease activity,[13] while other studies have not.[14] The oral lesions in this population may represent autoimmune inflammation and vasculitis[15]; however, this hypothesis has been disputed.[16]

Involvement of the temporomandibular joint (TMJ) has been reported in a few studies but is not always associated with SLE polyarthritis.[17,18] Conversely, TMJ involvement may be the only manifestation of this systemic disease.[19] Clinical findings associated with TMJ involvement are locking or dislocation, tenderness to palpation, crepitation, and pain on movement of the mandible. Radiographic changes of the condyles, including flattening, erosion, osteophytes, and sclerosis are also seen.[20]

Case reports of trigeminal sensory neuropathy have been reported with SLE.[21,22] Facial numbness, paresthesia, dysesthesia, and pain have been reported most frequently; however, other cranial nerves may also be involved.[23] Trigeminal neuropathy may be the initial feature of SLE or may follow the onset of the disease, usually developing slowly over the course of the illness.[23–25]

In a meta-analysis by Mitsikostas et al,[26] pooled data from 8 controlled and uncontrolled studies indicated 57.1% of SLE patients reported headache based on the International Headache Society criteria. Further investigation and other studies[27] revealed the prevalence of headache among SLE patients to be no different than in control subjects. Additionally, the authors did not identify a pathophysiological relationship for headache in SLE, suggesting that headache in SLE patients should be treated as primary headache.

Salivary gland pathology due to hyposalivation (including retrograde salivary gland infection) and conditions unique to SLE, such as focal parotid necrosis[28] and lupus erythematosus profundus (presenting as a bilateral submandibular mass), have been reported.[29] These painful salivary gland conditions may be confused with pain emanating from other orofacial structures such as the masseter musculature. Additionally, the possibility of a primary salivary gland lymphoma in SLE must be recognized.[30]

Table 1 American College of Rheumatology Criteria for Systemic Lupus Erythematosus (SLE)*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous-raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a. Pleuritis—convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion OR b. Pericarditis—documented by electrocardiogram, rub, or evidence of pericardial effusion
7. Renal disorder	a. Persistent proteinuria greater than 0.5 grams per day or greater than 3 if quantitation not performed OR b. Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a. Seizures in the absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, or electrolyte imbalance) OR b. Psychosis in the absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	a. Hemolytic anemia with reticulocytosis OR b. Leukopenia—less than 4,000 leukocytes per mm^3 total on 2 or more occasions OR c. Lymphopenia—less than 1,500 leukocytes per mm^3 on 2 or more occasions OR d. Thrombocytopenia—less than 100,000 leukocytes per mm^3 in the absence of offending drugs
10. Immunologic disorder	a. Anti-dsDNA antibodies OR b. Anti-Sm antibodies† OR c. Positive finding of antiphospholipid antibodies based on 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies OR 2. a positive test result for lupus anticoagulant using a standard method OR 3. a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

*The proposed classification of SLE is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person can be said to have SLE if 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. Specificity is ~95%: sensitivity is ~75%.

†Anti-Sm antibodies are a subtype of antinuclear antibody. The anti-Sm (Smith antigen) antibody test identifies antibodies to a protein. While many lupus patients do not have anti-Sm antibodies, they are rarely found in people without lupus.

dsDNA = double stranded DNA.

From: Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–1277. Updated by Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.

Rheumatoid Arthritis

Overview

Rheumatoid arthritis (RA) is a systemic, chronic, inflammatory disease of unknown etiology. The disease affects the articular surfaces of joints, including the synovial tissues, capsule, tendons, and ligaments. The inflammatory process, characterized by proinflammatory cytokines such as tumor necrosis factor-α and interleukins 1 and 6, secondarily leads to the destruction of the articular cartilage and subchondral bone.[31–34] Etiologic factors associated with RA include infectious organisms, particularly viruses; genetic predisposition; and autoimmune response with the production of inflammatory mediators.[35–38] The prevalence in Western populations is 0.5% to 1%, with a female-to-male ratio of approximately 3:1.[39] The disease can occur at any age; however, onset usually occurs between 25 and 50 years, peaking in the fourth and fifth decades of life.[40] The disease generally affects small joints of the upper and lower extremities, tends to be bilateral, symmetrical, and more general in its clinical presentation as compared to degenerative joint disease.[41,42] Cervical spine involvement is often present, which can affect

Table 2 Criteria for the Classification of Rheumatoid Arthritis (RA)

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, nodules over bony prominences, or nodules on extensor surfaces or in juxta-articular regions observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in < 5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or adjacent to the involved joints (osteoarthritis changes alone do not qualify)

For classification purposes, a patient can be said to have RA if he or she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made. PIP = proximal interphalangeal joint; MCP = metacarpal phalangeal joint; MTP = metatarsal phalangeal joint.

From: Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–324. © 1988; reprinted with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.

neurologic structures. Extra-articular manifestations such as pleuritis and pericarditis, peripheral neuropathy, dry eyes and/or mouth (secondary Sjögren or sicca syndrome), scleritis, Felty syndrome with splenomegaly, neutropenia, and recurrent infections occur in a subset of RA patients. It is rare for organ-threatening or life-threatening RA vasculitis or malignant RA to occur.[43] The American College of Rheumatology criteria for the classification of RA are presented in Table 2.

Orofacial Manifestations

The most common orofacial manifestation is involvement of the TMJ due to synovial inflammation and connective tissue degeneration. Approximately 50% of patients with RA exhibit clinical involvement of the TMJ,[44,45] and approximately 50% to 80% of RA patients have radiographic evidence of TMJ abnormalities.[46–49]

Symptoms include bilateral, deep, dull, aching pain exacerbated during function and clinical findings of tenderness and swelling in the preauricular regions, limitation of mandibular range of movement, TMJ stiffness upon awakening, intracapsular joint sounds (crepitus/clicking), and tenderness of the masticatory and/or cervical muscles.[32,41,50–52] As the disease progresses, limitation in mouth opening may worsen if fibrous or bony ankylosis occurs.[53]

Radiographic findings of the TMJ, although not evident in the early stages of the disease, become more apparent with disease progression. Imaging of the TMJ reveals changes such as joint effusions, disc displacements, and condylar abnormalities, including erosions, flattening, sclerosis, subchondral cysts, and osteophytes.[31,48,54,55] As the disease becomes more advanced and greater destruction of the condyles occurs, the patient may develop a progressive Class II malocclusion, with heavy posterior occlusal contacts and an anterior open bite caused by loss of condylar height.[41,56]

RA patients with longstanding active disease have an increased incidence of periodontal disease, including an increase in pocket depths, furcation involvement, loss of alveolar bone, and tooth loss.[57–59] Limited opening, limitations on oral hygiene due to arthritic involvement of the hands, and hyposalivation contribute to periodontal and dental complications.[57]

It is not uncommon for RA patients with secondary Sjögren's syndrome to complain of dry mouth and present with focal sialadenitis and decreased salivary flow rates.[59] This leads to multiple oral problems, including difficulty in swallowing food and speaking, oral soreness and burning (possibly caused by candidiasis), difficulty in functioning with oral prostheses, and an increase in caries.[60] Isolated trigeminal sensory neuropathy has been reported in patients with RA, but this manifestation is rather rare.[23,61] The pathogenesis for the sensory disturbances is thought to be related to RA-associated vasculitis.[62]

Sjögren's Syndrome

Overview

Sjögren's syndrome (SS) is an autoimmune disease characterized by chronic inflammation of the exocrine glands that primarily affects the lacrimal and salivary glands. Autoreactive lymphocytic infiltrates replace the functional epithelium, leading to decreased exocrine secretions, with the clinical manifestations of keratoconjunctivitis sicca, hyposalivation, xerotrachea, and vaginal dryness.[63] The syndrome is accompanied by major salivary gland enlargement in 60% of patients.[63] Other tissues that may be affected include the skin, lungs, kidneys, liver, peripheral nerves, and muscles. When the disease occurs alone it is referred to as primary SS and clinically manifests with the ocular complication of keratoconjunctivitis sicca and salivary gland dysfunction in the form of hyposalivation. When these manifestations occur in association with other autoimmune diseases such as RA, SLE, scleroderma, and polymyositis it is called secondary SS.[64,65] Importantly, approximately 5% of patients with SS will develop B-cell lymphoma later in the illness, which presents as a mass in the affected glands.[66,67]

Primary SS occurs in all ages but has a greater predilection for females between the ages of 40 and 60 years. The female-to-male ratio is 9:1, with the prevalence of the disease being approximately 3%.[63] However, this may be an underestimation, as many individuals with mild symptoms may not be diagnosed.

Autoimmunity is thought to be triggered by environmental factors acting on individuals with a susceptible genetic background. Another potential etiologic factor is an infection secondary to the Epstein-Barr virus due to either exposure to or reactivation of the virus.[68,69] SS is characterized by lymphocytic infiltration of the exocrine glands and B lymphocyte hyperactivity resulting in organ-specific inflammation and dysfunction.[64] A classification for SS has been established by the American-European Consensus Group (Table 3).

Orofacial Manifestations

The most common oral symptom associated with SS is xerostomia. This is often accompanied by a sensation of "burning" on the tongue (glossodynia).[70,71] Additional symptoms reported by SS subjects are difficulty eating dry foods, sensitivity to acidic and spicy foods, altered taste, coughing episodes and speech disturbances, increased caries risk, and difficulty with oral prostheses.[72] Oral clinical manifestations frequently identified are candidiasis and increased caries rate.[72,73] Candidiasis may also affect taste and cause a burning sensation. The clinical oral manifestations observed in SS individuals are related to hyposalivation.[74]

Neurologic features found in 10% to 20% of primary SS cases are symmetrical distal sensory neuropathies.[75] There have also been case reports of asymmetric neuropathies, although these are less common.[76] Mellgren et al[77] reviewed 33 patients with SS and peripheral neuropathy and found that 70% had sensorimotor neuropathy and 30% had a distal pure sensory pattern with autonomic neuropathy, mononeuropathy, or cranial neuropathy (especially trigeminal neuropathy). Peripheral neuropathy was superimposed on generalized neuropathy in approximately 25% of patients with SS.[77] Peripheral neuropathy may develop prior to the appearance of the common manifestations of SS.[78] Isolated cranial nerve sensory neuropathy has been reported in a number of patients with SS,[79,80] including trigeminal neuropathy,[80,81] and may be characterized by a slowly progressing unilateral or bilateral facial numbness or paresthesia with or without pain.[82]

Headaches have been reported in approximately 75% of SS patients, of whom nearly half had migrainous features accompanied by more frequent and severe headaches.[83–85] The mechanism underlying a greater prevalence and severity of migraine among SS patients is unknown but may be linked to Raynaud's phenomenon.[84]

Salivary gland enlargement, in particular swelling of the parotid glands is present in 30% to 40% of SS patients[72] and may lead to tenderness or pain upon eating, which may mislead the clinician to believe a myogenous source of pain exists. Swelling of the parotid is usually bilateral, intermittent, and nontender.[86] Pain is usually caused by retrograde gland infection.[87] The close anatomic proximity of the masseter muscle and parotid gland when heterotopic pain, muscle co-contraction, and autonomic symptoms are present may contribute to a complicated and misleading presentation.[88,89] A concern for practitioners is the presence of a long-standing asymptomatic and nonfluctuating bilateral parotid gland enlargement, which may represent mucosa-associated lymphoid tissue lymphoma.[90,91]

A relationship between SS and SLE is documented, with the prevalence of SS among SLE patients reported as 6% to 90%.[65,92–95] Therefore, salivary gland pathology and associated pain considerations are also applicable to SLE patients.

Table 3 Criteria for the Classification of Sjögren's Syndrome (SS)

I.	Ocular symptoms: A positive response to at least 1 of the following questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
II.	Oral symptoms: A positive response to at least 1 of the following questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food?
III.	Ocular signs–objective evidence of ocular involvement, defined as a positive result for at least 1 of the following 2 tests: 1. Schirmer's test, performed without anesthesia (≤ 5 mm in 5 minutes) 2. Rose bengal score or other ocular dye score (≤ 4 according to van Bijsterveld's scoring system)
IV.	Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1, defined as the number of lymphocytic foci (foci adjacent to normal-appearing mucous acini containing more than 50 lymphocytes) per 4 mm^2 of glandular tissue
V.	Salivary gland involvement: Objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following diagnostic tests: 1. Unstimulated whole salivary flow (≤ 1.5 mL in 15 minutes) 2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts 3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI.	Autoantibodies: Presence in the serum of antibodies to Ro(SSA) antigens, La(SSB) antigens, or both

For primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of SS, as long as either item IV (histopathology) or VI (serology) is positive
b. The presence of any 3 of the 4 objective criteria items (ie, items III, IV, V, or VI)
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in a clinical-epidemiological survey.

For secondary SS

In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered indicative of secondary SS.

Exclusion criteria: Past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency disease (AIDS), pre-existing lymphoma, sarcoidosis, and graft-versus-host disease, and use of anticholinergic drugs (since a time shorter than 4-fold life of the drug)

From: Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–558. Reprinted with permission from BMJ Publishing Group.

Systemic Sclerosis

Overview

Systemic sclerosis (SSc), formerly known as scleroderma, is a multisystem connective tissue disorder characterized by abnormal fibrosis and resultant dysfunction of the skin, vasculature, and internal organs. There are 3 distinct forms of progressive SSc: diffuse, limited, and localized scleroderma. The diffuse form manifests as a cutaneous disease involving the face, neck, trunk, and both proximal and distal parts of the limbs and can be associated with severe and rapid onset of functional changes in the lungs and kidneys. A limited form of scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), is characterized by thickening of the skin of the face and neck and distal parts of the limbs only. Morphea is a localized scleroderma involving the skin, subcutaneous tissue, and muscle without systemic manifestation. It occurs most often in children and young women. Morphea presents as single or multiple plaques of skin induration; a second form, known as linear scleroderma, may involve an extremity or the face.[96] Involvement of visceral organs may also occur in the absence of skin involvement and is referred to as systemic sclerosis sine scleroderma.[96] Often, there is significant diversity in presentation of SSc and overlap in symptoms with other rheumatologic disorders.[97]

SSc has a clear female predominance (female-to-male ratio of 3 or 4:1), an annual incidence of 3.7 to 19.1 per million, and a prevalence of 30.8 to 286 patients per million. SSc can affect any racial group but is more common and often of greater severity in African Americans. Disease onset most commonly occurs between 20 and 50 years of age, but it can occur in children and the elderly.

The etiologic factor is unknown, but abnormal and excessive fibrosis results in all cases, leading to end-organ structural damage and dysfunction.[98] Classification for SSc has been developed by the American College of Rheumatology (Table 4).

Table 4 American College of Rheumatology Criteria for the Classification of Systemic Sclerosis (SSc)

Glossary of Clinical Terms Used in Description or Classification of SSc

1. Typical sclerodermatous skin changes: tightness, thickening, and nonpitting induration, excluding the localized forms of scleroderma (morphea or linear scleroderma)
   a. Sclerodactyly: Aforementioned changes limited to fingers and toes
   b. Proximal scleroderma: Aforementioned changes proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck, or trunk (thorax or abdomen); usually bilateral, symmetrical, and almost always including sclerodactyly
2. Other skin manifestations attributable to SSc or comparison disorders
   a. Digital pitting scars or loss of substance from the finger pad: Depressed areas at tips of digits or loss of digital pad tissue as a result of digital ischemia rather than because of trauma or exogenous causes
   b. Bilateral finger or hand edema: Firm but pitting edema, especially involving fingers (includes puffy sausage-like swelling of fingers) or the dorsal aspect of the hands
   c. Abnormal skin pigmentation: Hyperpigmentation often containing areas of punctate or patchy hypopigmentation or depigmentation ("pepper and salt")
   d. Raynaud's phenomenon: At least 2-phase color change in fingers and often toes consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion, as determined by patient's history or physician's observation
3. Visceral manifestations
   a. Bibasilar pulmonary fibrosis: Bilateral reticular pattern of linear or lineonodular densities, which are most pronounced in basilar portions of the lungs on standard chest roentgenograph; may assume appearance of diffuse mottling or "honeycomb lung," and should not be attributable to primary lung disease
   b. Lower (distal) esophageal dysphagia: Substernal discomfort on swallowing or sensation of food holdup retrosternally
   c. Lower (distal) esophageal dysmotility: Hypoperistalsis or aperistalsis, as demonstrated by either cine-esophagram, fluoroscopy, or manometric study, often accompanied by evidence of decrease in lower esophageal sphincter tone with reflux of gastric contents into the esophagus
   d. Colonic sacculations: Wide-mouthed colonic diverticula located along the antimesenteric border found on barium enema examination. These sacculations may also occur in ileum and jejunum

From: Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581–590. © 1980; reprinted with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.

Orofacial Manifestations

The most characteristic orofacial manifestations are microstomia resulting in limited mouth opening due to fibrosis, mucogingival problems, fibrosis of the hard and soft palate and tongue, telangiectasis and pigmentation of facial skin and oral mucous membrane, hyposalivation, dry eyes, widening of the periodontal ligament space, TMJ dysfunction, and trigeminal neuropathy.[99–102] These manifestations are the result of the substitution of normal tissues with collagen or the deposition of collagen around nerves or endothelial tissues.[102,103] SSc patients also manifest periodontal involvement demonstrated by increased pocket depths and gingival scores.[104] Although restricted mouth opening may limit access and prevent adequate oral hygiene measures, increased dental caries is thought to be primarily due to hyposalivation, and periodontal manifestations are thought to be primarily related to the obliterative microvasculopathy or a combination of these factors.[103]

TMJ dysfunction in SSc may be related to gross changes in the mandible, which include osteolytic activity resulting in bone resorption or erosion of the coronoid process, condyle, and angle of the mandible and ramus.[100,101,103] These changes may result in the clinical presentation of articular pain and swelling due to tendonitis and synovitis, with the accompanying radiographic changes of bone resorption in the angle of the mandible.[105] Fibrosis of masticatory muscles, muscles of facial expression, and oral and perioral tissues may limit range of motion of the mandible.

Trigeminal sensory neuropathy may involve all 3 branches of the nerve and may precede other orofacial phenomena.[23,106,107] Isolated trigeminal sensory loss is reported in 4% of patients with SSc. It is manifested bilaterally and is frequently associated with pain that is described as throbbing, aching, scalding, burning, or lancinating with involvement of the intraoral tissues.[108] Other studies report symptomatology consisting of paresthesia, burning, and/or an intense sharp/stabbing pain that may be provoked by jaw movement, thus mimicking the presentation of idiopathic trigeminal neuralgia.[99,100,109]

There are reports in the literature of an association between temporal arteritis (giant cell arteritis)

and SSc; however, the etiology of this association is unknown. The practitioner should recognize that typically these patients complain of headaches, lethargy, and difficulty chewing and that immediate treatment is needed to avoid complications such as blindness associated with temporal arteritis.[110–112]

Headache has been reported in SSc patients. The most common headache characteristics are migrainous, with the frequency and severity of migraines being greater than those of controls.[83,84] The pathophysiology of migraine in SSc is yet to be determined.[84]

Graft-versus-host disease (GVHD), a frequent acute and/or chronic complication of allogenic hemapoietic cell transplantation, shares similar presentations to other autoimmune diseases, including lichen planus, SLE, and SSc.[113] The common elements amongst these conditions are multiorgan involvement and oral complications. GVHD manifests with involvement of single or multiple organs and sites, including dermatosis, pulmonary fibrosis, liver dysfunction, alterations in gastrointestinal and oral mucosa, and decreased salivary flow.[114–116] Oral complications of GVHD include reticular oral lesions, erythema, ulcerations, hyposalivation, pyogenic granuloma, candidiasis, and herpes simplex lesions.[117]

Given that SSc may occur in association with secondary SS,[118] considerations previously discussed for salivary gland enlargement in SS are applicable in SSc.

Mixed Connective Tissue Disease

Overview

Mixed connective tissue disease (MCTD) is an overlapping syndrome characterized by combinations of clinical features of SLE, SSc, polymyositis, and RA. High titers of circulating autoantibodies to nuclear ribonucleoprotein (RNP) antigen are present, which are now referred to as anti-U1 RNP and justify diagnosis of MCTD as a distinct clinical entity.[119,120] However, some feel that MCTD may represent a variation of SLE, SSc, or polymyositis.[121–123] MCTD has a female preponderance (female-to-male ratio of 10:1) and is not specific to any race or geographic region. The peak onset is in the second and third decades of life; however, it can manifest at any age. The most common presenting symptoms are Raynaud's phenomenon, swelling of the hands, arthralgia, myalgia, and fatigue, which may develop over months or years.[96]

Orofacial Manifestations

As in other connective tissue diseases, the dry mouth and eyes of SS[32,124,125] and cervical lymphadenopathy[126] may be identified in addition to oral mucosal ulceration.[127,128] Focal sialadenitis is common; it affects 90% of MCTD patients, with greater than 90% prevalence.[94,124,125] In addition, there is a significant association between focal sialadenitis and positive rheumatoid factor, antinuclear antibodies, and anti-SS-A and anti-SS-B antibodies (Ro and La, respectively).[124]

Neurologic abnormalities, of which trigeminal neuropathy has been the most frequently reported, occur in approximately 10% of MCTD patients.[129] Trigeminal neuropathy has also been reported, with symptoms of pain and numbness,[23,130] and it appears that neurovascular headache of mild to moderate severity is a relatively common comorbidity of this disorder.[127,128,131] The presence of facial telangiectasia has also been observed.[127,128]

Masticatory muscle tenderness and TMJ involvement, often with evidence of radiographic alterations of the joint, have been reported in this population[125] in addition to clinical findings of tenderness and associated clicking or crepitation.[32]

Sialadenitis may present as facial pain in patients with MCTD. This may be confused with masticatory muscle pain and may require further diagnostic tests given the proximity of the parotid gland and masseter muscle. In addition, the clinical picture may be complicated by the presence of heterotopic pain, muscle co-contraction, and autonomic symptoms.[88,89,124] Since MCTD has a close association to SLE and SSc with possible secondary SS comorbidity,[121,122] salivary gland enlargement, as previously discussed, should be considered in MCTD.

Dermatomyositis and Polymyositis

Overview

Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory myopathies.[132] DM and PM have common diagnostic criteria related to muscle abnormalities, with DM having the additional criterion of cutaneous manifestations.[133,134] DM predominately affects females (female-to-male ratio of 2:1)[132] and peaks in childhood and between the ages of 45 and 65 years. The incidence of DM is 1 to 10 cases per million persons per year.[135]

Table 5 Orofacial Manifestations of Connective Tissue Diseases

	Connective tissue disease					
Orofacial manifestations	SLE	RA	SS	SSc	MCTD	DM
Oral lesions	X		X	X	X	X
Glossodynia	X	X	X		X	
Dysgeusia	X		X		X	
Dysphagia	X	X	X		X	X
Xerostomia	X	X	X	X	X	X
Increased caries risk	X	X	X	X	X	X
Periodontal disease	X	X	X	X	X	
Salivary gland pathology	X	X	X	X	X	X
Salivary gland lymphoma	X		X	X	X	
TMD	X	X	X	X	X	X
Trigeminal neuropathy	X	X	X	X	X	
Headaches	X		X	X	X	

The etiology of the DM is unknown, but interactions between immunogenetic markers (predisposition), TNF-α polymorphisms, and environmental factors (exposure to an infection and seasonal effect) have been implicated.[136–138] The pathogenesis of DM is controversial and may be related to vascular inflammation (microangiopathy)[139] and/or an increase in levels of circulating inflammatory cytokines.[140–144] The pathogenesis of the cutaneous manifestation of DM remains an enigma. The etiology and pathogenesis of PM are unknown. Current theories suggest that PM and DM have similar etiologies. Cytokine studies suggest that their pathogenesis is shared, although this theory is controversial.[145]

DM/PM is a multisystem disorder; the skin (DM) and muscles (DM/PM) are most commonly affected. Cutaneous manifestations pathognomonic of DM include heliotrope rash and Gottron's papules. Heliotrope rash is a violaceous to dusky rash with or without swelling; it symmetrically involves the periorbital area. Gottron's papules are violaceous, sometimes scaly papules and plaques with telangiectasia within the lesions, which are found on bony prominences. Muscle symptoms of DM/PM include myalgia, fatigue, or weakness that progressively affects daily functioning.[146,147] The cutaneous manifestation of DM may precede the development of the myositis, and the cutaneous and muscle manifestations can have independent courses.[146,148] Other possible accompanying conditions of DM include arthralgias and arthritis affecting small joints, esophageal disease manifested by dysphagia, pulmonary disease (eg, pneumonitis), and cardiac involvement.[149–151] A relationship between DM/PM and malignancies exists, particularly gynecologic malignancies such as ovarian carcinoma.[152–154]

There is also a form of drug-induced DM. Hydroxyurea is the most widely recognized medication in this respect, but others, such as quinidine, nonsteroidal anti-inflammatory drugs, penicillamine, isoniazid, 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors, and TNF-α inhibitors, may also cause or exacerbate DM.[155–158]

Orofacial Manifestations

There have only been a few reports on mucosal involvement in both adult and pediatric patients with DM.[159,160] However, oral lesions can be an initial manifestation of DM.[161] The primary oral involvement with DM is telangiectasia, mucosal edema, and erythema.[162] Calcification of the oral mucosa may be seen in DM and rarely generalized calcinosis can result in obliteration of the pulp chamber of teeth.[159,163] Involvement of the tongue muscles can result in an inflexible tongue, which may produce eating and speech difficulties.[159,163]

Hyposalivation has been reported in 26% of DM or PM patients.[164] Also many DM and PM patients exhibit angular cheilitis and denture stomatitis due to candidiasis associated which hyposalivation. In addition, 35% of DM and PM patients display fibrosis of the minor salivary glands and 24% have interstitial-perivascular infiltration. These patients display an increase in caries prevalence and periodontal disease indices, which again, may be secondary to hyposalivation. Interestingly, there was no difference in the severity of periodontal destruction between these patients and healthy controls.[164]

Anatomic changes to the TMJ have been found.[164] Severe condylar resorption resulting in

anterior open bite has been reported in DM and may be due to the actual disease manifestation, since arthritic involvement has been reported in 28% of patients with DM and PM.[165,166] Mandibular deviation, crepitation and clicking on mouth opening, and tenderness in the lateral pterygoid muscles have all been reported. It has been suggested that weakening of the masticatory muscles may be an early manifestation of DM and PM.[164]

Table 5 provides a summary of commonalities between the various conditions described.

Conclusion

Commonalities exist amongst the systemic features of these various connective tissue diseases, with a corresponding overlap in their orofacial manifestations. It is important for the pain practitioner to recognize the oral manifestations of connective tissue diseases. Musculoskeletal and neuropathic conditions, dry mouth, mucosal involvement, and secondary infection are orofacial manifestations that can present as orofacial pain. The first sign or symptom of these multisystem systemic diseases may be an orofacial pain complaint. It is also possible for orofacial complaints to arise during the course of the connective tissue disease. An understanding of these oral manifestations by the pain practitioner may lead to an early referral to the appropriate medical and oral health-care provider for diagnosis and management of the systemic disease. Early initiation of therapy may allow a more conservative approach in treatment of the systemic disease and/or reduce the consequences of an advanced condition, thereby decreasing morbidity and mortality. Multidisciplinary team approaches involving various health-care specialties are utilized in treating these systemic diseases. As a member of this team, the role of the pain practitioner will be to manage the orofacial conditions that are associated with these autoimmune diseases.

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