Other Connective Tissue Diseases

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1. Undifferentiated Connective Tissue Disease

The American College of Rheumatology (ACR) has published criteria for several different diseases commonly referred to as connective tissue disease (CTD). The primary aim of such classification criteria is to ensure the comparability among CTD studies in the scientific community. These diseases include rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), polymyositis (PM), dermatomyositis (DM), and Sjögren's syndrome (SS). These are systemic rheumatic diseases which reflects their inflammatory nature and protean clinical manifestations with resultant tissue injury. Although there are unifying immunologic features that pathogenetically tie these separate CTDs to each other, the individual disorders often remain clinically and even serologically distinct. Immunogenetic data and autoantibody findings in the different CTDs lend further support for their distinctive identity and often serves to subset the individual CTD even further, as seen with the myositis syndromes, SLE and SSc. In other cases, it remains difficult to classify individuals with a combination of signs, symptoms, and laboratory test results. It is this group of patients that have an "undifferentiated" connective tissue disease (UCTD), or perhaps more accurately, an undifferentiated systemic rheumatic disease. As many as one-quarter of rheumatic disease patients presenting to rheumatologists may fall into this category of having isolated or multiple systemic symptoms but no definitively diagnosed disease. Although many such patients often evolve into the characteristic diseases listed above, the time course is variable, and some remain "undifferentiated" or perhaps even remit with time. However, there are some clinical features and autoantibody reactivities that may be considered specific for a particular CTD even when other manifestations are not present to sufficiently make a specific diagnosis (Table 1). Adding further confusion to the nosology of the rheumatic diseases is the fact that so many similar clinical features are shared among them. Such common features include Raynaud's phenomenon (RP), inflammatory polyarthralgias or polyarthritis, interstitial lung disease, vasculitis, and serositis. The dilemma of UCTD has been addressed with a multicenter collaborative study that has sought to define the clinical boundaries of early UCTD and to study the natural history of patient cohorts (see References).

Table 1

Clinical Features and Autoantibody Findings Possibly Specific for a Defined CTD

Clinical Feature
Malar rash
Subacute cutaneous lupus
Sclerodermatous skin changes
Heliotrope rash
Gottron's papules
Erosive arthritis

Autoantibody
Anti-dsDNA
Anti-Sm
Anti-topoisomerase
Anti-polymerase 3
Anti-centromere
Anti-Jo-1
Anti-Mi-2

Adapted from Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? J Rheumatol. *2005 Feb:32(2):213-215.*

In addition to patients meeting ACR criteria for a specific CTD and the large group with UCTD, there are numerous patients who meet defined criteria for 2 or more identifiable diseases. For example, many patients with rheumatoid arthritis have Sjögren's syndrome, the latter representing one entity that commonly overlaps with other rheumatic illnesses.

These "overlap syndromes" are quite common and will not be individually discussed (Table 2). The classic overlap syndrome of mixed connective tissue disease (MCTD) is discussed in the "Idiopathic Inflammatory Myopathy" section and includes features of SSc, SLE, myositis, and RA. Data suggest that many patients evolve into systemic sclerosis, and the original description of a benign prognosis was challenged by a reported 13% mortality rate at 12 years. However, supporting the idea that MCTD remains a distinct entity is the fact that specific autoantibodies (eg, anti-HSP 73) have been identified only in MCTD patients and are not found in other CTDs.

Some of these overlap syndromes are not only clinically defined but serologically distinctive. For example, many patients with an overlap of SSc and myositis have the anti-PM-Scl autoantibody. Although anti-PM-Scl is clearly not specific for this overlap syndrome, it is a frequent finding in patients manifesting features of both of these diseases.

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Table 2

Common Overlap Syndromes

Sjögren's syndrome (secondary) with rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus (SLE), or inflammatory myopathy
Mixed connective tissues diseases: systemic sclerosis (SSc), myositis, and rheumatoid arthritis (RA)
SSc and polmyositis (PM) or dermatomyositis (DM)
RA and SLE ("Rhupus")

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Clinical and Serologic Features

Clinical Manifestations of UCTD

Many clinical manifestations of systemic rheumatic disorders serve as disease-specific criteria for the CTD. For example, the photosensitive malar rash of SLE and Gottron's papules in DM are specific cutaneous features that are identified with these diseases (Table 1) while a symmetric, erosive, and deforming arthropathy is quite characteristic of RA. However, some clinical scenarios are much more generic and difficult to characterize. For example, patients presenting with RP often do not satisfy criteria for any of the commonly recognized rheumatic diseases. Although RP may be an early sign of systemic rheumatic disease, its prevalence in the general population approaches 10% and young women may have a higher prevalence. However, certain factors in association with RP are prognostically helpful in the predicted evolution to CTD. When RP develops at an older age and is more severe, the likelihood of a CTD is increased. Certain autoantibodies such as anti-topoisomerase or anti-RNA polymerase III and anti-centromere predict the development of diffuse and limited SSc respectively. Nailfold capillary microscopy abnormalities in RP patients have proven to be early indicators of a developing CTD. The presence of antinuclear antibodies alone should not necessarily lead to a diagnosis of CTD. A large prospective study of over 1000 patients with RP found about 15% of 819 subjects with a positive ANA. A defined rheumatic illness developed in only 22% of the ANA-positive group after a mean follow-up of 3 years.

Polyarthritis is another nonspecific finding often shared by different CTDs. A symmetric polyarthritis involving small- and medium-sized joints may be the presenting feature of RA, PM, DM, SLE, or even SSc. In a large 410 patient, multicenter study of CTD, evidence of arthritis was found in 71% of 213 patients with early UCTD. Twenty percent of patients originally classified as having unexplained polyarthritis developed RA over a subsequent 5-year follow-up period. Predictive factors for the development of RA included an older age at onset and swelling of small joints at baseline. A few of the patients with initial polyarthritis later evolved into another CTD such as SLE or SSc. Most, however,

maintained their "undifferentiated" status or went on to have no further evidence of active disease. In another large study, 54% of 1141 patients with undifferentiated arthritis experienced spontaneous remission. It is important to diagnose RA early (with the help of rheumatoid factor or anti-CCP positivity) to treat it aggressively and to prevent bony destruction.

Other nonspecific CTD manifestations in addition to RP and polyarthritis include pleuropericardial disease, proteinuria, anemia, constitutional symptoms, and interstitial lung disease. Patients presenting with these features may likewise fail to develop a full-blown CTD.

Serologic Features of UCTD

Much like the clinical features described above, certain autoantibodies identify specific CTDs. For example, double-stranded DNA and anti-Sm are seen almost exclusively in SLE; the anti-aminoacyl-tRNA synthetase autoantibodies and other "myositis specific autoantibodies" (see the "Idiopathic Inflammatory Myopathy" section) are found in myositis; and anti-topoisomerase, anti-RNA polymerase III, and anti-centromere autoantibodies are highly specific for SSc. However, many serologic tests are often positive in the undifferentiated CTD syndromes. These include antinuclear antibodies, rheumatoid factor, anti-single-stranded DNA, anti-U1 RNP, and anti-SSA and SSB. These autoantibodies are commonly found (alone or in combination) in many different rheumatic diseases. A cohort of 148 patients with anti-Ro/SSA autoantibodies and UCTD were followed and after 4.5 years 36 patients (24.3%) developed a well-defined CTD. Most patients developed Sjögren's syndrome (50%) or SLE (30.5%), and anti-dsDNA autoantibodies predicted the evolution to SLE ($P < 0.02$).

Thus, patients may present with incompletely expressed rheumatic diseases and nonspecific autoantibodies and be appropriately designated as having UCTD. To prematurely diagnose such patients with a specific rheumatic disease is inappropriate, especially as new and unique autoantibodies are being increasingly detected. Longer follow-up will be necessary to adequately characterize these clinical/autoantibody correlations. Prospective studies have been helpful. Longitudinal assessment of a 213-patient UCTD cohort found that RA developed in 20%, while another 13% developed SLE. The lupus patients were more likely to be younger and African-American and to have alopecia, serositis, discoid lesions, a positive Coombs test, anti-dsDNA and anti-Sm antibodies, and a false-positive RPR. A 5-year follow-up of a large 665 Hungarian patient cohort with UCTD showed 230 developing a well-defined CTD while 435 (65.4%) remained in the UCTD category. Interestingly, 82 (12.3%) achieved complete remission with no symptoms reappearing within the 5-year period. The highest probability of evolving to a defined CTD was during the first 2 years after onset of symptoms. Thus, a longitudinal, careful follow-up of large groups of heterogeneous patients can provide valuable input into the evolution of specific rheumatic diseases.

Management of the Patient

The diagnostic evaluation of patients with an UCTD depends on the clinical features at presentation. The patient with isolated RP should undergo serologic testing and nailfold microscopy and the patient with polyarthritis should likewise be checked for autoantibodies and undergo radiographic studies to detect early erosive disease. Some patients may simply require careful clinical follow-up without aggressive diagnostic intervention. The treatment of the UCTD patient should be problem oriented. Since many patients follow a benign course or even experience symptom remission, aggressive immunosuppressive treatment should be avoided if there is no evidence of serious organ involvement. Polyarthritis may be treated with hydroxychloroquine or sulfasalazine, while persistent synovitis or erosive disease requires methotrexate and/or the addition of anti-TNF agents. Corticosteroids at varying doses are necessary for complications such as cytopenias, serositis, alveolitis, vasculitis, and nephritis, and other more aggressive immunosuppressive agents should be used in the same fashion as they would in the setting of "differentiated" connective tissue diseases.

2. Idiopathic Inflammatory Myopathy

Introduction

The term idiopathic inflammatory myopathy (IIM), or myositis, is used to represent a group of diseases of unknown cause in which muscle injury results from inflammation. Polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), myositis associated with malignancy, myositis in overlap with another connective tissue disease (CTD), eosinophilic myositis, orbital myositis, myositis ossificans, and focal myositis are included among these disorders. Some also suggest adding myopathic dermatomyositis to the classification of IIM. This designation refers to patients with the classic cutaneous features of DM but no clinically evident muscle disease (see the "Clinical Features/Cutaneous Features" section below).

IIM affects individuals of all ages, and childhood myositis is defined as an onset before 18 years of age. The annual incidence of PM and DM ranges from 5-10 new cases per million, depending on the population studied. Myositis associated with malignancy and IBM is more common in individuals over 50 years of age. The average female-to-male incidence ratio exceeds 2:1, with women predominating in disease that occurs between ages 15 and 44 years. In myositis that overlaps with another CTD, females predominate 10:1, while males more commonly have IBM in a 2:1 ratio.

Classification and Diagnosis

The diagnostic criteria proposed by Bohan and Peter in 1975 remain the gold standard for the diagnosis of PM and DM (Table 3) even though their utility continues to be questioned in some circles. Creatine kinase (CK) is the most sensitive serum skeletal muscle enzyme, although other enzymes may be elevated and are routinely measured when evaluating patients for myopathy. They include lactate dehydrogenase (LDH), aldolase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). At some point in the course of disease, nearly all patients with myositis will have elevation of one or more muscle enzymes. However, the degree of enzyme elevation does not correlate with the severity of muscle weakness. In particular, some children and adults with severe DM may have a normal CK yet have very active myositis. Eleva-

Table 3

Criteria for the Diagnosis of IIM

Symmetric weakness of the limb girdle muscles
Muscle biopsy evidence of necrosis; phagocytosis; degeneration and regeneration of myofibers with endomysial, perimysial, perivascular or interstitial mononuclear cell infiltrates
Elevation of serum levels of muscle-associated enzymes: creatine kinase (CK); aldolase; lactate dehydrogenase (LDH); transaminases (ALT/SGPT and AST/SGOT)
Electromyographic features of short duration, low-amplitude polyphasic motor unit potentials; fibrillation potentials, even at rest; bizarre high-frequency repetitive discharges
Characteristic rashes of dermatomyositis: Heliotrope rash: lilac discoloration of the eyelids and periorbital area
Gottron's papules: scaly erythematous eruptions over the metacarpophalangeal and interphalangeal joints, or over other extensor surfaces (knees, elbows and medial malleoli)
Gottron's sign: erythema in the distribution of Gottron's papules but without the papules

Definite PM =	Four criteria without the rash
Probable PM =	Three criteria without the rash
Possible PM =	Two criteria without the rash
Definite DM =	Rash + 3 criteria
Probable DM =	Rash + 2 criteria
Possible DM =	Rash + 1 criterion

Note: The diagnosis of PM and DM by the Bohan and Peter criteria incorporate the exclusion of other diagnoses, which today would include specialized pathologic, genetic and other diagnostic studies in cases that suggest other inflammatory and noninflammatory myopathic conditions such as inclusion body myositis, hereditary syndromes and metabolic conditions.
Adapted from Bohan A, Peter JB. N Engl J Med. *1975;292: 344-7,403-7.*

tion of the CK-MB fraction may be due to muscle regeneration and not myocardial injury. It is best to order a cardiac troponin I level, which is the most sensitive assay available for myocardial damage and is usually not influenced by skeletal muscle injury. A rising or elevated CK in a treated myositis patient who is in remission (and is not demonstrably weak) may be a harbinger of a disease flare. Similarly, normalization of the CK may lag behind clinical improvement of muscle weakness in a treated myositis patient. The serum CK should not be exclusively used to assess disease activity and to dictate treatment in the IIM patient.

The electromyographic features noted in Table 3 indicate membrane irritability, and the EMG is a very sensitive but nonspecific diagnostic criterion in the evaluation of IIM. Similar changes may occur in any necrotizing myopathy such as infectious, toxic, or even metabolic myopathy. An EMG is helpful in directing the site of muscle biopsy and can distinguish myopathic weakness from neuropathic disorders such as peripheral neuropathy, myasthenia gravis, and motor neuron diseases.

The histologic findings on muscle biopsy remain critical for the diagnosis of myositis, and the biopsy should be obtained from a clinically weak, but not atrophic or end-stage muscle. The biopsy is best obtained from the contralateral side where the EMG was found to be abnormal so as to prevent an inflammatory artifact from needle placement and to increase the likelihood of detecting abnormalities in a symmetrically weak and electrically abnormal muscle. Characteristic features are listed in Table 3. One often sees perifascicular atrophy in DM and the pathologic hallmark of PM is invasion of nonnecrotic myofibers by lymphocytes. It is especially important to biopsy patients with PM in order to establish the diagnosis and to eliminate the many mimics of PM (Table 7). While the pathologic findings of PM and DM are similar, there are characteristic features that serve to immunologically and pathogenetically distinguish these entities:

- DM is a humorally mediated disorder in which the primary immunologic target is the blood vessel. The inflammatory infiltrate is composed of B cells with an increased ratio of CD4+ helper to CD8+ suppressor cells. Perivascular inflammation is more common in DM and terminal complement components—C5b-9 membrane attack complex—is deposited in the vessel wall. The perifascicular atrophy reflects this immunologic attack, whereby muscle fibers in the periphery of a fascicle become ischemic and subsequently atrophic.

- PM and IBM are characterized by an antigen-directed cytotoxic T-cell attack on myofibers within a fascicle. The inflammatory infiltrate is scattered throughout the fascicle and there are increased CD8+ T cells recognizing major histocompatibility complex class I antigens on myofibers. Unlike DM, vasculitis is unusual in PM.

Although the Bohan and Peter criteria represent a thoughtful approach to the clinical evaluation of patients with suspected myositis, criteria sets require periodic reevaluation as concepts of disease pathogenesis evolve and newer diagnostic modalities become available. The identification and characterization of autoantibodies associated with the IIM and the use of magnetic resonance imaging in myositis are two such examples.

Autoantibodies in Myositis

Our understanding of the myositis syndromes has grown considerably with the identification and characterization of autoantibodies associated with PM and DM. Utilizing standard immunofluorescence techniques, clinicians will find that up to 80% of myositis patients have positive antinuclear antibodies. In recent years, several autoantibodies have been found nearly exclusively in IIM patients, and they are termed myositis-specific autoantibodies or MSAs (Table 4). The 3 main classes of MSAs include the anti-aminoacyl-tRNA synthetases, anti-signal recognition particle (SRP), and anti-Mi-2; and each MSA is associated with characteristic clinical features in addition to myositis although they are relatively insensitive markers for myositis. The most common antibody in myositis patients is anti-Jo-1, which targets histidyl-tRNA synthetase and is found in approximately 20% of patients with IIM. The other antisynthetases (Table 4) are much less common. Patients with one of the antisynthetase autoantibodies often experience some or all of a constellation of symptoms referred to as the antisynthetase syndrome, and includes fever, myositis, interstitial lung disease, Raynaud's phenomenon,

Table 4

Myositis-Specific Autoantibodies

Autoantibody (Antigen)	Frequency in IIM (%)	Clinical Association
Antisynthetases		
Jo-1 (histidyl tRNA synthetase)	20	Antisynthetase syndrome (myositis ~95%, arthritis ~90%, interstitial lung disease (ILD)~70%-80%, mechanic's hands ~70%, Raynaud's phenomenon ~60%)
PL-7 (threonyl tRNA synthetase)	2-5	Antisynthetase syndrome
PL-12 (alanyl tRNA synthetase)	2-5	Antisynthetase syndrome; lower frequency of myositis
EJ (glycyl tRNA synthetase)	1	Antisynthetase syndrome; DM>PM
OJ (isoleucyl tRNA synthetase)	1	Antisynthetase syndrome
KS (asparaginyl tRNA synthetase)	1	Antisynthetase syndrome, ILD > myositis
Nonsynthetases		
SRP	4-5	Polymyositis; severe, acute onset; treatment-resistant; possible cardiac involvement
Mi-2	5-10	Dermatomyositis; good prognosis; prominent skin rash ("shawl sign")

polyarthritis, and "mechanic's hands" (see the "Clinical Features" section). The second MSA, anti-SRP, is an antibody directed against the signal recognition particle, a ribonucleoprotein found in the cytoplasm of all cells that is involved in translocation (a process by which proteins are transferred from the cytoplasm into the endoplasmic reticulum). Patients with anti-SRP have severe refractory polymyositis with markedly elevated serum CK levels and occasional cardiac involvement. Lung involvement, arthritis, Raynaud's phenomenon, and CTD overlap symptoms are unusual in SRP-positive patients, but some reports note the occasional nonspecificity of this antibody and an improved survival compared to initial reports. Because of their cytoplasmic location, both the antisynthetases and anti-SRP are often associated with a diffuse cytoplasmic staining pattern on immunofluorescence. Anti-Mi-2 is the third MSA but it is directed against a nuclear antigen (helicase) that is involved in transcriptional regulation. In general, anti-Mi-2 patients have a favorable response to therapy, but the rash can be severe.

A small number of patients with antisynthetase antibodies have no evidence of myositis but do manifest other features of the antisynthetase syndrome. For

example, anti-PL-12 antibody-positive patients are more likely to have ILD without myositis.

Another unifying feature of the MSAs is their characteristic immunogenetic associations. Anti-Jo-1 is associated with DR3, DRw52 and DRB1*0501, while the other antisynthetases are also associated with DRw52. DR5 and DRw52 are seen with anti-SRP, while DR7 and DRw53 are associated with anti-Mi-2.

Some antibodies to cytoplasmic and nuclear antigens are associated with myositis (so-called myositis-associated autoantibodies (MAAs)) but may be seen with other CTD as well. Anti-U1-RNP is the most common MAA and is clinically associated with mixed connective tissue disease (MCTD), a disorder in which patients have features of systemic lupus erythematosus, systemic sclerosis, PM or DM, and possibly RA. Patients with U1-RNP may have predominant features of one disease, or they may present with a mixed or undifferentiated syndrome before the syndrome eventually evolves into a single disease. Anti-PM-Scl was named for its frequent association with an overlap syndrome of myositis and scleroderma, and it has a strong nucleolar pattern on immunofluorescence. This antibody is typically associated with mild and treatment-responsive myositis, but it may be seen in patients with either myositis or scleroderma alone. Anti-Ku was originally described in Japanese patients and has more recently been reported in patients with an overlap between polymyositis and systemic sclerosis in the United States. Antibodies to Ro/SSA are quite common in IIM patients, occurring in up to 10% to 20% of patients. They are more frequently seen in myositis patients with antisynthetase autoantibodies. Many other MAAs against muscle-cell membrane proteins, proteasome subunits, and histones have been identified, but they are less common and not as well characterized clinically.

Magnetic Resonance Imaging

MR imaging can help in assessing the presence and extent of muscle inflammation and fibrosis in the IIM. The presence of edema, as detected by short tau inversion recovery (STIR) or other fat-suppressed T2-weighted techniques, suggests active muscle inflammation. Conversely, a T1-weighted image demonstrating atrophy and fatty infiltration is consistent with muscle fibrosis and inactive disease with damaged muscle. Utilizing both T1- and fat-suppressed T2-weighted images can therefore provide valuable information on the state of muscle tissue and its potential response to treatment. Because this technique is noninvasive, it can be serially utilized to follow the disease course and response to treatment, which may be helpful in JDM or adults with normal CK-active myositis in which more traditional markers of disease activity are lacking. However, it is important to note that the specificity of edema on MR imaging is not specific for PM or DM and can be seen in infectious or dystrophic processes.

Clinical Features

Muscle Involvement and Constitutional Symptoms

Proximal muscle weakness is the most common symptom of IIM, and its onset is most frequently insidious, bilateral, symmetric, progressive, and painless over a period of weeks to months. Individuals complain of difficulty getting up out of a chair or walking up steps, and their gait may become waddling from lower extremity weakness. Upper extremity symptoms include patients being unable to raise their arms above their head or having difficulty combing their hair. Neck flexor weakness is common and manifested by the inability to raise the head off the pillow. Although muscle pain is infrequent, it seems to occur more commonly in patients with DM.

Pharyngeal muscle weakness is a poor prognostic sign and results in proximal dysphagia for solid food with nasal regurgitation of liquids, pulmonary aspiration, and either hoarseness or a nasal-sounding voice. Ocular and facial muscle weakness is quite rare in IIM and its presence suggests myasthenia gravis or another myopathy.

Although muscle weakness is the cardinal feature of myositis, many patients present with rash, polyarthritis, Raynaud's phenomenon, sicca symptoms, or profound fatigue. These features may precede overt myositis features by months or years. The occasional patient will present with the explosive onset of systemic complaints of fever, Raynaud's phenomenon, "mechanic's hands" (see "Cutaneous Features" below), polyarthralgias or frank arthritis, muscle weakness, and dyspnea due to interstitial

lung disease. As described earlier, these are features of the antisynthetase syndrome, which tends to recur. When weight loss is observed with myositis, concurrent malignancy or pharyngeal dysfunction leading to poor caloric intake should be considered.

Cutaneous Features

The presence of skin involvement separates the patient with an inflammatory myopathy into the clinical classification of DM, and a variety of rashes and cutaneous features can be seen (Table 5). The specific rashes of DM may precede, follow, or develop simultaneously with muscle symptoms. Gottron's papules are scaly, erythematous, or violaceous plaques found over bony prominences, particularly the metacarpophalangeal and proximal and distal interphalangeal joints of the hands. Gottron's sign is a macular erythema (with less scaling) that may occur in the same distribution as Gottron's papules, but more commonly refers to involvement of other extensor areas, such as the elbows, knees, hips, and ankles. Later in the disease course, the affected skin lesions may become shiny, atrophic, and hypopigmented. The heliotrope rash, a less frequent finding, is purplish in color and located on the eyelids, often with associated edema. It is generally believed that these 3 rashes, Gottron's sign or papules along with the heliotrope rash, represent the 3 specific or pathognomonic rashes of DM. Other cutaneous features may be seen with DM but are not specific for the disease. For example, photosensitivity is common and may be manifested as a "V sign" over the anterior chest. The facial rash of DM usually involves the nasolabial fold as opposed to the malar rash of systemic lupus erythematosus, which spares the nasolabial area. The "shawl sign," seen in DM, is a rash located over the upper back and across the shoulders. It has been reported in patients with the anti-Mi-2 autoantibody (Table 4). Cuticular hypertrophy with periungual erythema, infarcts, and capillary dilatation are seen in some DM patients and in those with myositis in overlap with another CTD. Severe calcinosis with subsequent skin ulceration, a potentially devastating complication seen in juvenile DM (JDM), is rare in adults. Rashes on the scalp are commonly seen in DM and are often severe, misdiagnosed, and associated with patchy alopecia.

Cracking or fissuring of the lateral and palmar digital skin pads is termed "mechanic's hands." This is most frequently seen in patients with the antisynthetase syndrome, but it has also been reported in association with the anti-PM-Scl autoantibody. Vasculitic skin changes occur in children and adults with DM and may be rarely seen with malignancy. Panniculitis may be the presenting feature of IIM and is being increasingly reported in association with myositis. Other much less common cutaneous features in IIM patients are listed in Table 5.

Table 5

Cutaneous Features of the IIM

Specific Signs in Dermatomyositis
Gottron's papules/sign (60% to 80% patients)
Heliotrope rash (50% or less)
Less Specific Signs in Dermatomyositis
Photosensitivity
"V" neck sign
"Shawl sign"
Nailfold capillary changes and/or cuticular overgrowth
Pruritic scalp involvement
Other Skin Findings
"Mechanic's hands"
Panniculitis
Calcinosis
Vasculitis (including urticarial)
Linear extensor erythema
Vitiligo
Cutaneous mucinosis
Multifocal lipoatrophy
Poikiloderma (hyper- or hypopigmented skin changes)
Bullous pemphigoid
Acquired ichthyosis

Adapted from Semin Arthritis Rheum. *1996;26:459-67.*

Some patients with the classic skin rash of DM have no demonstrable myopathic features by physical examination, muscle enzyme testing, or even electromyography. These patients are said to have amyopathic DM or DM sine myositis if these findings have been present for 2 years or longer. Many such patients have a favorable outcome but some have developed malignancy.

Articular Findings

Polyarthralgias and polyarthritis occur in roughly 25% to 50% of patients with inflammatory myopathy. The most common presentation is that of a mild inflammatory arthropathy affecting the small joints of the hands, wrists, and knees in a symmetric distribution. This is more commonly seen in myositis associated with another CTD or in patients with anti-tRNA synthetase autoantibodies. A more chronic deforming arthropathy has been reported in anti-Jo-1-positive patients and it includes both erosive as well as predominantly subluxing changes, along with soft-tissue calcification and interphalangeal thumb joint instability ("floppy thumb sign").

Pulmonary Involvement

Pulmonary involvement is a common and serious symptom in IIM, occurring in as many as 40% to 50% of patients. Dyspnea may result from respiratory muscle weakness but leads to ventilatory failure in only a small percentage of patients. Aspiration pneumonia is often secondary to pharyngeal striated muscle involvement. Pulmonary problems can also be the result of infection or complications of therapy such as those associated with *Pneumocystis carinii* pneumonia or methotrexate, respectively.

Pulmonary parenchymal disease with diffuse alveolitis is an ominous feature. Chest radiographs may demonstrate predominantly bibasilar infiltrates or a more diffuse alveolar-interstitial pattern. High-resolution computed tomography reveals varying degrees of alveolitis with a "ground glass" appearance or fibrosis. The presence of alveolitis indicates a more favorable, potentially treatment-responsive condition. The progression of ILD is unpredictable but the more favorable histologies include NSIP and the organizing pneumonias, whereas UIP and diffuse alveolar damage portend a more ominous course. This form of pulmonary involvement may be fatal in weeks or months or can rapidly decompensate to adult respiratory distress syndrome. Alveolitis is associated with antisynthetase autoantibodies, and dyspnea may dominate the clinical presentation, with myositis being overlooked. A more slowly progressive form of ILD and pulmonary fibrosis may occur in PM, DM, or overlap syndromes, and some patients with myositis and pulmonary fibrosis may be completely asymptomatic. Bronchoalveolar lavage, radionuclide scans, and high-resolution computed tomography have been used to follow the course of pulmonary involvement in selected cases. Serologic markers such as anti-endothelial antibodies and serum KL-6 have been reported as indicators of lung involvement in IIM patients.

Although many patients with myositis-associated ILD with progressive fibrosis develop pulmonary hypertension, some patients develop primary pulmonary hypertension. Other less common pulmonary manifestations of myositis include pulmonary capillaritis with diffuse alveolar hemorrhage and spontaneous pneumomediastinum.

Cardiac Abnormalities

Although cardiac involvement is common in the IIM, its frequency is dependent on the diagnostic method used to assess disease activity. The precise relationship of electrocardiographic abnormalities to myositis-associated cardiac disease is unclear. Noninvasive modalities such as electrocardiography, Holter monitoring, and echocardiography may detect a high frequency of asymptomatic nonspecific abnormalities. Electrocardiographic abnormalities occur in about one-third of patients with polymyositis, and left ventricular diastolic dysfunction is frequently detectable but subclinical. Myocardial disease may be detected by antimyosin antibody scintigraphy. Less common but serious features of cardiac involvement include myocarditis leading to congestive heart failure, endomyocardial fibrosis, or pericardial effusion with tamponade.

Gastrointestinal Involvement

Dysphagia, found in up to 50% to 60% of patients at some time in their disease course, is common during active myositis and is considered a poor prognostic sign. Cricopharyngeal muscle involvement occurs in IBM as well as in PM or DM, and patients often cough with swallowing and complain of a blocking

sensation. Liquids are generally easier to swallow in patients with cricopharyngeal involvement, and the diagnosis is made by videofluoroscopy with concomitant observation by a speech therapist.

Distal dysphagia with pyrosis implicates dysfunction of the smooth rather than skeletal muscle and although these complaints are more likely in myositis patients with systemic sclerosis or other CTD, many patients with pure PM or DM have clinical, radiographic, or manometric evidence of distal esophageal motility. Megaesophagus or motor dysfunction of the entire gastrointestinal tract may occur in DM.

Gastrointestinal manifestations, including mucosal ulceration with perforation and hemorrhage due to vasculitis, are rarely seen in adults but can be devastating in JDM. The latter condition has a poor prognosis and vasculopathy in JDM can affect any portion of the gastrointestinal tract. Other uncommon gastrointestinal features of IIM include malabsorption, primary biliary cirrhosis, adult celiac disease, pneumatosis cystoides intestinalis, inflammatory bowel disease and celiac sprue.

Miscellaneous Complications

Vascular complications in adult IIM include Raynaud's phenomenon, antiphospholipid antibody syndrome, and, rarely, systemic vasculitis. Inflammatory vascular lesions include dermal and/or subcutaneous nodules, periungual infarcts, digital ulcerations, and retinal vasculitis causing visual loss. Central nervous system complications of PM and DM are rare, but progressive multifocal leukoencephalopathy and vasculitis have been reported with DM.

Kidney involvement is uncommon, but a rare patient with PM or DM may develop renal failure due to rhabdomyolysis with myoglobinemia and myoglobinuria causing acute tubular necrosis. Proteinuria has been reported, but glomerulonephritis is extremely uncommon and progression to any form of chronic renal failure is unlikely.

Although hyperthyroid myopathy may mimic PM, many thyroid disorders, such as Grave's disease and Hashimoto's thyroiditis, coexist with immune-mediated disorders such as myositis. Evans syndrome, an autoimmune hemolytic anemia with thrombocytopenia, and idiopathic thrombocytopenia has been seen with DM.

Inclusion Body Myositis

Inclusion body myositis (IBM) was first reported in 1967, and although awareness of this entity is improving, precise figures on incidence and prevalence are lacking. Some recent reports suggest that IBM constitutes up to 15% to 20% of all inflammatory myopathies.

IBM affects predominantly middle-aged and older individuals and, unlike the other IIM, has a male predominance. IBM has distinctive clinical features, but its slow progression often delays the diagnosis and it is often misdiagnosed as treatment-resistant PM. Although the presenting features of IBM may be identical to those of PM, the presentation is more typically characterized by painless proximal (early) and distal (later) muscle weakness of insidious onset (Table 6). Patients often have considerable difficulty in determining the onset of their symptoms and usually report a functional deficit as the initial feature of the disease.

Table 6

Clinical Features of IBM

Insidious and progressive proximal and distal muscle weakness with atrophy
Patients predominantly middle-aged and elderly with 2:1 male-to-female ratio
Low-level elevation or normal serum CK (usually less than 5-6 times normal)
Mixed myopathic and neuropathic electromyographic features
Poor response to corticosteroid and other immunosuppressive medications

Muscle weakness and atrophy are more asymmetric than in PM or DM, and the intrinsic muscles of the hand may be affected with finger flexor weakness, forearm atrophy, and the progressive inability to grasp or pinch. Foot drop is observed, and its presence in a middle-aged patient who has "refractory" myositis is strongly suggestive of IBM. Falling episodes occur more frequently as the disease progresses and as distal muscle involvement complicates established proximal deficits. Dysphagia secondary to cricopharyngeus muscle involvement is seen in approximately one-third of patients and may be severe, requiring a myotomy.

The serum CK is only moderately elevated and may be normal in many IBM patients. Autoantibodies are typically absent, but other CTD are occasionally seen with IBM, with Sjögren's syndrome being the most common. This raises the possibility of a unifying underlying autoimmune pathogenesis. Electromyography often reveals a mixed myopathic and neuropathic pattern, and the histopathologic features of IBM include myofiber necrosis with regeneration and a chronic inflammatory infiltrate in addition to 3 distinctive features: rimmed vacuoles, intranuclear and cytoplasmic inclusion bodies, and deposition of amyloidogenic protein in rimmed vacuoles.

Malignancy-associated Myositis

Although the relationship between inflammatory myopathy and malignancy is controversial, circumstantial evidence suggests a pathologic relationship between the two disease processes. Such evidence includes the recrudescence of muscle symptoms with tumor recurrence after complete resolution of myositis and cases of new onset DM occurring with tumor recurrence. Myositis with cancer, which is unusual in children, is more common in patients over the age of 50, with a male-to-female ratio of 1:1.

Recent reports strongly suggest an increased risk of cancer in patients with PM and DM. These include hospital-based series, national registries and population-based cohort studies. Standardized incidence ratios (SIR) clearly show an increased risk of malignancy in DM and a pooled analysis from the Scandinavian countries identified 198 of 618 DM patients having cancer (SIR 3.0). Of the 198 cases, 115 developed cancer after the diagnosis of DM was made. The strongest associations were with ovarian, lung, pancreatic, stomach and colorectal cancer and non-Hodgkin's lymphoma. Another Australian study also demonstrated an increased risk of malignancy in PM, DM and even IBM (SIR 2.4) and the overall risk was highest in the first 3 years after the diagnosis of myositis. A higher risk of malignancy persisted through all years of follow-up, emphasizing the importance of continued vigilance.

The types of cancers that occur with myositis are those expected based on the patient's age and sex. Ovarian cancer seems to be over-represented, but pelvic examination screening rarely detects this cancer prior to development of metastatic disease. Serum CA-125 screening may be useful but prospective studies are necessary. Asian and Chinese patients have a clear increase in nasopharyngeal carcinoma with DM. One population-based study failed to show an increased risk of cancer in DM patients treated with cytotoxic agents. The presence of pulmonary fibrosis, myositis-associated or specific serum autoantibodies or a clinically-confirmed associated connective tissue disease all decrease the likelihood of cancer.

In many cases the site of cancer is obvious, and the workup for malignancy should include a meticulous history and physical examination with a routine laboratory evaluation directed toward any detected abnormalities unexplained by myositis. Women should have a chest radiograph, mammogram, and pelvic ultrasound. Young men should undergo a careful testicular examination and older men a prostate-specific antigen test. Given the increased risk of the tumors noted above, it may also seem prudent to include chest, abdominal, and pelvic computed tomography with the routine studies noted above.

Myositis in Overlap with Another Connective Tissue Disease

Another CTD can be diagnosed in approximately 20% of individuals with inflammatory myopathy. These overlap syndromes include myositis in association with scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and other immune-mediated entities. In general, the overlap myositis syndromes are characterized by

higher frequencies of Raynaud's phenomenon, polyarthritis, and milder myositis with a favorable response to corticosteroids. Patients with scleroderma may have a bland noninflammatory fibrotic myopathy with normal or slightly elevated CK levels or, less commonly, overt myositis with high enzyme levels and other classic findings.

Muscle weakness is a common complaint in patients who have systemic lupus erythematosus, but myositis accounts for this symptom in only about 10% of patients. Abnormal muscle biopsies in patients with systemic lupus erythematosus may demonstrate myositis, vasculitis, or a vacuolar myopathy. Eleven patients with lupus myositis (ie, those fulfilling the criteria for each diagnosis) were retrospectively compared with 19 PM or DM patients. At presentation both groups showed similar significant increases in serum CK levels and comparable reductions in muscle strength. Over time, lupus myositis can be as severe as pure PM or DM and should be treated aggressively.

Muscular involvement in rheumatoid arthritis is rare, even though rheumatoid arthritis patients complain of significant weakness and limited endurance. Although muscle biopsies performed in patients who have rheumatoid arthritis more commonly demonstrate type II fiber atrophy, some patients have myositis with necrosis and mononuclear cell infiltration. Twenty-one (6%) of 350 rheumatoid arthritis patients from a single center developed muscle symptoms (most commonly weakness and atrophy) and/or an elevated CK (8 of the 21 patients), and were studied by electromyography and biopsy. In 13 cases a treatable disease, such as inflammatory or toxic myopathy, was identified, and in all but 1 patient the treatment response was satisfactory.

An overlap syndrome, termed mixed connective tissue disease, includes features of systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and myositis with circulating antiribonucleoprotein (U1-RNP) antibodies. The original claims that the syndrome was clinically identifiable by a unique group of features (ie, high-titer antibodies to ribonucleoprotein; rare cerebral, pulmonary, and renal involvement; lack of vasculitis; a benign prognosis; and responsiveness to low-dose corticosteroid therapy) have not stood the test of time. A subsequent evaluation of 22 of the original 25 patients 8 years later noted that 17 patients had sufficient data to make another diagnosis. Ten had scleroderma and 5 had coexistent myositis. High-dose corticosteroids were required for many of those patients, and sclerodermatous manifestations were generally unresponsive to steroids. A 13% mortality within 12 years was noted. The myositis of MCTD is frequently a benign, more corticosteroid-responsive feature (see the "Undifferentiated Connective Tissue Disease" section).

Myositis has been reported in patients with primary Sjögren's syndrome, although the association is probably present in less than 5% of patients. Patients usually respond to corticosteroids alone or to the addition of immunosuppressive drugs. Other immune-mediated disorders with a reported myositis component include polymyalgia rheumatica, seronegative spondyloarthropathies, primary biliary cirrhosis, psoriatic arthritis, inflammatory bowel disease, myasthenia gravis, Behçet's disease, Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa, adult Still's disease, amyloidosis, and graft-versus-host disease.

Less Common Subtypes

The term eosinophilic myositis represents a distinct syndrome of idiopathic eosinophilic inflammatory myopathy. Histopathology can show a localized or diffuse process ranging from isolated perimyositis to frank infiltration with eosinophils. Clinically, eosinophilic myositis may be associated with a variety of systemic features resembling those seen in immunologically mediated disorders, but laboratory findings are variable. A significant number of patients (25% to 35%) have a normal peripheral eosinophil count and/or serum CK level. The diagnosis is generally made by exclusion after ruling out an infectious process, drug or toxin ingestion, or an associated autoimmune disease.

Idiopathic orbital myositis is an inflammatory process affecting the extraocular muscles of the eye in the absence of thyroid ophthalmopathy. It occurs most commonly in young to middle-aged adults, and patients have pain that is exacerbated by eye movement. Vision remains normal, but diplopia, proptosis, eyelid swelling, conjunctival injection,

and rarely, a palpable mass may result. The medial rectus is most commonly involved, although any or all muscles may be affected. The differential diagnosis includes orbital cellulitis, tumor, Wegener's granulomatosis, arterial venous malformation, and cavernous sinus thrombosis, but thyroid eye disease is most commonly confused with idiopathic orbital myositis. An immune-mediated pathogenesis is suggested by its association with a variety of autoimmune disorders such as Crohn's disease, systemic lupus erythematosus, giant cell polymyositis, giant cell myocarditis, asthma, and rheumatoid arthritis. The treatment of choice is systemic corticosteroids, and the response is usually prompt.

Focal myositis generally presents with a painful mass in the lower extremity and often resolves without treatment. The serum CK is usually normal and systemic complaints are rare. Over 50% of patients have a painful calf or thigh mass often misdiagnosed as a tumor or thrombophlebitis. Other locations may be involved, including the neck muscles, psoas muscle, abdominal wall, and upper arms or forearms. Magnetic resonance imaging is helpful in both diagnosis and follow-up. Other disorders to consider include abscess, sarcoma, pyomyositis, and diabetic muscle infarction. The latter presents much like focal myositis with localized pain, swelling, limited range of motion, and a paucity of systemic features. The thigh is the most common site and patients usually have long-standing insulin-dependent diabetes mellitus with other end-organ vascular complications. Other forms of focal myositis, including localized nodular myositis, nodular fasciitis, and proliferative myositis, may present in a similar fashion but differ histopathologically. Focal myositis may recur and rarely evolves into polymyositis.

Myositis ossificans is heterotopic non-neoplastic ossification of muscle and connective tissue. Although commonly posttraumatic, this condition is associated with an identifiable trauma in only two-thirds of cases. Typically, one muscle group is involved, but myositis ossificans may follow repetitive injury such as occurs in horseback riding or rifle shooting. It can also occur in paraplegic patients in muscles below the level of spinal cord injury. Localized variants are generally benign and excision may be curative.

Myositis Mimics

There are many other causes of muscle weakness that must be considered in patients besides those associated with inflammatory disorders (Table 7). Drug or toxic myopathies are quite common and increasingly recognized. Endocrine-associated myopathies (particularly hypo/hyperthyroidism) can mimic features of inflammatory myopathy, as can metabolic and mitochondrial disorders. Acid maltase deficiency is one metabolic myopathy that presents very similar to PM, with marked elevations of the serum CK along with electromyographic features indistinguishable from PM. Similarly, inherited myopathies (muscular dystrophies) may present later in life and present similar patterns of muscle weakness to IIM. Amyloidosis can affect skeletal muscle and patients may complain of proximal muscle weakness in a pattern similar to PM.

Table 7

Mimics of Inflammatory Myopathy

Drug or toxic myopathies: alcohol, colchicine, statins, etc.
Endocrine myopathies: hyper/hypothyroid
Metabolic myopathies
Mitochondrial myopathies
Muscular dystrophies
Infectious myositis
Neuropathies/neurologic syndromes
Paraneoplastic syndromes
Other connective tissue disorders
Miscellaneous: amyloid, sarcoid

Treatment of Inflammatory Myopathy

Initial Treatment Considerations and Corticosteroid Use

The management of patients with idiopathic inflammatory myopathies is challenging due to their heterogeneous presentations, and the lack of well-controlled clinical trials comparing various methods of treatment. This problem has been recently addressed with the publication of guidelines to be used in the conduct of clinical trials in adult and juvenile myositis. Nevertheless, the treatment currently remains largely empiric and the management of each patient must be individualized and the monitoring of disease activity customized.

Corticosteroids are the agents of choice for the initial treatment of myositis. Options include a single morning dose or divided doses. Although a single daily dose will limit steroid-related toxicity, divided doses are more effective. Daily doses of 60 mg of prednisone (or 1-2 mg/kg) are usually chosen. A delay in diagnosis, for whatever reason, may unfavorably impact on disease prognosis, and patients with a long delay between the onset of muscle weakness and diagnosis of myositis are less likely to respond completely to prednisone than patients with shorter delays. For patients with severe disease or extramuscular manifestations such as interstitial lung disease or myocarditis, intravenous pulse methylprednisolone may be used to gain more rapid disease control.

Once initiated, the high daily dose of prednisone is continued until a definite treatment response is obtained. Ideally, strength has normalized and the serum CK (or other muscle enzyme) returns to normal. This usually takes 1-2 months but muscle strength may lag behind the improvement in muscle enzymes. Thereafter, prednisone is consolidated to a single morning dose and tapering begins. The prednisone taper is continued at approximately 20% to 25% of the existing dose each month. Patients are evaluated regularly by assessing manual muscle strength and functional status as well as measuring serum muscle enzyme levels. A conversion to alternate-day prednisone dosing may be attempted when the disease is judged to be in remission. Many will maintain prednisone therapy at a dose of 5-10 mg/day until the disease has been suppressed for approximately 1 year.

An alternative corticosteroid regimen more rapidly converts a high single daily dose of prednisone (80-100 mg/d) to a lower alternate-day dosage schedule. An initial 80- to 100-mg daily single dose for 3-4 weeks is followed by an approximate 12-week taper to an alternate-day dose schedule of 80-100 mg. The alternate "off-day" dose is gradually reduced by about 10 mg/week. The regimen must be individualized depending on the severity of the disease and rate of response. With disease relapse, defined by worsening weakness and an increase in muscle enzymes, prednisone dosage is increased or another immunosuppressive agent may be added. It may or may not be necessary to raise the prednisone dose to the level at which treatment was initiated to regain control of the disease. Many treatment failures or relapses are the result of not using enough corticosteroid for a long enough interval.

In some individuals, improvement in muscle strength will lag behind the normalization of muscle enzymes by weeks and sometimes months. Patients should be reassured that normal muscle enzymes often predicts future improvement in muscle strength. In others, strength may improve despite the fact that their CK or other muscle enzymes remain elevated. Occasionally, an excellent clinical response with normal muscle strength is coincident with a CK level that never returns to normal. Therefore, although useful and predictive in some patients, the enzyme level should not be used exclusively or in lieu of other disease activity parameters.

Although curative for some patients, the overzealous use of prednisone may lead to unwanted side effects. Corticosteroid myopathy, which causes selective atrophy of type II muscle fibers is suggested by continued or worsening proximal muscle weakness (after initial improvement) when the serum muscle enzyme level has improved, stabilized, or even normalized. The dilemma is whether the weakness represents a disease flare or steroid myopathy. No specific diagnostic test can effectively answer the question, but an EMG may

demonstrate myopathic but not "inflammatory" findings. However, a trial of corticosteroid dose reduction to see if weakness resolves, or raising the dose and seeing improvement in the setting of active inflammation, is often done. One study attempted to initially treat patients with myositis with lower doses of corticosteroids than conventionally recommended (<0.5 mg prednisolone/kg/d). A trend toward improved muscle function was observed in the group receiving lower steroid doses and there were no relapses in the low-dose group. There were less vertebral compression fractures as well.

A second immunosuppressive agent should be considered at the time of diagnosis. A retrospective analysis assessing the predictors of response to steroidal treatment regimens in the IIM found up to 40% of patients with corticosteroid-resistant disease. Patients with muscle symptoms greater than 9 months are less likely to respond completely to initial treatment and may benefit from early second-line therapy. Another retrospective analysis demonstrated a favorable outcome in patients receiving initial combined treatment when compared with those receiving corticosteroids alone.

The designation of myositis as "refractory" has not been adequately defined or uniformly agreed on. However, persistent disease activity despite adequate initial corticosteroids beyond 6 weeks to 3 months should lead one to consider adding a second agent and to reassess the accuracy of the initial diagnosis. Other diseases, such as IBM, metabolic myopathy, toxic myopathy, or muscular dystrophy, should be excluded (see "Myositis Mimics" section above).

Other Immunosuppressive Therapy

Although most patients with IIM have at least a partial response to corticosteroid therapy, many require additional immunosuppressive agents. These can be used as steroid-sparing agents in patients with serious steroid-induced complications or for disease relapse after repeated tapering attempts, for rapidly progressive disease with serious extramuscular manifestations, or for the ineffectiveness of prednisone alone. Methotrexate is probably the most commonly recommended immunosuppressive agent for myositis. Many reports have demonstrated the effectiveness of methotrexate in routine and refractory myositis, and one retrospective review suggested that weekly doses of 25 mg or less led to lower corticosteroid requirements. It can be administered orally, subcutaneously, intravenously, or intramuscularly. The subcutaneous route is recommended when doses exceed 20 mg per week, but intramuscular administration may raise serum muscle enzyme levels. Parenteral methotrexate may be increased to 30-50 mg/week with leucovorin administered for flu-like symptoms, mucositis, or gastrointestinal side effects. Daily doses of folic acid (1-2 mg) may also ameliorate methotrexate-related side effects.

Azathioprine has been used with prednisone, and in one of the few controlled, prospective, double-blind trials in myositis, patients using the combination of azathioprine and prednisone functioned better and required less maintenance prednisone at 1 and 3 years than those using prednisone alone. Azathioprine (2-3 mg/kg daily) typically has a slower onset of action than methotrexate and should not be considered a failure until continued for about 3-6 months.

A randomized crossover study suggested that the combination of oral methotrexate and azathioprine was superior to intravenous methotrexate. In fact, the oral combination was effective in patients who failed to respond to either drug alone, suggesting that the combination be considered in patients with treatment-resistant myositis. Mycophenolate mofetil has been reported to benefit patients with dermatomyositis, including the refractory rash.

The use of cyclophosphamide in patients with myositis is controversial. Several authors have reported favorable results with monthly pulse cyclophosphamide in patients who have lupus myositis, myositis with Sjögren's syndrome, and the ILD of PM and DM. Cyclophosphamide can be initiated orally at 50 mg per day, and the dose can be raised to approximately 2 mg/kg/d until leukopenia or other side effects develop. Chlorambucil, another alkylating agent, was used in 5 patients with DM refractory to prednisone, azathioprine, and methotrexate with improvement at 4 to 6 weeks in all 5 patients. Sixteen patients with severe IIM were treated with fludarabine (an adenine analog and antineoplastic agent) with fair results.

Combinations of immunosuppressive agents including prednisone, methotrexate, and either chlorambucil or methotrexate have been used, but these regimens include alkylating agents that pose the possible development of late malignancy. Cyclosporine inhibits T-cell activation and has been reported to be effective in several small, uncontrolled series or case reports of myositis. The dose ranges from 2.5-7.5 mg/kg/d, and improvement generally occurs in less than 2 months. The efficacy of cyclosporine A was compared to methotrexate in the treatment of 36 patients with inflammatory myopathy. In combination with corticosteroids, both drugs were effective but methotrexate-treated patients showed a slightly better and more rapid onset in clinical response compared to cyclosporine-treated patients. Tacrolimus (FK 506) is another immunosuppressive agent used to prevent organ rejection that was found to be effective in both refractory myositis and the ILD of patients with the antisynthetase syndrome.

Biologic agents have been increasingly reported in patients with myositis. Anti-TNF agents may be useful in some cases of refractory PM or DM and pilot studies on the use of rituximab in adult and juvenile dermatomyositis are also promising with improvement of both cutaneous and muscular manifestations. Larger controlled trials are currently underway to more intensively study these biologic agents in patients with both early as well as refractory myositis.

Intravenous Immune Globulin

Intravenous immune globulin (IVIg) has been used in many immunologically mediated diseases, including the inflammatory myopathies. In a randomized, double-blind, placebo-controlled trial, IVIg was found to be effective in 15 patients with refractory dermatomyositis. Given the B-cell-mediated pathogenesis of DM, the use of gamma globulin appears logical in that this therapy likely blocks Fc receptors and may eliminate circulating immune complexes. IVIg has not been systematically studied in PM and although its use as first line therapy in the IIM has been questioned, it may be indicated early in some instances such as JDM, in the setting of infection with active myositis or as bridge therapy in DM while other immunosuppressive agents take effect.

Treatment of Inclusion Body Myositis

IBM is often diagnosed well after its clinical features — muscle weakness and atrophy — are established and profound. The likelihood of a beneficial response is minimal at this point. Some believe that a persistent elevation of the CK level indicates ongoing muscle necrosis and a potentially reversible process. However, muscle biopsies were performed in a prospective trial before and after corticosteroid treatment, and although histologic inflammatory changes decreased and CK levels fell, muscle strength worsened. This suggests that the inflammatory response in IBM may be a secondary pathogenetic phenomenon. IVIg has been used in several small series of patients with IBM and the results are mixed. Perhaps the most reasonable approach to IBM would be to slow or stabilize the progression of disease since improvement of strength and reversal of atrophy are unlikely. A retrospective review combined with a randomized, prospective, immunosuppressive therapeutic trial showed that azathioprine and methotrexate halted disease progression in 23% of retrospectively analyzed patients, whereas 74% prospectively studied patients had disease improvement or stabilization with oral azathioprine and methotrexate combined with biweekly doses IVIg for 3-6 months. Due to the slow, inexorable deterioration in IBM the following therapeutic approach has been suggested:

1) In newly diagnosed IBM patients, 40-60 mg/d of prednisone for 1-2 months followed by a slow taper and reassessment at 3 months. A favorable response includes an increase in strength and improvement in functional status and a reduction in the serum CK level.

2) If improvement occurs, azathioprine or methotrexate is added as the corticosteroids continue to be tapered.

3) In patients with a high CK level, marked inflammatory infiltrates on muscle biopsy, or an associated autoimmune disease, another immunosuppressive agent is added after the initial corticosteroid trial for an additional 3-6 months even in the absence of a response to corticosteroids.

4) Immunosuppressive agents should be discontinued if there is no response after 6-12 months of therapy.

Adaptive devices, including leg braces or orthotics, may be necessary in IBM patients to allow ambulation and prevent falling episodes. Physical therapy may be beneficial but is unproven.

Treatment of Extramuscular Manifestations

The rash of DM may be refractory to treatment and often proceeds discordantly from muscle weakness. Both topical and systemic corticosteroids are helpful but not curative. Methotrexate is recommended by many dermatologists and hydroxychloroquine (200-400 mg daily) and CellCept® have been shown to be effective as well. Quinacrine (100 mg daily) and isotretinoin (0.5-1.0 mg/kg/d) may be helpful for some refractory rashes, and sunscreens are also important to use.

Subcutaneous calcinosis is unusual in adult myositis (except for overlap syndromes) and is extremely resistant to treatment. Secondary soft-tissue inflammation from calcinosis may respond to oral colchicine, but attempts to resolve the calcium deposits with such measures as low-dose warfarin, aluminum hydroxide, probenecid, and diltiazem have been generally unhelpful.

Pulmonary disease in the form of diffuse alveolitis is a serious problem in the IIMs. Corticosteroids also may be helpful, but additional immunosuppressive agents in the form of oral or monthly intravenous cyclophosphamide or cyclosporine should be considered. As described earlier, tacrolimus has shown to be effective in an uncontrolled trial in anti-Jo-1 antibody-positive patients with both refractory myositis and ILD.

Various esophageal, gastric, and intestinal problems may complicate the clinical course of myositis patients. Proximal dysphagia leading to pharyngeal weakness may be severe, requiring either parenteral or enteral hyperalimentation. Distal dysphagia with pyrosis may occur in pure forms of myositis as well as in overlap syndromes. Aggressive therapy with antacids, H2-blockers, and proton pump inhibitors may be necessary, along with more commonsense measures such as having patients elevate the head of their bed and not recline after meals. Cricopharyngeal achalasia (seen in IBM) can be treated with cricopharyngeal myotomy. Vasculitic gastrointestinal involvement requires high-dose corticosteroids and the addition of another immunosuppressive agent such as cyclophosphamide. It is very uncommon in adults but a serious problem in childhood DM.

Rehabilitative Measures

The heterogeneity among patients with myositis underscores the importance of an individualized approach regarding the timing and intensity of physical therapy intervention. During active myositis, therapy is directed toward maintenance of range of motion with a passive exercise and stretching program. More aggressive rehabilitative approaches have not led either to disease exacerbation or a rise in CK level even in patients with active myositis. During recovery, when strength and the serum CK level are also improving or normal, a more aggressive isometric program with continued range of motion and stretching can be instituted. Certainly when myositis enters remission, patients should perform active isotonic and even resistive exercises to improve muscle tone and strength. Due to patients' general deconditioning, an aerobic program should be considered for them as well.

Prognosis

Recent reports indicate a 90% survival rate among patients with PM and DM 5 years after their initial diagnosis. Improved survival is due to earlier diagnosis, improvement in general medical care, and more judicious use of immunosuppressive drugs for refractory disease and extramuscular organ involvement. The best survival rates are for IBM and myositis associated with another CTD. However, certain autoantibodies have adverse impact, as was discussed in earlier sections.

Factors associated with a poor prognosis include older age at onset of myositis, delayed initiation of therapy, pharyngeal dysphagia with pulmonary aspiration, ILD, and myocardial involvement. The determinants of disability are different from those

associated with death, and IBM patients have worse functional outcome but a very good survival rate. In a prospective longitudinal study of a national cohort of 257 patients with PM and DM, disability increased with disease duration and corticosteroid-related morbidity. Osteonecrosis and osteoporotic fracture contributed significantly to functional disability. Other sequelae leading to disability include calcinosis, arthropathy, pulmonary fibrosis, and congestive cardiomyopathy.

3. Scleroderma

Definition

The term scleroderma traditionally has been applied to the cutaneous changes of both systemic sclerosis (SSc) and a heterogeneous group of conditions designated collectively as localized scleroderma. Coexistence of these entities is rare. Systemic sclerosis is a chronic disorder of connective tissue characterized by inflammation, fibrosis and degenerative changes in the blood vessels, skin, synovium, skeletal muscle, and certain internal organs, notably the gastrointestinal tract, lung, heart and kidney. The hallmark of SSc is thickening of the skin (scleroderma) and other organs caused by excessive accumulation of connective tissue in both interstitial sites and blood vessels. In the localized forms of scleroderma, dermal fibrosis is more circumscribed, both vascular and internal organ involvement are absent, peripheral blood eosinophilia is frequent, and the characteristic serologic abnormalities of SSc are not found (Table 8).

Classification

Clinical Subsets

SSc is divided into two major clinical variants, diffuse cutaneous (dc) and limited cutaneous (lc) disease, which are distinguished from one another primarily on the basis of the degree and extent of skin involvement. The term "overlap syndrome" is used when features commonly encountered in other connective tissue diseases are also present (Table 8).

The dc variant is characterized by distal and proximal extremity and truncal skin thickening, whereas in the lc subtype, skin thickening is most often restricted to the fingers, hands and face. Generally the elbows and knees are considered the dividing line; a patient has dcSSc if skin thickening affects the upper arms, thighs or trunk (anterior chest, abdomen, back). CREST syndrome (an acronym referring to the findings of calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia) is closely analogous to lcSSc. Some patients with SSc have no detectable skin thickening (SSc sine scleroderma).

Additionally, many demographic, clinical and laboratory features help to distinguish dc from lc disease (Table 9). Diffuse disease is associated with palpa-

Table 8

Classification of Scleroderma by Clinical Subsets

Systemic (Systemic Sclerosis – SSc)
Diffuse cutaneous (dcSSc): symmetric widespread skin fibrosis affecting the distal and proximal extremities, and often the trunk and face; tendency to rapid progession of skin changes and early appearance of visceral involvement
Limited cutaneous (lcSSc): symmetric restricted skin fibrosis affecting the distal extremities (often confined to the fingers) and face; prolonged delay in appearance of distinctive internal manifestations (eg, pulmonary artery hypertension); prominence of calcinosis and telangiectasias
"Overlap" syndrome: diffuse or limited cutaneous manifestations and typical features of another connective tissue disease, most frequently polymyositis-dermatomyositis or systemic lupus erythematosus
Localized
Morphea: single or multiple plaques of skin fibrosis
Linear scleroderma: single or multiple bands of skin fibrosis; includes en coup de sabre (with or without facial hemiatrophy)
Eosinophilic fasciitis: fascial and deep subcutaneous fibrosis
Eosinophilia myalgia syndrome
Toxic oil syndrome

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ble tendon friction rubs, arthritis with joint contractures, serum anti-topoisomerase I (anti-Scl 70) or anti-RNA polymerase antibodies, and earlier, more frequent occurrence of visceral disease affecting the gastrointestinal tract, lung, heart and kidney. In contrast, lcSSc is correlated with calcinosis, telangiectasia, serum anticentromere antibodies, and the occasional late development of pulmonary fibrosis, pulmonary arterial hypertension or small bowel malabsorption. Overlap patients have convincing evidence of another connective tissue disease, such as polymyositis (myositis, dermatomyositis rash) or systemic lupus erythematosus (leukopenia, glomerulonephritis, pleuropericarditis, typical rash).

Serologic Subsets

Since the identification of anti-topoisomerase I and anti-centromere antibodies, several other serum autoantibodies relatively specific for SSc have been described. The proportion of patients having one of seven SSc-associated autoantibodies is nearly 85% (Figure 1). Persons with lcSSc most frequently have anti-centromere or anti-Th antibody. Individuals with dcSSc have anti-topoisomerase I or anti-RNA polymerase I and III antibody. Patients with SSc in overlap most often develop anti-U1RNP, anti-PM-Scl, or anti-U3RNP antibodies.

Figure 1

Classification of systemic sclerosis subsets and antibody types

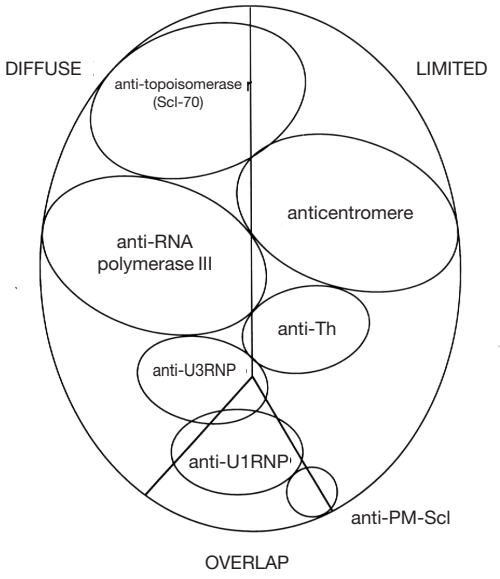

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Table 9

Features Differentiating Diffuse Cutaneous from Limited Cutaneous Systemic Sclerosis

	Diffuse	Limited
Age <50 at onset	Common	Uncommon
Female sex	Common	Almost always
Calcinosis	Uncommon	Common
Onset of skin thickening preceding onset of Raynaud's phenomenon	Common	Rare
Rapid progression of skin thickening	Common	Rare
Polyarthritis	Occasional	Rare
Tendon friction rubs	Common	Rare
Hand joint contractures	Almost always	Common
Myocardial involvement	Occasional	Rare
Pulmonary hypertension	Rare	Occasional
Renal crisis	Uncommon	Rare
Anticentromere antibody	Rare	Common
Anti-topoisomerase I antibody	Common	Occasional

Rare = <5%; Occasional = 6%-10%; Uncommon = 11%-20%; Common = 21%-70%; Almost always = 71+%

Epidemiology

The annual incidence of SSc in the United States has been estimated at 25 to 30 new cases diagnosed per million population at risk. Overall, women are affected three times as often as men, and this ratio is increased during the childbearing years. No significant overall racial differences have been found. Systemic sclerosis usually begins in persons between 30 and 50 years of age. Onset during childhood and after age 80 has been reported but is uncommon. In African-American women, disease onset occurs at a younger age, dcSSc is more common and survival is poor. Prevalence estimates for systemic sclerosis have been in the range of 200 per million.

Clinical Features

Initial Symptoms

In most cases of lcSSc, the initial complaint is Raynaud's phenomenon. In contrast, patients with dcSSc most often have diffuse swelling of the hands, skin thickening, or arthritis as the first manifestation. Occasionally, the earliest clue is visceral involvement, such as esophageal symptoms (dysphagia, heartburn) or dyspnea.

Features of Organ Systemic Involvement

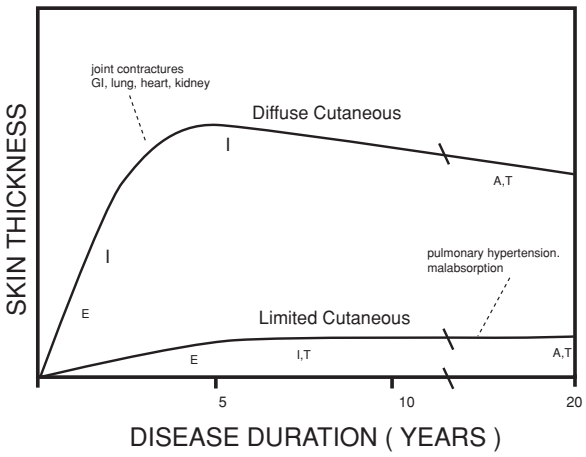
Skin. Initially, patients complain about tight, puffy fingers, especially on arising in the morning (edematous phase). Pitting or nonpitting edema of the fingers ("sausaging") and hands may occur. These changes extend beyond periarticular areas, assisting in the distinction from arthritis. Edema may last indefinitely (eg, fingers in lcSSc) or may be replaced gradually by thickening and tightening of the skin (indurative phase) after weeks or months. After several years, the dermis tends to soften somewhat and in many cases reverts to normal thickness or actually becomes thin (atrophic phase). At that time, the most striking finding is digital and facial telangiectasias, which consist of widely dilated capillary loops and distended venules.

The natural history of skin involvement in the two major variants of SSc is notably different (Figure 2). In lcSSc, skin thickening is either absent or remains minimal over many years and bears no relation to visceral sequelae. In contrast, in dcSSc early, rapid increase in skin thickness is the rule, reaching a peak after 1 to 2 years. Increasing skin thickness is temporally associated with the development of joint contractures and internal organ problems.

Skin biopsy in the active indurative phase discloses a striking increase of compact collagen fibers in the reticular dermis and hyalinization and fibrosis of arterioles, thinning of the epidermis with loss of rete pegs, atrophy of dermal appendages and variably large accumulations of mononuclear cells, chiefly T-lymphocytes, in the lower dermis and upper subcutis. The skin overlying bony prominences, and especially over extensor surfaces of the proximal interphalangeal joints and elbows, becomes tightly stretched as a result of contractures and is extremely vulnerable to trauma. In such areas, cutaneous thinning (atrophy) rather than thickening occurs. Patients are often plagued by painful ulcerations at these sites and, less commonly, over the bony prominences about the shoulders, elbows, and ankles. These ulcers heal extremely slowly and frequently become secondarily infected. Patients with lcSSc or late-stage dcSSc commonly develop intracutaneous and/or subcutaneous calcifications composed of hydroxyapatite. These palpable, yellow rock-hard deposits occur chiefly in the digital pads and periarticular tissues, along the extensor surfaces of the forearms, in the olecranon bursae, prepatellar areas, and buttocks. They can be confirmed radiographically. Calcinosis may be complicated by ulceration of overlying skin, intermittent extrusion of calcareous material and secondary bacterial infection (typically staphylococcal).

Figure 2

Natural history, skin thickness, and timing of some serious complications during the course of systemic sclerosis with the two major disease variants



E=edema;I=induration; A=atrophy; T=telanglectasia

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Peripheral vascular system. Raynaud's phenomenon is defined as paroxysmal vasospasm in response to cold exposure or emotional stress, leading to pallor and/or cyanosis of the digits, which also become cold, numb, and painful. During rewarming, reactive hyperemia is common. Raynaud's phenomenon occurs at some time during the disease in over 95% of persons with SSc. Small areas of fingertip ischemic necrosis or ulceration are frequent, often leaving pitted scars, but gangrene is rare. Angiographic and autopsy studies have disclosed narrowing and obstruction of the digital arteries. At necropsy, these vessels typically show

lumenal narrowing and prominent intimal and adventitial fibrosis without evidence of inflammation. Larger vessels, particularly the ulnar arteries, also may be affected. On microscopic examination, there are dilated or "giant" capillary loops and in dcSSc, dilatation and a paucity of nailfold vessels or "dropout." Such capillary abnormalities are an early predictor of evolution to SSc in persons who clinically appear to have Raynaud's phenomenon alone.

Joints and tendons. Symmetric polyarthralgias, joint stiffness and limitation of motion of the fingers, wrists, knees and ankles are frequent. Synovitis mimicking that of rheumatoid arthritis is uncommon, but may be the first manifestation of dcSSc. Some patients appreciate a "squeaking" sensation on movement of their extremities. A distinctive coarse, leathery crepitus (tendon friction rub) can be palpated over such areas during joint motion, particularly over the olecranon bursae, wrist and finger flexor and extensor tendons, distal lateral aspects of the quadriceps tendons superior to the knees, anterior tibial tendons above the ankles, and Achilles tendons. Friction rubs are due to fibrinous tenosynovitis and are relatively specific for dcSSc. They often antedate an explosive increase in skin thickening and are associated with renal involvement and reduced survival. Carpal tunnel syndrome is caused by fibrinous flexor tenosynovitis at the wrist.

Skeletal muscle. Weakness and atrophy of skeletal muscle result from disuse secondary to joint contractures or chronic disease in approximately 20% of patients. Typically, this is a subtle process with weakness noted by the examiner but not the patient, mild or no serum muscle enzyme elevation, and muscle biopsy showing focal replacement of myofibrils with collagenous connective tissue and perimysial and epimysial fibrosis without inflammatory changes. This bland myopathy is nonprogressive and does not warrant intervention. In contrast, a minority of patients exhibit more pronounced proximal muscle weakness and biochemical (elevated serum muscle enzymes), electrophysiologic (abnormal electromyogram), and pathologic (muscle biopsy) evidence of polymyositis. These persons have been classified as having either SSc with myositis or SSc in overlap with polymyositis.

Gastrointestinal Tract

Oral cavity. Thinning of the lips (microcheilia) and reduced oral aperture (microstomia) are frequent. Gingivitis and loosening of the teeth also have been noted. In addition, patients have mechanical difficulty in maintaining good oral hygiene (finger contractures, limited oral opening) and sometimes associated Sjögren's syndrome.

In this situation, dry mouth may be attributed to either lymphocytic infiltration of minor salivary glands on labial biopsy (15% to 20% of patients) or to periglandular and intraglandular fibrosis (a similar proportion). A few affected persons have serum anti-SSA/Ro and/or anti-SSB/La antibodies. As in primary Sjögren's syndrome, vasculitis involving the skin (palpable purpura and leg ulcers) and peripheral nervous system (sensory neuropathy and mononeuritis multiplex) may occur. Those at risk for this complication have lcSSc, anti-SSA and/or anti-SSB antibodies and hypocomplementemia.

Esophagus and stomach. Esophageal dysfunction is the most common visceral manifestation of SSc and eventually develops in nearly 80% of patients. As a result of incoordination of the normal propulsive peristalsis of the distal esophageal smooth muscle, solids (meat, bread) become transiently "stuck" in the mid or lower esophagus (retrosternal location). Incomplete closure of the lower esophageal sphincter leads to gastroesophageal reflux symptoms (heartburn) with peptic esophagitis. After years of inadequately treated reflux esophagitis, distal esophageal stricture is likely to develop. Radiographic abnormalities are found in three-fourths of patients studied, including some who have no esophageal symptoms. Cinefluoroscopic examination, the standard method of evaluation, reveals diminished or absent peristaltic activity in the distal esophagus, dilatation, and gastroesophageal reflux. Involvement of the stomach is uncommon. Heavy bleeding may result from an unusual condition termed "watermelon stomach," in which ectatic gastric antral capillaries and dilated submucosal vessels are prominent, grossly visible as broad stripes at endoscopy. Histologic changes are most significant in the lower two-thirds of the esophagus, where thinning of the mucosa, cellular infiltrates in the submucosa and increased collagen in the lamina propria and muscularis have been noted. The walls

of small arteries and arterioles and periadventitial sites are infiltrated with collagen.

Small intestine. In a small proportion of patients, the illness is dominated by severe post-prandial bloating and abdominal cramps. These symptoms are due to hypomotility of the small intestine and may result in a functional ileus (pseudo-obstruction) with symptoms simulating mechanical obstruction. Hypomotility favors the overgrowth of intestinal microorganisms that consume large amounts of vitamin B_{12} and interfere with normal fat absorption as a result of their deconjugation of bile salts. Profuse watery diarrhea with malabsorption can result in weight loss, and extreme wasting despite adequate caloric intake. Radiographic findings include prolonged retention of barium in the atonic and widely dilated second and third portions of the duodenum (loop sign) and irregular flocculation or hypersegmentation of barium or localized areas of dilatation of the jejunum and/or ileum. Collections of air in the bowel wall (pneumatosis cystoides intestinalis) has also been described. With the addition of serosal fibrosis, the pathologic changes in the small intestine are similar to those described for the esophagus.

Colon. Constipation, either alone or alternating with diarrhea, may signal colonic involvement. Reduced anorectal capacity, motility, compliance, and sphincter pressure have been reported. Rectal incontinence and prolapse are uncommon but disabling problems. Patchy atrophy of the muscularis leads to development of widemouthed diverticula, which usually occur along the ante-mesenteric border of the transverse and descending colon. Rarely, these outpouchings may perforate or become impacted with fecal matter, producing obstruction.

Lung. Pulmonary involvement occurs in over 70% of patients and during the past 15 years has emerged as the most common disease-related cause of death. Exertional dyspnea is present in nearly half of patients, pleuritic chest pain is uncommon, and exudative pleural effusion is rare. The 2 main clinical manifestations of lung involvement are interstitial lung disease (fibrosing alveolitis, pulmonary fibrosis) and pulmonary vascular disease (Table 10).

- ***Interstitial lung disease (ILD)***. ILD occurs in over one-third of patients with both dcSSc and lcSSc, although it usually occurs at an earlier stage and progresses more rapidly in the former. Dry bibasilar end-inspiratory "fibrotic" or "velcro"

Table 10

Pulmonary Manifestations of Systemic Sclerosis

	Pulmonary Fibrosis	**Pulmonary Hypertension**
Progression of dyspnea	Slow (over 2-10 years)	Rapid (over 6-12 months)
Physical examination	Bibasilar "velcro" rales	Increased P2 sound
Chest radiograph	Bibasilar interstitial thickening, normal heart size	Clear lung bases Increased PA and RV size
HRCT	Fibrosis and/or alveolitis	Normal lung fields
PFTs	Decreased FVC and DLCO	Very decreased DLCO with normal or near normal FVC
FVC	Cell count >20,000,000/mm^3	Cell count <20,000,000/mm^3
BAL	Increased neutrophils and/or eosinophiles	Alveolar macrophages Few neutrophils +/or eosinopils
Serum autoantibody	Antitopoisomerase I	Anticentromere, anti-Th

rales are frequently heard in these persons with clinically significant ILD. The chest radiograph shows interstitial thickening in a reticular pattern of linear, nodular, and lineonodular densities most pronounced in the lower lung fields, but chest radiography is an insensitive indicator of ILD. The diagnosis can also be established with pulmonary function testing (PFT) and high-resolution computed tomographic scanning (HRCT). A restrictive ventilatory defect, indicated by a reduction in forced vital capacity (FVC) and decreased diffusing capacity (D_{LCO}) is most common. A pronounced decrease in D_{LCO} (<65% normal) is usually associated with a reduced FVC in ILD but may occur with otherwise normal lung volumes in patients with isolated pulmonary hypertension (see below and Table 10). HRCT with thin section cuts (<3mm) is abnormal in 75% of patients with systemic sclerosis with normal chest radiographs. This technique may identify a "ground-glass" appearance which correlates with a biopsy showing predominately cellular inflammation (alveolitis). A reticular pattern is associated primarily with fibrotic disease on lung biopsy. While ground glass lesions are more likely to reverse on therapy than fibrotic changes, it remains unclear whether the former is necessarily a precursor of the latter.

- ***Bronchoalveolar lavage (BAL)*** fluid cell differential can reveal evidence of inflammation in ILD. The presence of elevated numbers of neutrophils and eosinophils in BAL fluid correlates with subsequent deterioration on PFT. Unfortunately, variability in technique and specimen processing has reduced the utility of BAL in routine clinical settings. Open lung biopsy may show diffuse alveolar, interstitial, peribronchial, and pleural fibrosis as well as inflammation. Although it remains the gold standard for the classification of ILD, the use of open lung biopsy in SSc has been other less invasive testing described above. Furthermore, the changing classification of ILDs has not been shown to add prognostic value to lung disease in SSc, where the predominant lesion is nonspecific interstitial pneumonitis (NSIP). Some patients with interstitial involvement develop progressive, fatal respiratory failure, over the course of 2 to 10 years. At highest risk are younger individuals, African-Americans, and males, as well as those with diffuse cutaneous disease and serum anti-topoisomerase I antibody. A moderate degree of "secondary" pulmonary hypertension, with a relatively slow progression, follows widespread pulmonary interstitial fibrosis.

- ***Pulmonary arterial hypertension***. A very different clinical entity is severe "isolated or primary" pulmonary arterial hypertension with minimal or no pulmonary interstitial fibrosis. This complication occurs predominantly in patients with limited cutaneous involvement after 10 to 30 years, but occasionally in individuals with diffuse skin thickening who also have anti-U3RNP antibody. The rate of progression of dyspnea is alarmingly rapid; a patient may go from normal exercise tolerance to oxygen dependence in 6 to 12 months. The pulmonic component of the second heart sound is accentuated and ultimately, right-sided cardiac failure develops. The diffusing capacity is extremely low, with preserved FVC, consistent with impaired gas exchange across thickened small pulmonary blood vessels, which histologically show intimal and medial hyperplasia, without inflammation, producing an "onion skin" appearance. Diagnosis can be confirmed by Doppler echocardiography or by right heart catheterization, which remains the gold standard. In the past, the mean duration of survival from detection of primary pulmonary hypertension was 2 years, emphasizing its serious nature, although newer therapies may improve prognosis (see below).

- ***Heart***. Cardiac involvement may be classified as primary or secondary. Primary disease consists of pericarditis with or without effusion, left ventricular or biventricular congestive failure, or a serious supraventricular or ventricular arrhythmia. Small pericardial effusions and pericardial thickening are detected frequently by echocardiography. Acute symptomatic pericarditis is unusual, and cardiac tamponade is rare. Pericardial effusion may antedate renal involvement and massive pericardial effusions have been noted to occur in a few persons with diffuse scleroderma and anti-topoisomerase I antibody. The few reported pericardial fluids were exudates with low white blood cell counts. Left-sided congestive failure secondary to myocardial fibrosis occurs in fewer than 5% of patients, nearly all of whom have diffuse cuta-

neous involvement. New noninvasive radionuclide studies, however, show that diastolic dysfunction is more frequent and may be associated with resting and reversible exercise and cold-induced myocardial perfusion defects, especially in patients with diffuse disease. Myocarditis has been reported in patients with scleroderma who also had typical polymyositis. Skeletal and cardiac muscle involvement may coexist with a high frequency of sudden death, presumably due to cardiac arrhythmias. Autopsies of patients with diffuse scleroderma may show extensive degeneration of myocardial fibers with replacement by perivascular fibrosis. The pathologic finding of "contraction band necrosis" is consistent with the concept that heart damage may, in part, be due to intermittent vascular spasm or "intramyocardial Raynaud's phenomenon." Cardiac arrhythmias include complete heart block and other electrocardiographic abnormalities. The conduction system in such patients has revealed fibrous replacement of the SA node, AV node (particularly in its proximal segment) and bundle branches. In most cases, however, arrhythmias have been attributed to disturbances of the myocardium. Secondary causes of heart disease in scleroderma are pulmonary hypertension and systemic arterial hypertension. Renal crisis frequently leads to acute myocardial dysfunction (congestive heart failure with a normal-sized heart) that is reversible with control of blood pressure.

- ***Kidney***. Renal disease is an important aspect of systemic sclerosis and prior to 1980 was the major cause of death. Clinically evident renal involvement is restricted almost exclusively to persons with dcSSc, especially those with rapidly progressive skin thickening of less than 3 years' duration. Ten to 15% of patients with dcSSc develop a dramatic complication termed scleroderma renal crisis, with the abrupt onset of accelerated hypertension, followed promptly by rapidly progressive oliguric renal failure (Table 11). The presenting symptoms are varied and include headache, visual blurring from hypertensive retinopathy, seizures, and acute dyspnea due to sudden left ventricular failure. Within several days or weeks, microscopic hematuria and low-grade proteinuria may be noted, along with rapidly increasing serum creatinine, and finally, oliguria or anuria. Microangiopathic hemolytic anemia and thrombocytopenia are prominent features and thus this presentation may be mistaken for thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Risk factors for scleroderma renal crisis other than rapidly progressive skin thickening include recent prior administration of corticosteroids (prednisone >15 mg/d), African-American race, and cold weather. Acute reduction of renal blood flow and sudden, severe volume depletion may also trigger this complication. Numerous small cortical infarcts are seen grossly in the affected kidneys. Microscopic alterations include subintimal proliferative changes in the arcuate and interlobular arteries, as well as intimal hyperplasia with acid mucopolysaccharide deposition, and necrosis of the walls of these vessels, afferent arterioles, and glomerular tufts. Concentric "onion skin" hypertrophy may be seen in the

Table 11

Characteristics of Scleroderma Renal Crisis

Setting: Diffuse scleroderma; disease duration <5 years; recent rapid increase in skin thickening; recent administration of prednisone >15 mg/day (or equivalent); serum anti-RNA polymerase III antibodies
Clinical features: Accelerated arterial hypertension; headache; visual blurring; seizures; dyspnea on exertion/orthopnea; retinal hemorrhages/exudates and arteriolar narrowing; oliguria/anuria
Laboratory abnormalities: Microscopic hematuria/proteinuria; RBC casts in urine; microangiopathic hemolytic anemia and thrombocytopenia; increased serum creatinine

interlobular arteries not unlike that seen in the pulmonary vessels in patients with pulmonary artery hypertension. Activation of the renin-angiotensin system is responsible for the marked hypertension although on occasion patients can develop renal crisis without hypertension.

Other Clinical Features

Symptomatic scleroderma involvement of the lower urinary tract is rare. Vaginal symptoms are common, including dryness, dyspareunia, and difficulty achieving orgasm. Vaginal tightness and constricted introitus contribute to these problems. Impotence without other obvious cause is common and is most likely due to reduced penile blood flow. Primary biliary cirrhosis occurs in some women with lcSSc, most frequently in association with Sjögren's syndrome. In typical systemic sclerosis, hematologic studies are normal. Abnormalities suggest either a specific complication or an associated illness. Some patients have anemia, the most common causes of which are chronic disease, gastrointestinal tract blood loss (erosive esophagitis or "watermelon stomach"), excessive destruction (microangiopathic hemolysis), or a nutritional cause (duodenal iron malabsorption). Primary symptomatic disorders of the nervous system are seldom encountered. Most neurologic abnormalities in patients with systemic sclerosis are either coincidental or represent secondary compressive phenomena, eg, carpal tunnel syndrome. Trigeminal sensory neuropathy, an infrequent finding, is associated most closely with myositis and serum anti-U1RNP antibodies. Peripheral vasculitis, believed due to coexisting Sjögren's syndrome, may cause a sensorimotor polyneuropathy or mononeuritis multiplex. Hypothyroidism, often clinically unrecognized, occurs in one-fourth of patients with SSc and is frequently accompanied by serum antithyroid antibodies.

Malignancy

The published frequency of cancer in large clinical series has varied from 3% to 7%. A subset of women develops breast cancer at or near the time of onset of scleroderma. Lung cancer is significantly more frequent than in the age- and sex-matched general population, occurs in the setting of long-standing scleroderma with ILD, and is independent of cigarette smoking.

Pregnancy

There is controversy concerning both fertility and the frequency of spontaneous abortion. Pregnancy appears to exert no consistent effect on the course of SSc. Moreover, the disease ordinarily does not interfere with pregnancy or parturition. However, women with early diffuse disease should be advised not to become pregnant until after skin thickening has peaked and has begun to improve (usually 3 or more years).

Other Serum Autoantibodies

Moderate hypergammaglobulinemia (1.4-2.0 g/dL) occurs in over one-third of patients, most often in those with overlap syndromes. Serum complement levels are normal except when SLE or Sjögren's syndrome with vasculitis coexist. One-third of patients have positive tests for rheumatoid factor, usually in low titer.

Disease Course

The course of systemic sclerosis is extremely variable. Early in the illness, it is difficult to judge prognosis with respect to either survival or disability. Many patients with dcSSc involvement experience steadily increasing sclerosis of the fingers and hands, leading to deforming flexion contractures. The most reliable early signs predicting subsequent dcSSc are the appearance of skin thickening before the onset of Raynaud's phenomenon, rapid progression of scleroderma toward the more proximal parts of the extremities, palpable tendon friction rubs, and serum anti-topoisomerase I or anti-RNA polymerase I or III antibodies (Table 9). Survival in lcSSc is significantly better compared to dcSSc, in part because the former patients rarely, if ever, develop myocardial or renal disease. Several large survival studies have been reported and summarized. Most authors agree that male sex, older age and involvement of the kidney, heart, and lung adversely affect outcome (Table 12). Survival has improved during recent decades for a variety of reasons, especially the successful management of renal crisis. The cumulative survival rates in our patients, first evaluated during 1989-1998, are 86% at 5 years and 74% at 10 years after first physician diagnosis.

Treatment

General Treatment

In the past, no drug or combination of drugs has been proven to be of value in adequately controlled prospective trials. Anti-inflammatory agents and corticosteroids have been disappointing. Because of their potential toxicity, including precipitation of acute renal failure, corticosteroids are typically restricted to patients with inflammatory myopathy or symptomatic serositis inadequately controlled with nonsteroidal anti-inflammatory agents. D-penicillamine was shown in two retrospective United States studies of early diffuse disease to result in striking improvement in skin thickening, reduced frequency of subsequent renal involvement, and increased survival using drug doses up to 1000-1500 mg/d. However, in a recent double-blind randomized multicenter study, both high dose (mean 833 mg/d) and low dose (mean 72 mg/d) D-penicillamine were followed by a mean improvement in skin score of 30% after 2 years. D-penicillamine use is frequently accompanied by side effects; up to one-fourth of patients may not tolerate the drug. The use of immunosuppressive measures seems justified in patients with early, rapidly progressive, life threatening and/or disabling diffuse disease. Azathioprine, 5-fluorouracil, chlorambucil, plasmapheresis, cyclosporin A, interferon alpha, antithymocyte globulin and methotrexate have been used with unimpressive results. There have been several encouraging reports on recombinant interferon-gamma therapy. Autologous stem cell transplantation has been attempted with some promising results, but carries some early, procedure-related mortality risk. To date, there is no general agreement regarding the effectiveness of immunosuppressive or immunomodulating forms of therapy. Agents designed to protect injured endothelial cells and to prevent platelet aggregation and subsequent release of platelet-derived growth factors, such as dipyridamole and aspirin, have not altered disease progression.

Organ-Specific Treatment

Raynaud's Phenomenon

Common sense self-management includes avoiding undue cold exposure, dressing warmly, and abstaining from tobacco use. Vasodilating drugs such as the calcium channel blocker nifedipine have proved useful. Thoracic sympathectomy may be followed by partial (usually transient) improvement in Raynaud's phenomenon but not by significant or sustained influence on the course of cutaneous changes or visceral sclerosis. Digital sympathectomy has been used successfully in some difficult cases, but these observations are uncontrolled and lack long-term follow-up. When large vessels are involved, eg, the radial or ulnar arteries, and vascular insufficiency results, microvascular surgical reconstruction should be considered. Digital tip amputation occasionally may be required, especially if osteomyelitis has occurred.

Calcinosis

Reliable medical treatment to eradicate or prevent calcinosis is not available. Surgical excision of large calcareous masses may be helpful in selected instances. Suppression of local sterile inflammation surrounding these hydroxyapatite deposits has been achieved with colchicine, which is given in brief, 7- to 10-day courses.

Table 12

Factors Associated with Reduced Survival in Systemic Sclerosis*

Host Factors	Disease Features
Age >45	Truncal skin thickening
Male sex	Kidney involvement
Non-Caucasian race	Heart involvement Lung involvement Elevated ESR Anemia

** Based on 9 published studies including more than 2000 patients*

Skin
Digital tip ulcerations can be protected by plastic finger "cages." Noninfected skin ulcers heal nicely with the use of "wet to dry" dressings or occlusive preparations. If these lesions become infected (almost always with staphylococci), half-strength hydrogen peroxide soaks and gentle local debridement are employed, and oral antibiotics are sometimes needed. Deeper soft tissue infections, septic arthritis and osteomyelitis must be treated vigorously with intravenous antibiotics, excision of infected and devitalized tissue, joint fusion and rarely, amputation.

Joints and Muscles
Articular complaints may be treated with salicylates or other nonsteroidal anti-inflammatory drugs, with careful attention to their potential to aggravate gastroesophageal reflux and to reduce renal blood flow. Dynamic splinting does not prevent progression of digital contractures with deformity, but a vigorous twice-daily range of motion exercise program can improve joint range of motion. Severe flexion contractures of the proximal interphalangeal joints leave them vulnerable to trauma with repeated skin breakdown and infection, including septic arthritis. In this circumstance, proximal interphalangeal joint fusion is preferred. Healing of surgical incisions has been good.

Active polymyositis with proximal muscle weakness should be treated with moderate doses of corticosteroids (prednisone, 15-20 mg/day). Methotrexate, azathioprine, or another immunosuppressive agent can be added in the event that the response is incomplete.

Gastrointestinal Tract
Metoclopramide stimulates both gastric and esophageal emptying and erythromycin also functions as a prokinetic drug. Nifedipine prescribed for Raynaud's phenomenon is capable of decreasing lower esophageal sphincter pressure and contraction amplitude in the body of the esophagus and thus may aggravate esophageal symptoms.

Reflux esophagitis can be minimized by appropriate common sense measures, such as complete mastication, more frequent smaller-sized meals, sitting upright during and after eating, avoiding food intake 2 hours before bedtime and raising the head of the bed on blocks to prevent nocturnal reflux. The most dramatic results are achieved with the proton pump inhibitor drugs, which virtually eliminate gastric acidity. Esophageal stricture may require periodic endoscopic dilatation. Successful gastroplasty combined with fundoplication has been reported. Bleeding telangiectases and the ectatic vessels of "watermelon stomach" can be treated with sclerotherapy and laser coagulation, respectively. Transient improvement in steatorrhea and other signs of intestinal malabsorption may follow rotating, 2-week courses of broad-spectrum antibiotics, but the underlying hypomotility is unaffected. Octreotide has been used with variable results. In advanced circumstances, one must resort to parenteral hyperalimentation, which can improve nutrition (increased weight, hematocrit and serum albumin), as well as improve quality of life. In severe malabsorption, the likelihood of septicemia of hyperalimentation catheter origin, serious bacterial infection, and premature death from other causes is high.

Lung
Patients with ILD who have bacterial bronchitis or pneumonitis require prompt and vigorous antibiotic treatment. Prophylactic influenza and Streptococcus pneumoniae vaccinations should be given. There is no treatment that has been definitively proven to alter the course of ILD in SSc. However, there is expectation that early treatment of inflammatory disease will slow the rate of progression of fibrotic disease. Corticosteroids with or without immunosuppressive drugs (particularly cyclophosphamide) may be efficacious short-term therapy. When there is resting or exercise-precipitated hypoxia, supplemental oxygen should be administered. In isolated pulmonary arterial hypertension both intermittent and continuous intravenous use of prostacyclin analog has resulted in improvement during its administration, but recurrence promptly follows discontinuation. The oral nonselective endothelin receptor antagonist, bosentan, has proven short-term efficacy. Other agents may be beneficial, including the inhaled prostacyclin analog iloprost, and the phosphodiesterase inhibitor sildenafil. Right-sided heart failure requires the use of diuretics. Anticoagulation is often prescribed in patients with right-sided failure and venous stasis that may predispose to venous thrombosis. Anticoagulation also should be used

when there are laboratory features of the antiphospholipid antibody syndrome because of the association of this disorder with venous and/or arterial thrombosis and pulmonary hypertension. Heart-lung or single-lung transplantation is an option that is being increasingly considered for patients with end-stage SSc lung disease.

Heart

Symptomatic pericarditis is treated with nonsteroidal anti-inflammatory drugs or corticosteroids. Hemodynamically significant pericardial effusion should be managed with pericardiocentesis or, if recurrent, with an open pericardial window procedure. If myocarditis is identified clinically or by endomyocardial biopsy, high-dose glucocorticoids should be tried. The typical progressive left ventricular failure caused by myocardial fibrosis is unaffected by any therapy and is uniformly fatal, unless some correctable nonsclerodermatous problem is also present. Serious arrhythmias complicate myocardial fibrosis and respond inconsistently to anti-arrhythmic drugs. Congestive heart failure in SSc responds poorly to digitalis and there is increased risk of digitalis toxicity, requiring greater reliance on diuretics. There is no substantial published experience with the use of implantable pacemakers or defibrillators for this condition.

Kidney

The most important aspect of therapy for renal crisis is early detection. A new increase in systolic blood pressure by 30 mm Hg or greater is a harbinger of renal crisis. In the 1970s, the mortality of scleroderma renal crisis was virtually 100% within 1 year. The availability of new and more potent antihypertensive agents and of improved dialysis procedures and care has dramatically increased survival. The angiotensin-converting enzyme (ACE) inhibitors are the drugs of choice and result in adequate con-

Table 13

Treatment of Organ System Involvement: Supporting Measures

Raynaud's phenomenon: Avoiding cold exposure; discontinue smoking; dress warmly (truncal and head warming); calcium channel blockers/other vasodilators; digital sympathectomy
Joints/muscles: Exercise program; NSAIDs; corticosteroids/immunosuppressive drugs for myositis
Gastrointestinal tract: Esophageal reflux: common sense measures; prokinetic drugs; gastric acid-reducing drugs (H2 blockers, proton pump inhibitors); dilatation of strictures Gastric antral bleeding: sclerotherapy/laser Small intestinal hypomotility: prokinetic drugs; rotating antibiotics Malabsorption syndrome: rotating antibiotics; parenteral hyperalimentation Colonic hypomotility/incontinence: increased stool bulk; pessary or surgery
Lung: Prompt treatment of secondary bacterial infections; Pneumovax®; annual flu vaccine; alveolitis: cyclophosphamide with or without corticosteroids; pulmonary hypertension: prostacyclin analogs; anticoagulation; end stage disease: consider lung transplantation
Heart: Pericarditis: NSAIDs or corticosteroids; pericardiocentesis; Pericardial window myocarditis: corticosteroids LV failure: diuretics Arrhythmias: anti-arrhythmic drugs
Kidney: Antihypertensive drugs (especially ACE inhibitors); dialysis (hemo- or peritoneal); for end-stage disease: renal transplantation

trol of blood pressure in up to 90% of patients. Regardless, some individuals require dialysis but many persons maintained on ACE inhibitors can discontinue dialysis after 3 to 24 months. Survival continues to be reduced for patients requiring long-term renal dialysis. Numerous successful renal transplants have now been reported.

4. Sjögren's Syndrome

Definition

Sjögren's syndrome is a chronic autoimmune disease characterized by lymphocytic and plasma cell infiltration of the salivary and lacrimal glands resulting in xerostomia (dry mouth), enlargement of the major salivary glands, and xerophthalmia (dry eyes). The disorder can be limited to these exocrine glands or be a more widespread systemic condition with involvement of the musculoskeletal, pulmonary, gastrointestinal, renal, vascular, dermatologic, and neurologic systems. Sjögren's syndrome may occur alone (primary) or in association with another connective tissue disease (secondary), particularly rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc).

Diagnosis

Several sets of criteria for the diagnosis of primary and secondary Sjögren's syndrome have been proposed by different study groups. One example is the San Diego criteria developed by a consensus of experts (Table 14). These criteria require both ocular and oral symptoms and objective signs, and also give credit for Sjögren's syndrome-related serologic abnormalities, including rheumatoid factor, antinuclear antibody, and anti-SSA (Ro) and anti-SSB (La) antibodies.

The differential diagnosis of Sjögren's syndrome (Table 15) includes infiltrative diseases of the salivary glands, such as sarcoidosis, hyperlipoproteinemias, amyloidosis, and HIV infection. The latter patients may suffer from diffuse infiltrative lymphocytosis syndrome (DILS), an infiltrative process with prominent oral dryness, CD8+ but not CD4 cells in the affected salivary glands and absence of Sjögren's syndrome serologic findings. In addition, the physician must be aware of a variety of conditions that can mimic the ocular and oral symptoms of Sjögren's syndrome, such as age-related sicca findings, medications with anticholinergic properties, and conditions causing glandular infiltration as noted above. Blepharitis, due to blockage or infection of the meibomian glands, can mimic or complicate Sjögren's syndrome. Blepharitis may be caused by excessive use of ocular lubricants or by artificial tears.

Clinical Features

Epidemiology

The prevalence of Sjögren's syndrome in the population has been estimated to be 0.5%-2.7%. The disease occurs worldwide at all ages but is rare in childhood. The most frequent age of onset is 30-50. The female-to-male ratio is 9:1.

Presenting Symptoms

The disease presentation is variable, but most patients complain of dry eyes and/or dry mouth if they are properly questioned. On occasion, a systemic feature will usher in the disease.

Sicca Symptoms

The most common complaint suggesting xerophthalmia is a "gritty" or "sandy" foreign body sensation in the eyes. Other symptoms include burning, pain, sensitivity to bright lights, and mucous accumulation, especially on awakening. Corneal ulceration may occur due to inadequate moisture cover of the cornea. The Schirmer test is a good screening test for reduced tearing; for normal individuals, wet a strip of filter paper inserted into the lower canthus of the eye a minimum of 10 mm in 5 minutes. Additional studies can be performed by an ophthalmologist, including slit lamp examination, rose bengal or fluorescein staining, and tear breakup time.

Table 14

San Diego Criteria for Sjögren's Syndrome

Primary Sjögren's Syndrome
Symptoms and objective signs of ocular dryness
Schirmer's test: less than 8 mm wetting in 5 minutes, and
Rose Bengal test: staining of cornea or conjunctiva demonstrating keratoconjunctivitis sicca
Symptoms and objective signs of dry mouth
Decreased parotid flow rate using Lashley cups or other methods, and
Abnormal findings from biopsy of a minor salivary gland (focus score of 2+ based on average of four evaluable lobules)
Serologic evidence of systemic autoimmunity
Elevated rheumatoid factor >1:320, or
Elevated antinuclear antibody >1:320, or
Presence of anti-SSA (Ro) or anti-SSB (La) antibodies
Secondary Sjögren's Syndrome
Characteristic signs and symptoms of Sjögren's syndrome plus clinical features sufficient to allow a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyositis, scleroderma, or biliary cirrhosis
Exclusions
Sarcoidosis, preexistent lymphoma, human immunodeficiency virus, hepatitis virus B or C, primary fibromyalgia, and other known causes of autonomic neuropathy, keratitis sicca, or salivary gland enlargement
Definite Sjögren's requires IA1 and A2; IB1 and B2; and one of IC 1, 2 or 3
Probable Sjögren's requires IA1 and A2; IB1 and any of IC 1, 2 or 3

Modified from Fox and Saito. Primer on Rheumatic Diseases. *Chapter 22:Table 22-1.*

Table 15

Differential Diagnosis of Sjögren's Syndrome

Infiltrative diseases: Lymphoma, sarcoidosis, amyloidosis, hemochromatosis, fatty infiltration from hyperlipidemic states or alcoholism
Infectious diseases: HIV, HTLV-1/2, hepatitis B and C, mumps, EBV, syphilis, tuberculosis
Neuropathic dysfunction of glands: multiple sclerosis, 7th nerve cranial neuropathies
Autonomic neuropathy
Medications with anticholinergic properties: antihypertensives, antidepressant drugs for peptic ulcer, Parkinson's disease, cardiac arrhythmias, muscle spasm, decongestants
Ocular diseases: Chronic conjunctivitis, blepharitis

Dryness due to reduced saliva flow (xerostomia) causes frequent ingestion of liquids, especially at mealtimes and at night. Patients may complain of difficulty in chewing, propelling foods through the oral cavity, and swallowing. Abnormalities of smell and taste have been reported. On physical examination the parotid glands are enlarged in up to half of patients, but this may be intermittent. Persistent firm asymmetrical enlargement of a parotid gland may indicate a neoplasm. Superimposed bacterial parotitis results in abrupt pain, swelling, erythema, and tenderness of the gland with fever. The tongue and mucous membranes in Sjögren's syndrome are dry, red, and smooth, and the normal visible salivary pool in the sublingual vestibule is absent. Salivary secretion can be quantitated by whole saliva sialometry. The patient sucks a piece of sugarless candy and expectorates into a container for a total of 3 minutes; a volume of less than 10 cc suggests salivary insufficiency. Biopsy of the inner aspect of the lower lip shows collections of lymphocytes infiltrating and surrounding minor salivary glands. Xerostomia may lead to fissures at the corners of the mouth (cheilitis), excessive dental caries, and gingivitis. Dryness of the upper respiratory tract can result in hoarseness, cough, and increased risk of bacterial infections such as sinusitis, bronchitis, and pneumonia. The differential diagnosis of oral and ocular dryness in Sjögren's syndrome is summarized in Table 15. Skin and vaginal dryness are also common complaints.

Extraglandular Manifestations

The extraglandular findings in Sjögren's syndrome are listed in Table 16. Fatigue, which may be profound, is a frequent symptom and patients often report vague changes in cognitive function. In the absence of objective findings, one must consider other causes of fatigue, such as fibromyalgia (nonrestorative sleep pattern), anxiety and/or depression, hypothyroidism, and medication side effects.

Musculoskeletal

Symmetrical polyarthralgias and/or polyarthritis affect the wrists and small joints of the hands in a symmetrical distribution in over half of patients. Joint deformity or bony erosive changes are rare. Myalgias often occur with arthralgias, but proximal muscle weakness due to true polymyositis is uncommon. Fibromyalgia may coexist in patients with Sjögren's syndrome.

Peripheral Vascular

Raynaud's phenomenon is frequent in Sjögren's syndrome but is rarely severe or complicated by digital tip ulceration or gangrene. Some patients have anticentromere antibody without sclerodactyly or telangiectasias.

Lung

The trachea and bronchial tree have abundant mucosal glands that can be affected by lymphocytic infiltration resulting in xerotrachea. Peribronchial lymphocytic infiltration is the most common pathologic finding. Interstitial lung disease with lymphocytic alveolitis and interstitial fibrosis occur in less than 10% of patients. Pulmonary function tests show restrictive abnormalities and decreased diffusion capacity. Pleuritis is rare, as is pulmonary hypertension. When either pulmonary nodules or mediastinal lymphadenopathy is detected, pseudolymphoma or frank lymphoma should be suspected.

Heart
Pericardial effusion has been found in a number of patients, but myocardial involvement is rare.

Gastrointestinal Tract
Dysphagia, nausea, and epigastric pain can be attributable to distal esophageal hypomotility or atrophic gastritis with lymphocytic infiltration. A reduced volume of saliva contributes to dysphagia on a mechanical basis and to heartburn because of reduced acid neutralization. Some Sjögren's syndrome patients have pancreatitis, probably related to lymphocytic infiltration of the pancreatic ducts, but increased serum amylase of pancreatic origin without clinical evidence of pancreatitis is more common. Chronic liver disease, particularly primary biliary cirrhosis, is clearly associated with Sjögren's syndrome. These patients have pruritus, hepatomegaly, elevated serum alkaline phosphatase levels, and serum antimitochondrial antibodies.

Table 16

Common Extraglandular Findings in Sjögren's Syndrome

Skin: dryness, photosensitivity, vasculitis
Musculoskeletal: arthralgias/arthritis, myalgias, myositis
Vasculitis: cutaneous, systemic
Raynaud's phenomenon
Pulmonary: xerotrachea, lymphocytic interstitial pneumonitis
Renal: interstitial nephritis, renal tubular acidosis
Hematologic: anemia, leukopenia, lymphadenopathy, splenomegaly, lymphoma
Neurologic: cranial neuropathy sensory on sensorimotor polyneuropathy, transverse myelitis, multiple sclerosis-like findings
Gastrointestinal: dysphagia, atrophic gastritis, chronic hepatitis
Cardiac: pericardial effusion
Other: primary biliary cirrhosis, autoimmune hypothyroidism

Kidney
Interstitial nephritis is the most frequent renal manifestation, presenting with inability to acidify the urine and hypokalemic, hyperchloremic distal renal tubular acidosis. Lymphocytic infiltration in the renal interstitium is the typical histopathologic finding. Proliferative or membranous glomerulonephritis with hypocomplementemia are infrequent complications and may be seen with coexistent cryoglobulinemia. Chronic renal insufficiency is rare.

Vasculitis
Some patients have palpable purpura that, on skin biopsy, is due to vasculitis of small vessels, either of the neutrophilic/leukocytoclastic type or lymphocytic type. Vasculitis can also affect other organs, including the central nervous system (CNS), lungs, and kidneys. Neutrophilic vasculitis is more frequently associated with serum anti-SSA and anti-SSB antibodies, serum rheumatoid factor, and hypocomplementemia.

Neurologic
Neurologic findings are highly varied and include peripheral sensory and/or motor neuropathy, trigeminal, facial, auditory or other cranial neuropathy, autonomic neuropathy, myelopathy, and CNS involvement. Sensory or sensorimotor abnormalities often accompany cutaneous vasculitis. Objective abnormalities may be found on electroencephalogram (EEG), magnetic resonance imaging (MRI), or neuropsychometric testing. A demyelinating or thrombotic multiple sclerosis-like syndrome has been described with CSF and MRI findings identical to those typically found in MS.

Thyroid
Autoimmune hypothyroidism of the Hashimoto's type may occur with increased frequency in patients with Sjögren's syndrome.

Laboratory Abnormalities

The most common laboratory abnormalities found in Sjögren's syndrome are listed in Table 17. Routine blood counts are usually normal, although leukopenia is not infrequent. The routine urinalysis is normal but may show mild proteinuria. If renal tubular acidosis is present, there may be a high urine pH, hypokalemic and hyperchloremic acidosis in the peripheral blood, and sometimes mildly increased serum creatinine.

The 2 autoimmune phenomena characteristic of primary Sjögren's syndrome are polyclonal B-cell activation and oligoclonal B-cell expansion. Most patients have hypergammaglobulinemia. Included are specific autoantibodies, including those directed against nuclear antigens (ANAs), against the cellular antigens SSA/Ro and SSB (La), and against immunoglobulins (rheumatoid factor, cryoglobulins). Anti-SSA and anti-SSB are found most frequently in patients with Sjögren's syndrome compared with other connective tissue diseases, but in typical large series do not exceed 50%.

Table 17

Laboratory Abnormalities in Sjögren's Syndrome

Increased ESR
Leukopenia
Polyclonal hypergammaglobulinemia
Rheumatoid factor
Antinuclear antibodies
Anti-SSA (Ro) and/or anti-SSB (La) antibodies
Hypokalemic, hyperchloremic acidosis
Proteinuria
Pulmonary fibrosis
Cryoglobulinemia
Anemia of chronic disease

Natural History, Prognosis, and Treatment

Lymphoproliferative Disease

Patients with Sjögren's syndrome have a dramatically increased risk, up to 44 times that of a normal population, of developing non-Hodgkin's lymphoma (NHL) at some time during their life. Clues are the new occurrence of lymphadenopathy or splenomegaly and the disappearance of serum rheumatoid factor. Lymphomas may affect the salivary glands or the major internal organs. Mucosa-associated lymphoproliferative disease (MALT lymphoma) has been described. The vast majorities of lymphomas are of B-cell origin and tend to be of 2 types: highly undifferentiated B-cells or well-differentiated immunocytes. Their grading is variable, requiring an individualized therapeutic approach. In some individuals an intermediate picture of disseminated lymphocytic infiltration occurs without immunohistologic confirmation of malignancy. In this circumstance, the term "pseudolymphoma" is used. These patients may have a beneficial response to corticosteroids and/or immunosuppressive agents or progress to frank malignant lymphoma. Monoclonal paraproteinemia and cryoglobulinemia are serological features that should raise suspicion of the development or presence of NHL.

Treatment

Xerophthalmia is treated symptomatically with artificial tears and common sense measures such as avoiding low-humidity conditions. Punctal occlusion (with temporary plugs) may be attempted and, if successful, permanent punctal obliteration by electrocautery may be helpful. Medications that reduce lacrimal flow should be avoided if possible, including diuretics and certain antidepressant and antihypertensive agents (Table 15). Treatment of xerostomia may involve carrying drinking water throughout the day and using sugarless lemon drops to stimulate salivary flow. Rigorous oral hygiene is required to prevent dental caries, and topical fluoride treatments may retard dental demineralization. Muscarinic agonists such as pilocarpine have proved beneficial to many patients.

Secondary fungal infection (oral candidiasis) is common in Sjögren's syndrome, especially in patients taking corticosteroids and/or multiple courses of antibiotics. Diffuse erythema of the oral mucosa and angular cheilitis may be the only physical examination findings. Antifungal drugs with little or no glucose (the latter contributes to dental caries) should be used. Antifungal vaginal suppositories which dissolve or oral troches are commonly prescribed. Dentures need to be disinfected as they may be the source of reinfection.

Nonsteroidal anti-inflammatory drugs are the first choice in treating polyarthralgias. Hydroxychloroquine is often useful for fatigue and polyarthritis and may also improve the hemoglobin and ESR levels and reduce hypergammaglobulinemia. Corticosteroids and/or other immunosuppressive drugs are necessary to treat severe extraglandular involvement, such as pulmonary or renal disease, neurologic complications, or systemic vasculitis. Cyclophosphamide should be reserved for vasculitis and pseudolymphoma, but the best strategy would be to use intermittent intravenous rather than daily oral cyclophosphamide because the former carries a lower risk of subsequent lymphoma.

Surgery poses problems for Sjögren's syndrome patients, including increased risk of corneal abrasion due to anesthetics, which decrease the blink reflex and nonhumidified oxygen leaking around a facemask. Tooth damage during intubation and postoperative mucus plug inspissation/atelectasis are other complications that may occur.

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