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An Overview about Systemic Sclerosis (Scleroderma)

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Abstract: Background: Systemic sclerosis, often known as scleroderma, is a rare connective tissue illness whose cause is uncertain and complex. Scleroderma is classified into two types: localised scleroderma (including morphea, linear scleroderma, and scleroderma en coup de sabre) and systemic sclerosis. Based on clinical and serological criteria, systemic sclerosis can be defined as limited systemic sclerosis (previously known as CREST syndrome, which includes calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) or diffuse systemic sclerosis. Localised scleroderma primarily affects the skin and subcutaneous tissue, whereas systemic sclerosis has systemic symptoms and involves internal organs, which increases mortality. Scleroderma symptoms can closely resemble those of other rheumatological or immunological illnesses. The harshness of the presentation can also change based on the timing.

Keywords: *Systemic Sclerosis*

Introduction

Scleroderma, or systemic sclerosis, is a complex and uncommon connective tissue illness whose cause is unclear. Systemic sclerosis and localized scleroderma (including morphea, linear scleroderma, and scleroderma en coup de sabre) are the two main types of scleroderma. Based on clinical and serological criteria, systemic sclerosis can be further divided as either diffuse systemic sclerosis or confined systemic sclerosis. The former is characterized by calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; the latter is sometimes called CREST syndrome.Researchers have come a long way in our understanding of scleroderma's pathogenesis, yet the illness still causes a lot of suffering and even death for those who suffer from it.[1][2]

Similar to the histological abnormalities shown in thickened skin in systemic sclerosis, patches of thickened skin can be observed on biopsy in localized scleroderma, which mainly affects the skin and subcutaneous tissue. Nonetheless, there is no correlation between it and digital ischemia events, the Raynaud syndrome, or organ

involvement. Even while antinuclear antibodies are found in as many as half of all cases of localized scleroderma, the disorder is characterized by the absence of more specific autoantibodies including anti-centromere, anti-Scl-70, and anti-RNA polymerase III.the thirdThe risk of death is not higher in cases of localized scleroderma.Contrarily, skin involvement is the basis for classifying systemic sclerosis, which is linked to many systemic symptoms, involvement of internal organs, and higher mortality.[4] Skin thickening distal to the elbows and knees and/or on the face without involvement of the trunk is a hallmark of limited cutaneous systemic sclerosis, formerly called CREST syndrome. Contrarily, areas near the elbows, knees, face, and/or trunk may see skin thickening in diffuse cutaneous systemic sclerosis. It is common for patients with restricted or diffuse cutaneous systemic sclerosis to have positive autoantibodies and a number of systemic symptoms. More than 90% of SS cases may have antinuclear antibodies, and as many as 70% of SS cases show certain autoantibodies, such as anti-centromere, anti-Scl-70, or anti-RNA polymerase III. Some of the most common organs affected by scleroderma include the skin, gastrointestinal tract, lungs, kidneys, skeletal muscle, and pericardium.Scleroderma symptoms can be quite similar to those of other autoimmune or rheumatological disorders [5]. When systemic sclerosis is diagnosed might also affect how severe the symptoms are.

Systemic sclerosis has an unclear origin, although researchers suspect a combination of hereditary and environmental variables.

Genetic Factors

There is evidence of familial clustering in cases of systemic sclerosis, and families with this disease tend to have several autoimmune diseases.[6][7]The major histocompatibility complex genetic area is involved with systemic sclerosis and other autoimmune diseases, according to genomewide association studies. This includes rheumatoid arthritis and systemic lupus erythematosus. Some human leukocyte antigens (HLA) have long been known to be associated with systemic sclerosis. These include HLA DRB1*1104, DQA1*0501, and DQB1*0301.It has also been suggested that non-HLA loci including PTPN22, NLRP1, STAT4, and IRF5 contribute to the development of systemic sclerosis.[8]

Environmental Factors

Infectious agents like Cytomegalovirus (CMV), Epstein-Barr virus, and parvovirus B19 are among the environmental triggers linked to the recurrence of systemic sclerosis.[9]In addition to organic solvents, silica dust, xylene, trichloroethylene, and polyvinyl chloride, systemic sclerosis can also develop after infrequent exposure to additional substances. Importantly, there is no evidence that smoking increases the likelihood of developing systemic sclerosis.

Environmental exposures can cause a variety of scleroderma-like disorders; for example, toxic oil syndrome, which is differentiated from systemic sclerosis by clinical, histopathological, and laboratory features, and eosinophilia-myalgia syndrome, which is linked to L-tryptophan.[10]Furthermore, bleomycin and cocaine are two of the medications linked to the development of disorders similar to systemic sclerosis.

Epidemiology

Systemic sclerosis is uncommon, which means there isn't a lot of data on its epidemiology. Factors like case definition, location, and methods of ascertainment affect the reported incidence and prevalence rates. Every year, there are anywhere from 8 to 56 new cases per million people, with a prevalence rate of 38 to 341 cases per million.the eleventh

An American study found a prevalence of 242 cases per million people in the Detroit area between 1989 and 1991, with an estimated annual incidence of 19.3 per million individuals.443 instances per 100,000 persons were discovered in a different investigation conducted in Quebec in 2003 [12].in [13]Asia (particularly Japan and Taiwan) and Europe (generally) have lower incidence rates than the US and AU.[14]Geographical variations in the incidence of this ailment are highlighted by the fact that the Choctaw Native Americans from Oklahoma had the greatest prevalence of systemic sclerosis at 660 cases per million persons [15].[16]

There are approximately five times as many females as males diagnosed with systemic sclerosis. The disease usually manifests in females at a younger age compared to males. For African-American women, the peak age of onset is 45–54, while for European-American women, it is 55–64. It should be noted that systemic sclerosis

is extremely uncommon in children and teenagers under the age of fifteen.African-American girls have an incidence of 21.2 per million and European-American females 11.16 per million, respectively, for disease onset in individuals aged 15 to 24. African-American patients have a more rapid illness onset, more severe symptoms, and a higher likelihood of developing systemic sclerosis.[18] in

Systemic sclerosis is a complex disease with a complicated mechanism. Vascular injury, autoimmunity, and tissue fibrosis are the three primary features of the disease. Variations in the involvement of these elements in the development of systemic sclerosis in individual patients are thought to explain why the disease manifests in a variety of clinical forms. The initial vascular insult in systemic sclerosis can be initiated by a variety of stimuli, including viruses, environmental exposures, autoantibodies, proteolytic enzymes, and inflammatory cytokines. The cascade of events begins with this first vascular insult, which activates endothelial cells, which in turn triggers the overexpression of adhesion molecules, which activates platelets, and so on.

In addition to promoting leukocyte adhesion, vascular smooth muscle cell proliferation, and fibroblast activation, activated endothelial cells produce ET-1, a powerful vasoconstrictor.[19]There are noticeable functional problems, such as reduced response to vasodilators like prostacyclins and nitric oxide, when these stimulated endothelial cells transdifferentiate into mesenchymal cells. Also, thromboxane-A2, platelet-derived growth factor, transforming growth factor-β (TGF-β), and active thrombin are released by activated platelets. This leads to thrombosis, vasoconstriction, coagulation, and fibroblast activation. Hyperoxia of the tissues is a final outcome of the first vascular damage. Chronic tissue hypoxia and oxidative stress are factors in systemic sclerosis patients' symptoms, which include impaired compensatory vascular repair processes, microangiopathy, microvasculature loss, and decreased angiogenesis.

Inflammation and immunological dysregulation, affecting both the humoral and innate immune systems, are critical components of systemic sclerosis pathophysiology. Tissue and peripheral blood samples from people with systemic sclerosis include an abundance of activated T lymphocytes. Systemic sclerosis patients exhibit a preponderance of Th2 cytokines, which is an imbalance of types 1 and 2 helper T cells. The imbalance in the Th2 profile leads to more fibrosis because pro-fibrotic cytokines like TGF-β and interleukins (ILs) 4, 5, and 13 promote myofibroblast transdifferentiation and greater collagen synthesis, while less anti-fibrotic cytokines like interferon-γ have a less impact.

Further promotion of vascular damage and fibrosis is achieved by activated macrophages, monocytes, and dendritic cells, which in turn activate T- and B cells and produce cytokines that are pro-fibrotic and pro-inflammatory. Humoral autoimmunity and the presence of autoantibodies are observed in nearly all patients with systemic sclerosis. These directly pathogenic autoantibodies are produced by activated B cells and are key diagnostic markers for the disease.[20]In addition, several phenotypes of systemic sclerosis are linked to particular autoantibody patterns. The activation and differentiation of mesenchymal cells contribute to tissue fibrosis as a result of vascular injury and inflammation caused by autoimmunity. The pathologic epithelial-mesenchymal transition, an increase in the microvascular pericyte compartment, myofibroblast persistence, uncontrolled fibroblast activation, and irreversible extracellular matrix accumulation are all outcomes of this process.

Systemic sclerosis is characterized by a noninflammatory proliferative or obliterative vasculopathy that is later followed by vascular or interstitial fibrosis. Systemic sclerosis patients who have had the disease for a long time do not have the inflammatory perivascular infiltrates of CD4+ T cells that are seen in early stages of the disease. Mild intimal proliferation, basement membrane thickening, capillary rarefaction, microthrombi development, platelet aggregation, and loss of vascular endothelial cadherin are all hallmarks of systemic sclerosis vasculopathy. Immune complex deposition or vasculitis is extremely unusual. But substantial perivascular fibrosis, increasing luminal obstruction, and tissue fibrosis are visible in the latter stages of systemic sclerosis. Dermal edema and perivascular inflammatory infiltrates mostly composed of T cells and monocytes are hallmarks of early-stage systemic sclerosis. Later stages of the disease are characterized by the development of dermal fibrosis. Hair follicles, sweat glands, sebaceous glands, and dermal capillaries are usually missing from histopathological analyses of skin lesions.Dense collagen and hyaluronic acid buildup characterize a

noticeable dermal expansion. It is also usual to see the subcutaneous adipose layer and dermal lymphatics disappear.

Systemic sclerosis is characterized by skin pathology and extensive involvement of the lungs. Inflammatory alterations, fibrosis, and vascular damage are the early symptoms of pulmonary involvement in the disease.[21]Lymphocytes, macrophages, and plasma cells infiltrate the alveolar walls, marking the beginning of inflammatory alterations. Nonspecific interstitial pneumonitis is the most prevalent lung involvement in systemic sclerosis. It is characterized by type II pneumocyte hyperplasia, interstitial inflammation, and generally uniform distribution of fibrosis. In a different form, known as typical interstitial pneumonia, the fibrosis is distributed patchily with scattered fibroblastic foci, and the prognosis is worse. When the pulmonary microvasculature deteriorates as a result of progressive pulmonary fibrosis, a condition known as pulmonary arterial hypertension (PAH) sets up.

Systemic sclerosis rarely involves the kidneys. Unless there is an overlapping condition, glomerulonephritis is uncommon, but chronic ischemia alterations are sometimes seen. Changes similar to those observed in thrombotic microangiopathy or malignant hypertension are linked to the extremely unusual and potentially fatal sclerosis renal crisis.[22]The histological examination of these instances typically reveals narrowing of the luminal lumen and growth of the elastic lamina, also known as onion skinning, in the tiny interlobular and arcuate renal arteries.

The main symptom of systemic sclerosis, which impacts more than just the skin, is fibrosis. The thyroid gland, salivary glands, penile blood arteries, and the gastrointestinal tract (from the mouth to the rectum) are among the organs that might experience fibrosis. Systemic sclerosis alone or overlap syndromes can also present with inflammatory myositis. Important findings brought about by cardiac involvement include constrictive pericarditis, fibrosis or effusions around the heart, and patchy fibrosis of the heart muscle.

History and Physical

The clinical appearance of systemic sclerosis varies greatly across individuals due to the complexity of the condition and its impact on various systems. As a result of more widespread and severe involvement of internal organs, symptoms of diffuse cutaneous systemic sclerosis are often more severe and the death rate is higher than that of limited cutaneous systemic sclerosis. Systemic sclerosis is also more common among older adults, those of African American descent, and men. The disease tends to have a more severe manifestation in these demographics.

Raynaud Phenomenon

Raynaud phenomenon is a common and early symptom of systemic sclerosis, seen in more than 95% of individuals.[23] TheTriphasic color changes, caused by cold-induced vasospasms, most commonly impact the fingers and, more specifically, the upper limbs. Other parts of the body, like the ears, nose, and tongue, might also experience these color changes. Image: Bilateral Signs of Raynaud Phenomenon in a Patient's Hands shows the progression of color changes, which begin with pallor and clearly defined white discoloration, progress to ischemic alterations, which appear as a dusky blueish color, and eventually, reactive hyperemia, which causes a reddish discoloration. Bear in mind that not every patient will report all three color phases. In cases of limited cutaneous systemic sclerosis, Raynaud phenomenon can appear years before visceral involvement begins.In the case of diffuse cutaneous systemic sclerosis, however, the development of skin alterations and the Raynaud phenomenon can happen at the same time or very soon after. It is worth mentioning that about 15% of the general population experiences Raynaud's phenomenon without having underlying connective tissue disorders or systemic sclerosis. This condition is known as primary Raynaud and it typically manifests in young adults (often younger than 20 years old), has mild symmetrical symptoms, normal nailfold capillaries, a lack of ischemic complications, a 4:1 ratio of female to male affected individuals, and a benign course. Systemic sclerosis is associated with secondary Raynaud, which might cause serious consequences.[24]

In systemic sclerosis, the intimal hyperplasia and fibrosis that characterize the underlying non-vasculitic vasculopathy exacerbate the vasospastic insult generated by the Raynaud phenomenon. Another factor that leads to vessels being less flexible is when local vasomotor control is not regulated properly. Autoamputation

may be necessary due to digital ischemia and dry gangrene, which are symptoms of systemic sclerosis that appear as pitting, ulcers, and tissue loss. Furthermore, subsequent infections are prevalent consequences. Capillary dilatation, hemorrhages, and dropout are symptoms of an aberrant nailfold capillary examination that further describe Raynaud syndrome in systemic sclerosis.

Cutaneous Manifestations

Almost all patients with systemic sclerosis have skin involvement, albeit the degree and severity of this involvement might vary. It is the most noticeable aspect of systemic sclerosis.[25] TheThe level of skin involvement defines the limited cutaneous subtype of systemic sclerosis, as opposed to the diffuse cutaneous subtype. Typically, the trunk remains unaffected in limited cutaneous systemic sclerosis, which manifests as skin involvement beyond the elbows and knees. Diffuse cutaneous systemic sclerosis, on the other hand, affects the skin near the knees, elbows, and/or trunk. Depending on the severity of the disease, localized or diffuse cutaneous systemic sclerosis may manifest with facial involvement.

During the first, "puffy finger phase," you may have swelling and inflammation in your hands that doesn't bleed, which can last for a few months. Itchy skin, burning discomfort, and pruritus are common complaints. Carpal tunnel syndrome and other compression neuropathies can develop when edema presses on underlying structures. Skin becomes dry and unpleasant when skin appendages are lost. The fibrotic phase follows the initial phase, which is characterized by the development of thickened skin and fibrosis.

During the second protracted fibrotic phase, a disease called sclerodactyly begins distal to the metacarpophalangeal joints and gradually moves proximally, thickening and fibrosis of the skin. Joint mobility is impaired and persistent contractures develop as a result of the thick, leathery skin and fibrosis of deeper subcutaneous structures. Subcutaneous adipose tissue and skin appendages may continue to deteriorate, a condition known as lipodystrophy. Pursed Mouth in a Female Patient With Scleroderma) is a narrow oral aperture that shows up as facial involvement. It's also called fish-mouth or masked facies.

Ulcers can form on the extensor surfaces of joints such the elbow, interphalangeal, or metacarpophalangeal after trauma. Depigmentation in otherwise pigmented patches of skin can also give the skin a salt-and-pepper look. On rare occasions, the last stage of skin softening may not appear until years after the first symptoms appear. In this stage, the subcutaneous tissue underneath the skin may stay fibrotic, but the skin on the trunk and upper arms may relax and seem clinically normal again.

Hands, faces, mucosal surfaces, and, on rare occasions, the trunk can display telangiectasias, a characteristic of systemic sclerosis caused by dilated capillaries. Applying pressure causes these telangiectasias to blanch, and they may even become larger with time. There is an increased risk of PAH when they are present. Limited cutaneous systemic sclerosis (LCSS) and patients positive for anti-centromere antibodies are more likely to have subcutaneous calcinosis, but it can be found in both types of cutaneous sclerosis.[26] inFinger pads and elbow extensor surfaces are common sites for the development of calccinosis, a condition caused by localized deposits of subcutaneous calcium hydroxyapatite. A skin ulcer and subsequent infection are possible complications of this calcinosis.

Musculoskeletal Manifestations

Nearly all patients with systemic sclerosis will experience symptoms involving the musculoskeletal system. Myalgia and arthralgia are two of the most commonly reported types of this. Some people experience inflammatory arthritis with genuine synovitis, which can impact joints like the metacarpophalangeal, proximal interphalangeal, wrist, and ankle joints. This pattern is similar to rheumatoid arthritis. Erosions are rare but possible, especially when periarticular calcinosis is present. Although cases of diffuse cutaneous systemic sclerosis involving major joints are rare, they do occur. Furthermore, in as many as 5% of instances, rheumatoid arthritis and systemic sclerosis are shown to overlap.[27][28] in

In the later phases of diffuse cutaneous systemic sclerosis, patients may have distal bone resorption and osteolysis. Large joint contractures are uncommon in this disease type, however they are widespread in the hands. Tendon friction rubs are associated with a poor prognosis and can happen in as many as 30% of cases, especially in diffuse cutaneous systemic sclerosis, where they are caused by inflammation, swelling, and

fibrosis of the tendon sheath. There are a number of factors that contribute to myopathy, or muscle involvement, in sclerosis. Around 10% of individuals experience polymyositis-like inflammatory myopathy, which manifests as fast weakening of the proximal muscles, increased levels of muscle enzymes, and biopsy results that are typical of inflammatory myositis. Inadequate nutrition or deconditioning as a result of joint illness or skin fibrosis can also lead to weaker muscles.

A fibrosing myopathy, defined by atrophy and fibrosis of the muscles, can develop when systemic sclerosis directly affects the muscles. A muscle biopsy will usually show atrophy and fibrosis with little to no inflammation, and patients with this disorder may have slightly raised levels of muscle enzymes. Typically, anti-inflammatory medications have no effect on these patients, in contrast to inflammatory myopathies. In systemic sclerosis, myopathy often indicates a bad prognosis.

Signs and Symptoms in the Digestive System

All forms of systemic sclerosis, including limited cutaneous and diffuse forms, nearly always include the gastrointestinal tract. Any part of the digestive system is vulnerable, and symptoms can be moderate to severe. Gingivitis, periodontitis, restricted oral aperture, and tightening of the perioral skin are symptoms of oropharyngeal involvement. Inflammatory infiltrates in secondary Sjögren syndrome or systemic sclerosis can cause the salivary glands develop fibrosis, leading to dry mouth. Up to 90% of people with systemic sclerosis experience dysphagia and heartburn as a result of esophageal dysmotility, which is mostly caused by fibrosis affecting the distal two-thirds of the esophagus.

Hypotonicity of the lower esophageal sphincter worsens reflux symptoms. Dysmotility of the esophagus can lead to complications such as bleeding, Barrett's esophagus, esophageal strictures, or esophagitis. A delay in gastric emptying, also known as gastroparesis, can cause symptoms such as early fullness, gas, nausea, vomiting, and anorexia, which in turn can cause weight loss and malnutrition.[29][30]

Gastric telangiectasias can cause gastric antral vascular ectasia, or "watermelon stomach," which in turn can cause small or substantial quantities of internal bleeding. Overgrowth of germs in the intestines, diarrhea, and constipation are all symptoms of intestinal dysmotility. Occult gastrointestinal bleeding can be caused by mucosal telangiectasias. Serious pseudo-obstruction can result from intestinal dysmotility. Unique to systemic sclerosis is the development of wide-mouthed diverticula as a result of muscle atrophy in the intestinal mucosa. Rectal prolapse and incontinence can be caused by a decrease in anal sphincter tone. While systemic sclerosis is not commonly linked to hepatic involvement, there have been reports of primary biliary cirrhosis in a few individuals.[31]

Pulmonary Manifestations

Patients with systemic sclerosis are most often killed by lung diseases. Pneumoniasis and interstitial lung disease are the hallmarks of pulmonary involvement. Among the less common pulmonary symptoms include pleuritis, aspiration pneumonia, cryptogenic organizing pneumonia, pulmonary bleeding, and obstructive airway disease. Systemic sclerosis has a wide range of pulmonary diseases, from those that cause no symptoms at all to those that lead to respiratory failure and significant disability.[32]

Bibasilar pulmonary fibrosis, the clinical manifestation of interstitial lung disease, is more common and severe in some populations, including those with anti-topoisomerase I antibodies, African Americans, males, and those with widespread cutaneous systemic sclerosis. Despite the lack of symptoms, approximately half of all instances of systemic sclerosis are associated with clinically severe interstitial lung disease. Interstitial lung disease was found in over 80% of sclerosis patients found during postmortem exams. Symptoms of interstitial lung disease often appear in the first four to five years following a diagnosis of systemic sclerosis. Although there is a mixed pattern, nonspecific interstitial pneumonitis is more common than normal interstitial pneumonia. Dyspnea, lethargy, and, in the later stages of the disease, a cough that does not produce mucus are symptoms.

A restrictive pattern is shown by a decrease in lung volumes and a FEV1/FVC ratio on the pulmonary function test. A diminished carbon monoxide diffusing capacity (DLCO) could be a result of preexisting pulmonary vascular disease. Enhanced subpleural lung attenuations in the bilateral posterior basal regions can be seen in

early stages of the disease using extremely sensitive high-resolution computed tomography (HRCT) of the chest. Additional observations may include honeycombing, traction bronchiectasis, thickening of the interlobular septa, and ground-glass opacities, which could be signs of alveolitis.[33]

There is a wide range of PAH symptoms, from no symptoms at all to severe PAH with right heart failure, making it another prevalent pulmonary presentation. Systemic sclerosis (MS) is a progressive disease, and PAH usually doesn't show up until much later on, usually over a decade after the first diagnosis. This illness can impact anywhere from 30 to 50% of people with systemic sclerosis; cases of limited cutaneous systemic sclerosis seem to have a higher frequency. Multiple telangiectasias, anti-U3-RNP antibodies, and a later age at diagnosis are risk factors for PAH in systemic sclerosis. Initially, you may experience difficulty breathing; later on, you may experience chest pain, swelling in your lower extremities, dizziness, and syncope. Potentially audible is an amplified "P component" of the second cardiac sound (S2).

An isolated decrease in diffusion capacity is shown by a pulmonary function test. It is also possible for there to be increased amounts of NT-proBNP in the blood. An increased peak right ventricular systolic pressure could be shown on echocardiography. A right heart catheterization should be done when PAH is suspected in order to confirm the diagnosis and rule out other possible causes. If the pulmonary capillary wedge pressure is normal and the mean pulmonary arterial pressure is 25 mm Hg or above, then it is likely that the patient has pulmonary arterial hypertension (PAH).

Cardiac Manifestations

Arrhythmias, dilated cardiomyopathy, pericarditis, and pericardial effusion are cardiac symptoms. One complication of PAH is left ventricular diastolic dysfunction. There is a poor prognosis and higher risk of infection when the heart is involved.on page 34Small, exudative pericardial effusions are the norm, and tamponade is very unusual. Diffuse cutaneous systemic sclerosis is associated with an increased risk of scleroderma renal crisis, which is characterized by the presence of pericardial effusions. Myocardial fibrosis develops in patches, leading to dilated cardiomyopathy. Although arrhythmias such as premature ventricular contractions, heart block, intraventricular conduction delays, and supraventricular tachycardia have been documented, fibrosis within the conduction pathways is the most common cause of these abnormalities.

Renal Manifestations

Scleroderma renal crisis is a classic example of the kidney-related symptoms of systemic sclerosis. This condition was the leading cause of death in patients with systemic sclerosis prior to the development of ACE inhibitors.[22]Scleroderma renal crisis usually appears after three years of diagnosis and affects around 10% of people with systemic sclerosis, mostly those with diffuse cutaneous sclerosis. People of African American descent, those with tendon friction rubs, new-onset anemia, diffuse cutaneous systemic sclerosis, an anti-RNA polymerase III antibody, and those using high-dose or chronic low-dose corticosteroids are at increased risk of developing scleroderma renal crisis. Signs of a worsening scleroderma renal crisis include being male, being older when symptoms first appear, and having serum creatinine levels higher than 3 mg/dL.[35]

Vasculopathy, not glomerulonephritis, is the main pathology of scleroderma renal crisis, similar to the vascular alterations seen in other organs affected by systemic sclerosis. It typically appears clinically with renal insufficiency and new-onset hypertension or malignant hypertension. Thrombocytopenia and hemolytic anemia are common complications of the microangiopathy that often accompanies this illness. Microscopic hematuria is common but usually moderate, and proteinuria may happen at the same time.

Other Manifestations

Other manifestations of systemic sclerosis include hypothyroidism, which occurs in up to 15% of patients, particularly those with limited cutaneous systemic sclerosis, often due to thyroid gland fibrosis. Moreover, autoimmune thyroid diseases, such as Hashimoto thyroiditis and Graves disease, are more prevalent among systemic sclerosis patients. These individuals also have a higher risk of developing other autoimmune conditions, such as primary biliary cirrhosis and secondary Sjögren syndrome. Additionally, thrombocytopenia has been observed in some cases.[36]

Overlap syndromes are common in systemic sclerosis and can involve conditions such as rheumatoid arthritis and polymyositis. Additionally, patients with systemic sclerosis have an elevated risk of psychological disorders such as depression, affecting up to 50% of individuals. Another variant, systemic sclerosis sine scleroderma, is characterized by internal organ manifestations of systemic sclerosis, particularly in the pulmonary and gastrointestinal systems, without skin thickening. These patients typically exhibit the Raynaud phenomenon, along with abnormal nailfold capillary exam results and positive antinuclear antibodies.

Classification Criteria

In 2013, the American College of Rheumatology published the updated classification criteria for systemic sclerosis, offering improved sensitivity and specificity compared to the older 1980 criteria.[37]

Clinical Evaluation

Using a scale from 0 (no thickening) to 3 (extreme thickening), the modified Rodnan skin score determines how much skin is present in an area. The predictive value of the score makes it crucial to track its evolution over time. If a patient presents with Raynaud phenomenon and a suspicion of systemic sclerosis, a nailfold capillary examination should be performed. At each appointment, we check for underlying organ involvement by performing a thorough physical examination that targets many organ systems. Individuals newly diagnosed with diffuse cutaneous systemic sclerosis, those experiencing new-onset hypertension, or those with a significant worsening of existing hypertension should undergo regular blood pressure monitoring at home and in the clinic. This is especially important because these symptoms can signal the beginning of scleroderma renal crisis.

Autoantibody Tests

Autoantibodies provide crucial information about the phenotype and prognosis of a disease, making them an indispensable diagnostic tool. More than 90% of sclerosis patients show positive results for antinuclear antibodies as detected by direct immunofluorescence.[38]If antinuclear antibodies come back negative, it's crucial to make sure there aren't any other possible diagnosis before confirming systemic sclerosis. Adding to the diagnostic specificity, particular autoantibodies have a positive rate of 60% to 70%. These incompatible antibodies, as will be discussed later on, can show up months or even years before the symptoms of systemic sclerosis become noticeable.

Anti-centromere antibody: Although they do occasionally appear in widespread cutaneous systemic sclerosis, anti-centromere antibodies mostly target four centromere antigens (CENP -B, -A, -C, D). Systemic lupus erythematosus and Sjögren syndrome are two other diseases that might cause their manifestation. The risk of PAH is elevated in individuals with anti-centromere antibodies. In comparison to other autoantibodies, they are associated with lower risk of interstitial lung disease, less skin involvement, and better overall survival rates.

Anti-topoisomerase I (Scl-70) antibody: Anti-topoisomerase I (Scl-70) antibodies target the catalytic region of DNA helicase topoisomerase I. They are predominantly observed in diffuse cutaneous systemic sclerosis and infrequently in limited cutaneous systemic sclerosis. The presence of anti–Scl-70 antibodies is linked to an elevated risk of diffuse cutaneous involvement, interstitial lung disease, and cardiac involvement.[39]

Anti-RNA polymerase III antibody: Anti-RNA polymerase III antibodies target the eukaryotic RNA polymerase III. They are particularly associated with diffuse cutaneous systemic sclerosis and are linked to rapidly progressing and aggressive diffuse skin involvement, poor cutaneous outcomes, and scleroderma renal crisis. Additionally, these antibodies are also associated with a lower risk of interstitial lung disease and PAH. Some studies have indicated an association between anti-RNA polymerase III antibodies and malignancies in systemic sclerosis patients.

Anti–U3-RNP (fibrillarin) antibody: Anti-U3-RNP (fibrillarin) antibodies are prevalent in African Americans and are associated with an overall poor prognosis in systemic sclerosis. Their presence correlates with increased internal organ involvement, diffuse cutaneous manifestations, interstitial lung disease, PAH, scleroderma renal crisis, myositis/myopathy, and cardiac complications.[40]

Other autoantibodies: Other autoantibodies include anti-Th/To antibodies that are associated with limited skin disease. Anti–PM/Scl antibodies associated with limited skin disease and overlap syndrome predispose to inflammatory myositis and interstitial lung disease. Anti–U1-RNP antibodies are more prevalent in African Americans and are associated with overlap syndrome and mixed connective tissue disease. This antibody profile is linked to limited cutaneous involvement and increased risk of inflammatory arthritis, myositis, lupus skin rashes, and lupus nephritis. Anti-Ku antibodies are also associated with overlap syndrome in systemic sclerosis, which is associated with more inflammatory arthritis and myositis.

Laboratory Evaluation

Complete blood counts to assess for anemia may be multifactorial.[41] Renal function and 24-hour urine protein or urine protein:creatinine ratio should be closely monitored. Although inflammatory markers typically do not provide significant diagnostic significance, notable elevations may indicate active inflammatory myopathy or inflammatory arthritis. Muscle enzymes, including creatine kinase and aldolase, may be elevated, especially in the presence of inflammatory myopathy.

Ancillary and Radiographic Evaluation

X-rays of the extremities can reveal calcinosis and loss of distal phalanges. Periarticular erosions are rare and uncommon, although periarticular osteopenia can be seen. Musculoskeletal ultrasound can be used to show features of tenosynovitis. When muscle involvement is suspected, electromyography/nerve conduction velocity testing is the initial diagnostic choice. If abnormal results are obtained, a muscle biopsy may be warranted. High-resolution CT (HRCT) scan is the preferred imaging modality for assessing interstitial lung disease, as it can detect subtle findings that may not be visible on a chest x-ray.[29]

Pulmonary function tests, including spirometry, lung volumes, and diffusion capacity, can detect a restrictive pattern in interstitial lung disease very early in the disease process. A lung biopsy is of very limited value and should be avoided unless other diagnostic concerns are concurrent. When PAH is suspected, transthoracic echocardiography is usually initially performed, although right heart catheterization should follow to confirm the diagnosis and rule out other etiologies. Electrocardiography and Holter monitoring can be useful in detecting arrhythmias.

Pericardial effusions can be well visualized on transthoracic echocardiography. In patients suspected of myocardial involvement, a cardiac MRI may be necessary. When esophageal and upper gastrointestinal involvement is suspected, upper gastrointestinal endoscopy, esophageal manometry, barium swallow studies, and a 24-hour pH probe can be utilized.[42] A characteristic finding indicative of esophageal dysmotility is a dilated esophagus with excessive air observed on a CT scan.

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