AUTOIMMUNE DISEASES

The term autoimmune disease refers to a disorder in which there is evidence of an immune response against self, caused by the body producing an immune response against its own tissues (self-antigen), which mean the loss of tolerance to selfantigen. It may be primarily due to either antibodies (autoantibodies) or immune cells, but a common characteristic is the presence of a lymphocytic infiltration in the target organ. Normally, the immune system recognizes the tissues in the body are not "foreign" also called self-antigen and does not attack them; this is what's called tolerance (the normal status of immunologic non responsiveness to self-antigen).

Autoantibodies

In some autoimmune diseases, B cells mistakenly make antibodies against tissues of the body (self-antigens) instead of foreign antigens.These autoantibodies either interfere with the normal function of the tissues or initiate destruction of the tissues. (e.g.) People with myasthenia gravis experience muscle weakness because autoantibodies attack a part of the nerve that stimulates muscle movement.

Typical features of autoimmune disease:-

- Significantly more common in women.
- Onset often in middle age.
- Family history frequently positive.
- Levels of immunoglobins (autoantibodies) usually raised.
- Circulating autoantibodies frequently also detectable in un affected family members.
- Often an increased risk of developing other autoimmune diseases.
- Immunoglobuline and/or complement often detectable at sites of tissue damage (e.g. pemphigus vulgaris).
- Immunosuppressive treatment frequently limits tissue damage.

Autoimmune disorders fall into two general types:

1-Those that damage many organs (systemic autoimmune diseases)
2- Those where only a single organ or tissue is directly damaged by the autoimmune process (localized). However, the distinctions become blurred as the effect of localized autoimmune disorders frequently extends beyond the targeted tissues, indirectly affecting other body organs and systems.

Some of the most common types of autoimmune disorders include:

Systemic Autoimmune Diseases

- Rheumatoid arthritis (RA) and Juvenile RA (JRA) (joints; less commonly lung, skin)
- Lupus [Systemic Lupus Erythematosus] (skin, joints, kidneys, heart, brain, red blood cells, other)

• Scleroderma (skin, intestine, less commonly lung)
• Sjogren's syndrome (salivary glands, tear glands, joints)
• Goodpasture's syndrome (lungs, kidneys)
• Wegener's granulomatosis (blood vessels, sinuses, lungs, kidneys)
• Polymyalgia Rheumatica (large muscle groups)
• Guillain-Barre syndrome (nervous system)

Localized Autoimmune Diseases
• Type 1 Diabetes Mellitus (pancreas islets)
• Hashimoto's thyroiditis, Graves' disease (thyroid)
• Celiac disease, Crohn's disease, Ulcerative colitis (GI tract)
• Multiple sclerosis , Addison's disease (adrenal)
• Primary biliary cirrhosis, Autoimmune hepatitis (liver)
• Temporal Arteritis / Giant Cell Arteritis (arteries of the head and neck)

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Systemic Lupus Erythematosus
Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease characterized by the production of numerous autoantibodies. Organ injury is secondary to either the direct binding of autoantibodies to self-antigens or the deposition of immunocomplexes in vessels or tissues. In addition to systemic and isolated cutaneous lupus (chronic discoid lupus), a distinct syndrome of drug-induced lupus is recognized. Unlike SLE, drug-induced lupus rarely affects the kidney and is reversible on discontinuation of the offending agent.

Clinical Manifestations
Skin is affected in up to 85% of SLE patients. In addition, cutaneous lupus can occur without multisystem involvement. Skin lesions of lupus can be classified into l**upus-specific** (having diagnostic clinical or histopathological features) and **nonspecific lesions**.
Three subtypes of **lupus-specific skin lesions** have been described: **acute, subacute, and chronic.**
Acute cutaneous lupus : represented by the butterfly rash—mask-shaped erythematous eruptions involving the malar areas and bridge of the nose. Bullous lupus and localized erythematous papules also belong to the acute lupus category.
Chronic cutaneous lupus affects the skin of the face or scalp in about 80% of cases .
The least common subtype, **subacute cutaneous lupus**, includes papulosquamous (psoriasiform) and annular-polycyclic eruptions usually on the trunk and arms.
Nonspecific but suggestive skin manifestations of lupus are common and include alopecia , photosensitivity, Raynaud’s phenomenon, livedo reticularis, urticaria, erythema, telangiectases, and cutaneous vasculitis.

ETIOLOGY

The specific etiology of SLE is not known with certainty, but immunocomplexes, autoantibodies, and genetic, infectious, environmental, and endocrine factors play significant roles.

Renal Manifestations. Kidney involvement occurs in up to 50%–60% of patients with SLE and is a primary cause of morbidity and mortality in this population Clinically, renal disease in SLE can range anywhere from asymptomatic proteinuria to rapidly progressive glomerulonephritis with renal failure.

Musculoskeletal : Musculoskeletal manifestations occur in about 95% of patients with SLE, and arthralgia is the first presenting symptom in about 50% of cases. Nonersive symmetric arthritis most commonly affecting hands, wrists, and knees is typical of SLE.

Central Nervous System :occurs in about 20% of patients with SLE and is usually due to cerebral vasculitis or direct neuronal damage. CNS manifestations include psychosis, stroke, seizures and transverse myelitis and are associated with poor overall prognosis.

Cardiovascular Cardiovascular involvement in SLE is classically manifested by vasculitis and pericarditis.

Other Manifestations

Fatigue, depression, and fibromyalgia-like symptoms are commonly present and can be debilitating.

Oral Manifestations

The oral mucosa is affected in a significant percentage of lupus patients, with the predominant types of oral lesions being **ulcerations, erythematous lesions, and discoid lesions**. These ulcerations cannot be easily distinguished from other common oral conditions, such as aphthous ulcers, although they occur with increased frequency on the palate and in the oropharynx and are characteristically painless.

Discoid oral lesions are similar to those occurring on the skin and appear as whitish striae frequently radiating from the central erythematous area, giving a so-called *brush border*. Atrophy and telangiectases are also frequently present. Buccal mucosa, gingiva, and labial mucosa are the most commonly affected intraoral sites. **Isolated erythematous** areas are also common, especially on the palate.

Laboratory Findings

Anemia, leukopenia, and thrombocytopenia are among the most common manifestations of SLE. Elevation of erythrocyte sedimentation rate with normal C-reactive protein levels is characteristic of SLE.

Diagnosis

Diagnosis of SLE is based on the compatible symptoms and signs in the presence of suggestive laboratory abnormalities. Diagnostic criteria include:

1. Acute cutaneous lupus (e.g., malar rash or photosensitivity and other)

2. Chronic cutaneous lupus (e.g., classic discoid lupus and other)
3. Oral ulcers or nasal ulcers
4. Nonscarring alopecia
5. Synovitis involving 2 or more joints, characterized by swelling or effusion
OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis
7. Renal :Urine protein greater than or equal to 500 mg protein/24 hours
OR red blood cell casts
8. Neurologic disease (Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confused state).
9. Hemolytic anemia
10. Leukopenia (<4000/mm3 at least once)
OR Lymphopenia (<1000/mm3 at least once)
11. Thrombocytopenia (<100,000/mm3) at least once
Immunologic criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity
5. Low complement
Low C3
Low C4
Low CH50
6. Direct Coombs' test in the absence of hemolytic anemia

The proposed classification rule is as follows: classify a patient as having SLE if 4 of the clinical and immunologic criteria are satisfied, including at least one clinical and one immunologic criterions, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANAs) or anti-double-stranded DNA (dsDNA) antibodies.

Discoid lupus erythematosus

- DLE is essentially a skin disease with mucocutaneous lesions indistinguishable clinically from those of systemic lupus.
- Significant autoantibody production is present.
- It occurs predominantly in females in the third or fourth decade of life.
- Typical cutaneous lesion appear as red patches in sun-exposed area, such as face, extremities, these lesions expand by peripheral extension and are usually disk-shaped.

Signs

Discoid lupus erythematosus well-defined red plaques with an adherent scale and follicular plugging which may result in scarring and post-inflammatory hyperpigmentation

TREATMENT

The oral ulcerations of SLE are transient, occurring with acute lupus flares. Symptomatic lesions can be treated with high-potency topical corticosteroids or intralesional steroid injections.

Dental Management

The dental management of the lupus patient should take into account the complex pathologic manifestations of the disease, including oral aspects and complications of immunosuppressive treatment.

Risk of Infection

Daily treatment with higher doses of prednisone (over 7.5– 10 mg/day) or other glucocorticoids, treatment with high doses of cyclophosphamide, and high disease activity are risk factors for infection in SLE patients. Impaired immune function that is part of this disease is also felt to contribute to their increased susceptibility to infection.

A baseline complete blood count should be obtained before dental treatment of SLE patients, as leukopenia, neutropenia, and/ or thrombocytopenia can occur. If possible, elective oral surgical procedures with the potential for bacteremia should be delayed until the absolute neutrophil count is over 1000 cells/mm3, as neutropenia may be transient and respond to treatment with glucocorticoids.

Risk of Bleeding

Traditionally, platelet transfusions have been recommended in surgical patients with platelet counts below 50,000 per mm3.

Adrenal Suppression/Secondary Adrenal Insufficiency

The surgical duration of an oral surgery procedure, the use of general anesthesia, the presence of infection, whether or not additional glucocorticoids are administered to reduce postoperative swelling, and the underlying health of the patient should be considered when deciding if it is necessary to prescribe supplemental glucocorticoids.

Oral Complications

SLE can be found in conjunction with Sjögren's syndrome, which is usually termed secondary Sjögren's syndrome. Sjögren's syndrome increases the risk of caries and other oral complications, which should be managed accordingly.

Scleroderma

Describes a group of clinical disorders characterized by thickening and fibrosis of the skin. The generalized form, systemic sclerosis, is a multisystem connective tissue disease in which the fibrosis extends to the internal organs, including the heart, lungs, kidney, and gastrointestinal tract. There are two main forms, **systemic sclerosis (SSc) and localized sclerodema**.

SSc is further divided into **limited cutaneous scleroderma** (previously called CREST syndrome for calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) and **diffuse cutaneous scleroderma**.

Patients with limited scleroderma often have a long history of Raynaud's phenomenon before the appearance of other symptoms. They have skin thickening limited to hands and frequently have problems with digital ulcers and esophageal dysmotility.

Diffuse scleroderma patients have a more acute onset, with constitutional symptoms, arthritis, carpal tunnel syndrome, and marked swelling of the hands and legs. They also characteristically develop widespread skin thickening (progressing from the fingers to the trunk), internal organ involvement (including gastrointestinal and pulmonary fibrosis), and potentially life-threatening cardiac and renal failure. Other possible variants are overlap syndromes with SLE, Sjögren's syndrome, RA, and dermatomyositis.

Localized scleroderma refers to scleroderma primarily involving the skin, with minimal systemic features. There are two major types of localized scleroderma: linear scleroderma and morphea.

Linear scleroderma is characterized by a band of sclerotic induration and hyperpigmentation occurring on one limb or side of the face.

Morphea is characterized by small violaceous skin patches or larger skin patches that indurate and lose hair and sweat gland function.

ETIOLOGY AND PATHOGENESIS

The etiology of SSc is unclear, but the pathogenesis is characterized by vascular damage and an accumulation of collagen and other extracellular matrix components at involved sites.

CLINICAL MANIFESTATIONS

PSS sclerosis is a chronic multisystem disorder characterized by intense fibrosis involving the skin, vasculature, synovium, skeletal muscles, and internal organs. The following is an overview of frequently encountered clinical manifestations.

Raynaud's Phenomenon. Raynaud's phenomenon, a paroxysmal vasospasm of the fingers that results in a change in the

colorof the fingertips as a response to cold or emotion, is the most common finding of PSS.

Cutaneous Manifestations. The thickening of the skin of PSS patients always begins in the fingers. Early skin changes, starting with pitting edema, often involve the whole

hand and the extremities. In several months, the edema is replaced by a tightening and hardening of the skin, which results in difficulty in moving the affected parts.

Musculoskeletal Manifestations. Polyarthralgias and morning stiffness affecting both small and large joints are frequent in patients with scleroderma. Inflammatory joint pain with markedly swollen fingers often appears to be true synovitis and can lead to the premature diagnosis of rheumatoid arthritis.

Gastrointestinal Manifestations. Distal esophageal motor dysfunction is the most frequent gastrointestinal finding; it results from weakness and in coordination of esophageal smooth muscle and leads to distal dysphagia. Intestinal fibrosis leading to severe intestinal malabsorption can also occur.

Cardiac Manifestations. *Patchy fibrosis* is a term used to describe the myocardial lesions associated with SSc. Hypertension, dysrhythmias, conduction disturbances, and left ventricular hypertrophy can develop.

Pulmonary Manifestations. Pulmonary interstitial fibrosis is now the most frequent cause of death in patients with scleroderma since renal disease has become a treatable complication.

Renal Manifestations. Until recently, renal involvement was the most dreaded and deadly complication of scleroderma. The use of high-dose corticosteroids for the treatment of scleroderma has been implicated in precipitating renal crisis in some patients.

Laboratory Evaluation and Diagnosis

The 2013 criteria include and apply various weights to the skin thickening, pulmonary manifestations, Raynaud's syndrome, telangiectases, and laboratory abnormalities (anticentromere, antitopoisomerase I and anti-RNA polymerase III).

Circulating antinuclear autoantibodies are present in >90% of scleroderma patients. anticentromere, antitopoisomerase I and anti-RNA polymerase III are highly specific for the disease.

TREATMENT

The treatment of PSS depends on the extent and severity of skin and organ involvement. D-penicillamin has shown promise in the management of PSS by decreasing both skin thickening and organ involvement.

Oral Manifestations

The clinical signs of scleroderma of the mouth and jaws are consistent with findings elsewhere in the body. The lips become rigid, and the oral aperture narrows considerably. Skin folds are lost around the mouth, giving a masklike appearance to the face. The tongue can also become hard and rigid, making speaking and swallowing difficult.

Involvement of the esophagus causes dysphagia. Oral telangiectasia is equally prevalent in both limited and diffuse forms of PSS and is most commonly observed on the hard palate and the lips. When the soft tissues around the temporomandibular joint are affected, they restrict movement of the mandible, causing pseudoankylosis.

The linear form of localized scleroderma may involve the face as well as underlying bone and teeth. Dental radiographic findings have been reported and widely described; these classic findings (which include uniform thickening of the periodontal membrane, especially around the posterior teeth) are found in less than 10% of patients.

Other characteristic radiographic findings include calcinosis of the soft tissues around the jaws.The areas of calcinosis will be detected by dental radiography and may be misinterpreted as radiographic intrabony lesions. A thorough clinical examination will demonstrate that the calcifications are present in the soft tissue.

Patients may also have oral disease secondary to drug therapy or xerostomia. Gingival hyperplasia can result from the use of calcium channel blockers; pemphigus, blood dyscrasias, or lichenoid reactions may result from penicillamine use.

Xerostomia results in an increased susceptibility to dental caries, *Candida* infections, and periodontal disease.

DENTAL MANAGEMENT

The most common problem in the dental treatment of scleroderma patients is the physical limitation caused by the narrowing of the oral aperture and rigidity of the tongue. Procedures such as molar endodontics, prosthetics, and restorative procedures in the posterior portions of the mouth become difficult, and the dental treatment plan may sometimes need to be altered because of the physical problem of access. The oral opening may be increased an average of 5 mm by stretching exercises. One particularly effective technique is the use of an increasing number of tongue blades between the posterior teeth to stretch the facial tissues. In addition, mechanical devices that assist the patient in performing the stretching exercises are available. If these approaches are insufficient, a bilateral commissurotomy may be necessary. When treating a patient with diffuse scleroderma, the extent of the heart, lung, or kidney involvement should be considered, and appropriate alterations should be made before, during, and after treatment. Patients with extensive resorption of the angle of the mandible are at risk for developing pathologic fractures from minor trauma, including dental extractions. Patients with Sjögren's syndrome should have daily fluoride treatments and make frequent visits to the oral hygienist.

Rheumatoid Arthritis

RA is a disease characterized by symmetrical, inflammatory arthritis of small and large joints affect up to 2% of the population in the United States over the age of 60 years, with a higher prevalence in women.

SUBTYPES

Juvenile arthritis (JA) is a term to describe any arthritis in children. A subset, juvenile idiopathic arthritis (JIA) includes those children with chronic arthritis. Some clinicians refer to this subset as juvenile RA.

In general, symptoms of JIA include joint pain, swelling, tenderness, warmth, and stiffness for at least 6 weeks without another cause. Similar to RA in adults, these children may have severe joint and organ damage.

There are seven classifications of JIA: systemic arthritis, oligoarthritis, polyarthritis—rheumatoid factor (RF) negative, polyarthritis—RF positive, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. Felty's syndrome is characterized by neutropenia and splenomegaly in conjunction with RA. These patients have additional susceptibilities to bacterial infection if neutropenia is severe.

ETIOLOGY

The pathogenesis of RA is unknown, but it appears to be multifactorial, involving genetic,immune, and infectious etiologies.

CLINICAL MANIFESTATIONS

RA is a symmetric polyarthritis often involving the proximal interphalangeal joints of the fingers and metacarpophalangeal joints of the hands. ; the wrists, elbows, knees, and ankles also can be affected. In some patients, all joints may be involved, including the TMJ and the cricoarytenoid joint of the larynx. Affected joints develop redness, swelling, and warmth, with eventual atrophy of the muscle around the involved area. Cervical spine disease may cause C1–C2 subluxation and spinal cord compression. One long-term complication of RA is a marked increase in cardiovascular disease.

Oral Manifestations

The treatment of RA can cause oral manifestations. The long-term use of methotrexate and other antirheumatic agents such as D-penicillamine and NSAIDs can cause stomatitis. Cyclosporine may cause gingival overgrowth. Direct effects of the disease are also seen. Patients with long-standing active RA have an increased incidence of periodontal disease, including loss of alveolar bone and teeth. Although the increased dental and periodontal disease may be chiefly related to a decreased ability to maintain proper oral hygiene. Sjögren's syndrome is a common complication of RA.

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DIAGNOSIS AND LABORATORY EVALUATION

The initial diagnosis of RA is made primarily by observing clinical features. As with many autoimmune diseases, a list of diagnostic criteria is used to evaluate patients.

Rheumatoid arthritis: add score A through D; a score of ≥6 of 10 is needed for classification of a patient as having definite rheumatoid arthritis

Classification	Score
A. Joint involvement	
• 1 large joint (shoulders, elbows, hips, knees, ankles)	0
• 2–10 large joints	1
• 1–3 small joints (with or without large joints)	2
• 4–10 small joints (with or without large joints)	3
• >10 joints (at least one small joint)	5
B. Serology (at least 1 test result is needed for classification)	
• Negative rheumatoid factor (RF) and negative anticitrullinated protein antibody (ACPA)	0
• Low-positive RF or low-positive ACPA	2
• High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
• Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
• Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1

DENTAL MANAGEMENT

The most common complication that affects dental treatment relates to the toxicity of the drugs used to treat RA. It is imperative that the dentist knows the drugs the patient is currently taking and their possible side effects and interactions with other drugs. The most common adverse effects of NSAIDs involve the gastrointestinal (GI) tract and the kidneys. In addition, many patients take aspirin at dosages approaching 5 g per day or take an equivalent dosage of NSAIDs. These drugs affect platelet function, causing a prolongation of the bleeding time and possible hemorrhage after surgery. Patients with severe RA who have had joints surgically replaced with prosthetic joints may require prophylactic antibiotic therapy before invasive dental procedures.

Patients with cervical spine disease may have C1–C2 subluxation and spinal cord compression. Hyperextension of the neck must be avoided. Prolonged morning stiffness is common in RA, so later morning appointments may be best for patients. Patients with severe RA who have prosthetic joints may require prophylactic antibiotic therapy beforeinvasive dental procedures, though the evidence for the practice is very limited. Patients with Sjögren's syndrome may require additional instruction in personal oral care and instruction on diet and dietary modifications.

The dentist should determine if the RA patient has a form of the disease that affects the bone marrow (such as Felty's syndrome) since such patients have an increased risk of developing infection due to neutropenia and hemorrhage secondary to thrombocytopenia.

T.M.J involvement

R.A. is the important inflammatory disease of T.M.J (T.M.J involvement ranges from 40 to 80%).

The clinical features of T.M.J involvements are:

- Limitation in movement of mandible.
- T.M.Js bilaterally involved, tenderness, swelling over the joint area
- Morning stiffness
- Deviation of mandible on opening
- Ankylosis of the joint with facial asymmetry

Management :

- On diagnosis the clinical radiograph shows flatting of the condyle, loss of contour and irregularity of the articular surface.
- Joint space may be widened (acute phases) but later narrowed.
- Underlying bone may be osteoporotic.

Treatment of TMJ disorders:

- By giving of non-steroidal anti-inflammatory drugs.
- Any abnormalities in occlusion should be corrected.
- In severe symptoms (intra-articular steroids should be considered).
- Surgical treatment (placement of prosthetic joints) is indicated in sever functional impairment or pain).
- Use of a flat plane occlusal appliance may be helpful (if Para functional habits are increasing the symptoms).

Reference: Burket's Oral Medicine **,** 12th edition ,2015