

TITLE: Connective Tissue Diseases

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Introduction

The connective tissue diseases have a pattern of organ involvement that overlaps and often makes specific diagnosis difficult. When first recognized as a distinct histopathologic characteristic, the perivascular collagen deposition prompted the name collagen vascular disease. Their association with immunologic reactions to body proteins subsequently caused the name change to autoimmune diseases. These entities are, however, more correctly called connective tissue diseases. Biochemical and ultrastructure studies indicate that collagen derangement and evidence of autoimmunity may not be the primary disease.

The exact cause of connective tissue diseases remains obscure. Specific autoantibodies are associated with some of these entities, supporting the presumption of an autoimmune mechanism. Definite evidence demonstrating loss of self-tolerance or specific antigens is lacking.

The prevailing histopathologic feature of these diseases is a varying amount of connective tissue and blood vessel inflammation with abundant fibrinoid deposits. It is the tissue distribution of the inflammatory response and the pattern of organ involvement that differentiate one connective tissue disease from another. The clinical patterns resulting from this unique tissue response give the members of this family of diseases their individual names. These diseases are difficult to diagnose because many of their symptoms are nonspecific and the signs and symptoms tend to overlap.

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus is a common multisystem connective tissue disease. The systemic manifestations include myocarditis, nephritis, serositis, photosensitive skin eruptions, pneumonitis, and central nervous system (CNS) involvement. Diagnostic criteria are listed below:

The incidence is 1 in 1000 and has a 9:1 female to male prevalence and affects most

commonly females of child bearing age. The survival rate of SLE is 80% at 10 years and 65% at 20 years.

Head and neck manifestations of SLE are primarily skin and mucosal lesions. An erythematous, often pruritic, maculopapular eruption may be found following sun exposure. A malar or “butterfly” rash is the presenting sign in 50% of patients. Painful oral ulcerations with bleeding may be present which possess localized telangiectasis producing a red halo effect around effected mucosa. Secondary moniliasis and xerostomia are frequently experienced. Up to 25% of SLE patients experience dysphagia. Acute enlargement of the parotid gland occurs in 10% of SLE patients and may be unilateral, tender and confused with acute parotitis. Cranial neuropathy exists in 15% of patients and may involve the motor supply to the extra ocular muscles, the sensory divisions of the trigeminal nerve, the motor divisions of the facial nerve, the vestibular portion of the vestibulocochlear, or the optic nerve. In 3-5% of well-established cases, there is ulceration or perforation of the nasal septum. Involvement of the larynx and trachea is rare, but may include true vocal fold thickening or paralysis, cricoarytenoid arthritis, and subglottic stenosis. Sudden sensory neural hearing loss has been described with SLE, but a definitive link has not been established.

Discoid lupus is a subtype of SLE that involves primarily cutaneous lesions that result in significant scarring, but no visceral involvement. The lesions are well-demarcated, erythematous papules that depigment and scar on resolution. The face is involved 85% of the time while the scalp and ear are involved 60% and 44% respectively.

Treatment of patients with SLE should involve a rheumatologist. Avoidance of sun exposure and the use of sunscreens are recommended. Non-steroidal anti-inflammatory drugs, topical and low dose systemic steroids as well as antimalarials are generally recommended. Low-dose methotrexate may be an alternative to systemic steroids. Azothioprine, cyclophosphamide and high dose systemic steroids are restricted to cases with serious visceral involvement. Symptomatic treatment includes saliva substitutes, mouthwashes such as Klack’s solution (tetracycline, cortisone, benadryl, and nystatin), and postprandial rinses of 1:1 mixture of H₂O₂:H₂O.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammation of synovial tissue with symmetric involvement of peripheral joints, hand, feet, and wrists being most commonly affected. RA can also affect nonarticular muscular structures such as tendons, ligaments, and fascia. Occasionally, there are also systemic manifestations such as vasculitis, visceral nodules, Sjogren syndrome, or pulmonary fibrosis present. Pathogenesis results from lymphocytic infiltration and synovial proliferation. Laboratory tests for RA include RA associated nuclear antigen (RANA) and anti-RA-33 autoantibodies. Diagnostic criteria are listed below:

1. Morning stiffness (>1h)
2. Swelling of three or more joints
3. Swelling of hand joints (prox interphalangeal, metacarpophalyngeal, or wrist)
4. Symmetric joint swelling
5. Subcutaneous nodules

6. Serum Rheumatoid Factor

7. Radiographic evidence of erosions or periarticular osteopenia in hand or wrists

Criteria 1-4 must have been present continuously for 6 weeks or longer and must be observed by a physician. A diagnosis of rheumatoid arthritis requires that 4 of the 7 criteria are fulfilled.

RA occurs in 1% of the population, affecting women 2-3 times more often than men. The most common age of onset is in the 4th to 5th decade, but there exists a distinct juvenile form as well.

Head and neck manifestations of RA include articular involvement of the ossicles, the temporomandibular joint (TMJ), the cricoarytenoid joints and the cervical spine. TMJ involvement is common and 55% of patients have symptoms of TMJ involvement and up to 70% of patients display radiographic evidence of joint erosion. Symptoms include pain or tenderness at the joint or in the muscles of mastication, crepitus, limited mobility or deviation. Contractures of the muscles of mastication may result in an open bite deformity. Juvenile RA may lead to micrognathia. RA is the most common cause of arthritis in the cricoarytenoid joint. 30% of patients are hoarse and 86% show pathologic involvement of the joint. Exertional dyspnea, otalgia, and globus sensation may all be attributed to cricoarytenoid joint involvement. Hoarseness may also be caused by rheumatoid nodules within the vocal cords and ischemic recurrent nerve paresis or paralysis. Sudden onset stridor in RA patients requires systemic steroids and possible tracheotomy. The middle ear may be involved in severe cases of RA if synovitis develops in the ossicular joints, but rarely results in a conductive hearing loss except during an acute RA exacerbation. The tympanic membrane may lose its stiffness as seen in tympanometry. RA of the cervical spine may lead to subluxation.

Treatment of RA includes physical therapy, daily exercise, splinting and joint protection. Salicylates, nonsteroidal anti-inflammatory agents, gold salts, penicillamine, hydroxychloroquine and immunosuppressive agents have been traditionally used to treat RA. In recent years, Cyclosporin-A has been used successfully to treat RA. Prognosis at 10-15 years of disease includes 50% of patients are fully employed, 10% are completely incapacitated, and 10-20% experience a complete remission.

Sjogren's Syndrome

Sjogren syndrome is a chronic disorder characterized by immune-mediated destruction of exocrine glands. Sjogren syndrome occurs in primary and secondary forms. The primary form is a diagnosis of exclusion, an isolated disorder of the lacrimal and salivary glands. The secondary form refers to the sicca complex accompanying any of the connective tissue diseases. Sjogren syndrome occurs in 1% of the population and in 10-15% of RA patients. There is a 9:1 female: male preponderance with the average age of onset at 40-60 years of age. Sjogren syndrome is associated with a 33-44 times increased risk of lymphoma. Clinical manifestations include xerophthalmia and secondary keratoconjunctivitis, xerostomia with or without salivary gland enlargement. These manifestations are known as the sicca complex. Sjogren syndrome can also affect the skin, vagina, external genitalia, chronic bronchitis, GI tract, and the renal tubules. Minor salivary gland biopsy demonstrates heavy lymphocytic infiltration, although parotid biopsy may be more sensitive and specific. Rheumatoid factor and anti-nuclear

antibodies are elevated in most patients. Sjogren syndrome A (Ro/SS-A) and Sjogren syndrome B (La/SS-B) are noted in 60% and 30% of patients respectively. Diagnostic criteria are listed below:

Diagnostic criteria ^a	Percent/incidence
Malar rash	64
Discoid rash	17
Photosensitivity	37
Oral ulcers	15
Arthritis	90
Proteinuria (0.5 g/dL) or cellular casts	20
Seizures or psychosis	19
Pleuritis or pericarditis	19
Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia	11–40
Antibody to DNA or Sm antigen, + LE prep, or false +RPR	15–60
Positive fluorescent antinuclear antibody ^b	95

^aThe diagnosis of SLE requires the presence of four of the 11 criteria (96% sensitivity, 96% specificity).

^bIncreased antibodies to double-stranded DNA are pathognomonic.

Head and neck manifestations are predominantly due to exocrine gland dysfunction, with 80% of patients complaining of xerostomia as their most prominent symptom. Other symptoms include difficulty chewing, dysphagia, changes in taste, fissures of the tongue and lips, increased dental caries, and oral candidiasis. Decreased secretion of tears may lead to keratoconjunctivitis sicca and ocular complaints of dryness, itching and foreign body sensation of the eyes. Often the patient will give a history of recurrent salivary gland enlargement, either bilateral or unilateral. Loss of nasal gland secretions leads to nasal crusting, epistaxis, and hyposmia.

Treatment of Sjogren syndrome includes symptomatic relief with the use of increased oral intake, saliva substitutes, pilocarpine and artificial tears. Decongestants, antihistamines, diuretics, and other drugs with anticholinergic side effects should be avoided. Oral candidiasis is treated with antifungal. Close dental follow up is essential as is surveillance for any developing

malignancy.

Scleroderma (Systemic Sclerosis)

Scleroderma, also known as systemic sclerosis, is characterized by sclerotic skin changes that are often accompanied by multisystem disease. Progressive fibrosis, resulting from increased deposition of collagen in the interstitium and intima of small arteries and connective tissue of involved organs is the pathologic hallmark of the disease. Scleroderma may be limited to relatively benign cutaneous involvement (extremities distal to the elbows and knees and the face and neck) or may exist as an aggressive systemic disease. There are 4-12 new cases per million per year, with a 3-4:1 female preponderance. The average age of onset is between the 3rd and 5th decade. Men have a worse prognosis than women and black women a worse prognosis than white. Initial presentation includes Raynaud's phenomenon, edema of the fingers and hands and skin thickening. The American College of Rheumatology criteria for scleroderma include one major criterion (scleromatous skin changes proximal to the metacarpal-phalangeal joints) and two of three minor criteria: sclerodactyly, digital pitting scars, and bibasilar pulmonary fibrosis on chest radiograph. Visceral manifestations are seen in the GI tract, lung, heart, kidneys and thyroid. Arthralgias and muscle weakness are common complaints.

80% of patients with systemic sclerosis have signs and symptoms involving the head and neck, and in 30% of these patients the head and neck symptoms were part of the presenting complaints. Facial features include tight skin, thin lips and vertical perioral furrows. These skin changes are secondary to the underlying dermal and subcutaneous inflammatory process. Edema precedes epidermal atrophy and loss of appendages. Eventually 35% of patients will develop facial tightness, with an initial complaint of an inability to open their mouth in 19%. Additional skin changes include telangiectasis, calcinosis, and linear scleroderma involving the cheeks and chin. Dysphagia is the most common initial complaint with 80% of patients demonstrating pathology of the distal 2/3 of the esophagus. Half of these patients are symptomatic. Decreased or absent peristalsis with mild to moderate dilation is prevalent and hiatal hernia is common. Gingivitis and periodontal thickening are common, and the finding of a translucent zone around the dental roots is considered pathognomonic by some. 25% of patients report xerostomia, xerophthalmia or both. Laryngeal involvement occurs and approximately 50% of patients complain of hoarseness. Raynaud's of the tongue is an infrequent finding that presents with blanching and dysarthria. Trigeminal neuralgia and facial nerve palsy are also infrequent findings.

Treatment for scleroderma is symptomatic. Proton pump inhibitors are recommended for reflux esophagitis and calcium channel blockers are used for Raynaud's. Angiotensin converting enzyme inhibitors are useful in treating renal disease. NSAIDs and low dose steroids may relieve arthralgias and myalgias and patients may benefit from hand rehabilitation exercises.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are subsets of the inflammatory myopathies, a group of disorders characterized by proximal muscle weakness and nonsuppurative inflammation of skeletal muscle. There are 5 cases per million per year, with a 2:1 female prevalence. The average age of onset is from 40-60 years of age, and pediatric variant affects patients 5-15 years

old. Diagnostic criteria include proximal muscle weakness, elevated serum creatinine kinase, myopathic changes on electromyography, and muscle biopsy with evidence of a lymphocytic inflammation. Diagnosis is definitive with all four criteria, probable with three, and possible with two. For a diagnosis of dermatomyositis, a characteristic skin rash must be present with the above criteria. Anti-tRNA synthetase antibodies are often present. Polymyositis may be associated with other connective tissue diseases such as SLE, RA and systemic sclerosis. Up to 20% are associated with a malignancy, particularly of the lung, ovary, breast, prostate, colon, and stomach being the most common. Association with parotid and tonsil malignancy has been reported. An increased incidence of nasopharyngeal carcinoma has been reported in patients with dermatomyositis living in an endemic area for this neoplasm.

Head and neck involvement reflect proximal muscle involvement. Patients present with weakness of the neck muscles. Difficulty with phonation and deglutition suggest involvement of the tongue musculature. Nasal regurgitation is common because of involvement of pharyngeal and palatal muscles. 30% of patients experience dysphagia secondary to involvement of the upper esophagus, cricopharyngeus, pharynx and superior constrictors. Dysfunction of these muscles may lead to aspiration and pneumonia. Skin and mucous membrane involvement vary, but have a predilection for sun-exposed areas.

Treatment includes steroids for symptomatic patients while methotrexate and other immunosuppressive agents are reserved for non-responders. Metoclopramide and proton pump inhibitors are used for the treatment of esophageal involvement.

Relapsing Polychondritis

Relapsing polychondritis is characterized by episodic recurring inflammation of cartilaginous structures that are eventually replaced by granulation tissue and fibrosis. Women are 3 times more likely to be affected than men and the age of onset is 35-45 years. There appears to be a racial predilection for whites. Defined features of the disease include recurrent chondritis of the auricles, nonerosive inflammatory polyarthritis, chondritis of the nasal cartilages, ocular inflammation, chondritis of laryngeal or tracheal cartilage, and cochlear or vestibular damage. Diagnosis requires three of these features in the absence of histologic confirmation, two of these features with response to steroids or dapsone, or any one of these features with histologic confirmation. Auricular chondritis and nonerosive arthritis are the most common presenting symptoms. Auricular chondritis is characterized by sudden onset erythema, pain, sparing the lobule as it lacks cartilage. Resolution occurs in 5-10 days with or without treatment. Patients may have concomitant serous otitis or SNHL. Nasal chondritis develops in 75% of patients and does not always coincide with auricular symptoms. Nasal and auricular chondritis act similarly in that they both result in deformity and dysfunction. Laryngeal involvement presents as a non productive cough and progresses to hoarseness and stridor. 53% of all patients will have airway involvement. In most cases, steroids are the main form of treatment, although dapsone and methotrexate have shown to be of clinical benefit.

Mixed Connective Tissue Disease

Mixed connective tissue disease describes a distinct entity with coexisting features of SLE, scleroderma, and polymyositis. Patients are found to have high titers of anti-U1RNP, a

ribonucleoprotein antibody. The disease prevalence is unknown, but 80% are female and the age of onset is 30-60 years. Head and neck manifestations are a combination of the features seen in other connective tissue diseases. Mucocutaneous changes include malar rash, discoid lupus, sclerodermatous skin thickening, oral mucosal ulceration, and nasal septal perforation. Sicca complex has also been described. Esophageal dysfunction is common also. Corticosteroids and immunosuppression are the mainstays of treatment.

Vasculitides

The vasculitides are a group of diseases characterized by non infectious necrotizing vasculitis and resultant ischemia.

Polyarteritis Nodosa

Polyarteritis nodosa has been considered the prototype of vasculitides. It occurs less than 1 in 100000 per year. Males and females are equally affected. Age of onset is 50-60 years of age. Polyarteritis nodosa involves the small and medium-sized arteries and can be the result of Hepatitis B infection. 30% of patients are Hep B positive. The tissues affected include the GI tract, the hepatobiliary system, kidney, pancreas, and skeletal muscles. Patients usually present with non specific multisystem complaints such as malaise, weight loss, anorexia and fever. Polyarteritis nodosa can lead to progressive arthritis, myopathy, neuropathy, hepatic and renal failure and GI bleeding. There are few head and neck manifestations and they primarily involve the ear. These include sudden bilateral SNHL or vestibular disturbance. The proposed mechanism is thromboembolic occlusion of inner ear arteries. Other head and neck manifestations include cranial nerve palsies, with cranial nerve vii being the most commonly involved.

Churg-Strauss Syndrome

Churg-Strauss syndrome, also called allergic angiitis granulomatosis, is a disease consisting of systemic small-vessel vasculitis, extravascular granulomas and hypereosinophilia. It occurs in patient with preexisting asthma and allergic rhinitis. The vasculitis generally presents with peripheral neuropathy or pulmonary infiltrates. Tissue eosinophilia is another feature of this disease.

Hypersensitivity Vasculitides

The hypersensitivity vasculitides are a heterogenous group of small-vessel vasculitides that universally involve the skin, arteritic involvement of small vessels (ie post capillary venules) and leukocytoclasia. Diseases in this group include hypersensitivity angiitis, Henoch-Schonlein purpura, and cryoglobulinemia vasculitis. These syndromes appear immune complex mediated and may be triggered by a foreign antigen, which is often not identified. Therapy is directed on identification and elimination of inciting antigens. Glucocorticoids, immunosuppressive agents and plasmapheresis are commonly used treatments.

Wegener Granulomatosis

Wegener granulomatosis is a necrotizing granulomatous vasculitis of the upper airway,

lower airway, and kidney. Patients display bilateral pneumonitis (95%), chronic sinusitis (90%), mucosal ulceration of the nasopharynx (75%) and evidence of renal disease (80%). The hallmark pathologic lesion is necrotizing granulomatous vasculitis. Antineutrophil cytoplasmic antibody (c-ANCA) is present and the sensitivity ranges from 65-90%, with a high specificity though patients with polyarteritis nodosa and Kawasaki disease may also test positive. A tissue diagnosis must be made to confirm Wegener granulomatosis. This entity carries an untreated mortality rate of 90% at two years. Head and neck manifestations include nasal symptoms of crusting, epistaxis, rhinorrhea, erosion of septal cartilage, saddle nose deformity and most commonly recurrent sinusitis. Oral cavity manifestations include hyperplasia of gingiva and gingivitis. Upper airway findings include edema, ulceration of the larynx (25%) and significant subglottic stenosis (8.5%). Otologic symptoms include serous otitis media, CHL, suppurative otitis media possibly with granulation tissue, SNHL and pinna changes similar to those found in polycondritis. Treatment consists of meticulous dental and nasal care, removal of crusts from the nose and Eustachian tube orifices and middle ear drainage. Cyclophosphamide and prednisone achieve remission in 93% of patients. Azathioprine or methotrexate are alternatives to cyclophosphamide. For isolated sinus disease, treatment includes low dose steroids, topical steroids, saline irrigations and antibiotics as needed. Airway compromise is alleviated with systemic steroids and subglottic stenosis may warrant tracheotomy.

Giant Cell Arteritis (Temporal Arteritis)

Temporal arteritis is a form of giant cell arteritis with only extracranial vessels affected. It consists of focal granulomatous inflammation of medium and small arteries and is the most common vasculitis. The prevalence increases with age to 850/100,000 at age 80 and older. The symptoms of temporal arteritis reflect cranial blood supply. Headache (constant, boring) is the most common initial complaint (47%), and up to 90% will develop headaches with temporal arteritis. In giant cell arteritis, the ESR is usually greater than 50mm/hr. Confirmation of temporal arteritis is from temporal artery biopsy of the affected side. If negative, biopsy of contralateral side is warranted. It is prudent to keep in mind that the arteritis may occur in skip lesions in the temporal artery, thereby necessitating a 5-7cm length of artery at biopsy. Temporal artery biopsy has a false negative rate of anywhere from 5-40%. Head and neck manifestations include a tender and erythematous temporal artery (50%) and a tender scalp. Jaw ischemia (50%) and lingual ischemia (25%) are frequent oral symptoms observed. Otologic manifestations include vertigo and hearing loss. Ascending pharyngeal artery involvement may lead to dysphagia. Cranial nerve deficits, vertebrobasilar insufficiency and psychosis reflect intracranial disease. Blindness occurs in 1/3 of untreated patients. Treatment is long-term and consists of prednisone and normalization of ESR.

Polymyalgia Rheumatica

Polymyalgia rheumatica is an accompanying syndrome in 50% of patients with giant cell arteritis. It is a clinical syndrome of muscular pain, morning stiffness of proximal muscles, increased ESR without inflammatory joint or muscle disease. Systemic symptoms include low-grade fever, weight loss, and malaise. If it occurs by itself, it will respond to low-dose prednisone but will require high-dose prednisone if it occurs with giant cell arteritis.

Behcet's Disease

Behcet's disease is a triad of oral and genital ulcers and uveitis or iritis. The oral ulcers are aphthous-like ulcers with a "punched out" appearance with or without surrounding erythema, covered with a pale pseudomembrane. The lesions are painful; occur in clusters on the lips, gingival, buccal mucosa, and tongue and occasionally on the palate and oropharynx. The genital ulcers are similar in appearance to the oral lesions. The ulcers heal in days to weeks with some scarring. Other associated findings include progressive sensory neural hearing loss, tinnitus, and vertigo. Patients may experience ulceration of nasal, laryngeal, or tracheal mucosa. Morbidity is from CNS involvement, bowel dysfunction and large vessel arteritis. Treatments of azathioprine or methotrexate may be beneficial.

Cogan's Syndrome

Cogan's syndrome is a rare disease of young adults in which vestibuloauditory dysfunction, interstitial keratitis, and a non reactive syphilis test present following a URI. Vestibuloauditory symptoms are usually bilateral and can include hearing loss, vertigo, tinnitus, and aural pressure as seen in Meniere's. Ocular symptoms include photophobia, lacrimation, and eye pain. Cogan's may resolve spontaneously and reappear months later. When advanced, hearing loss is progressive and severe with decreased or absent vestibular responses on caloric testing. Evidence exists that hearing loss may be avoided if treated with steroids within 2 weeks of onset.

Kawasaki Disease

Kawasaki disease is also known as mucocutaneous lymph node syndrome and is a disease of the pediatric population. Symptoms include fever, conjunctivitis, red dry lips, erythema of the oral mucosa, polymorphous truncal rash, desquamation of the fingers and toes, and cervical lymphadenopathy. Oral cavity erythema and cervical adenopathy are often the presenting symptoms. Cardiac anomalies may result in a 1-2% mortality rate.

Conclusion

Connective tissue diseases result from immunologic or autoimmune reactions. The prevailing histologic feature of these diseases is inflammation of blood vessels and connective tissues with associated fibrinoid deposits. The tissue distribution of the inflammatory response, the pattern of organ involvement, and the presence of specific autoantibodies are the factors that differentiate one connective tissue disease from another.

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