Crest Syndrome

( Calsinosis, Raynaud’s, Esophageal Dysmotility, Sclerodactily, Telangiectasis)

Blondina Marpaung, Dwi Handayani Nasution
Rhematology Division
Medical Faculty of North Sumatera University / Adam Malik General Hospital

ABSRTACT

Systemic sclerosis (SSc / Scleroderma) is a chronic autoimmune disorder such as connective tissue disorder of unknown etiology, heterogenous clinical manifestations and often progressive course.1,2,3 The distinctive involvement of multiple internal organs, most notably the lungs, gastrointestinal tract, heart, and kidneys1,2,5 Diagnostic criteria by The American College of Rheumatology: thickened and symmetric induration of the skin of the fingers proximal to metacarpophalangeal or metatarsophalangeal joints (major criteria) or at least two of the following: sclerodactyly, digital pitting scar, bibasilar pulmonary fibrosis (minor criteria)4,5,6,7. Patient can be classified into two main subsets: Diffuse cutaneous scleroderma; rapid development of symmetric skin thickening, starting in the fingers and ascending from distal to proximal extremities, face, and the trunk. Limited cutaneous scleroderma: skin involvement limited to face and extremity distal to elbows, better prognosis, has features of CREST syndrome (calsinosis, Raynaud’s, esophageal dysmotility, sclerodactily, telangiectasis)1,2,3,5,6. Incidence 20 new patients per million/year in the United States, 4–5 times more common in women than men, the average age of diagnosis is 30-50 years.3,8 Laboratory clue: anti Scl 70, anti centromere1,2,3,9,10. There is no cure for scleroderma, but many of its problems and complications can be treated1,2,3.

A Female, Mrs DH 45 years with main complain digital ulcers that doesn’t healed, along with hard lumps for 1 year. Thickening, tightening of the skin on the hands and feet for 2 years. Fingers blanch when weather and cold air and return to normal after 1 hour when heated for 3 year. Stiffness and painful joints in the hands, feet and hip joint for 2 year, Limitation of motion and mouthfish 1 year. On physical examination found Pursed lip. Digital ulcer and Calsinosis on the digitii II-III manus dextra and digitii III sinistra, digitii II pedis dextra and sinistra. Sclerodactily on fingers and toes. Raynaud’s Phenomenon(+), The laboratory found positive ANA test: 178 (strong>60). Histopathological of the skin: scleroderma. Radiology of thorax: cardiomegaly. Radiology on pelvic: OsteoArthritis on right hip joint. Echocardiografi: Pulmonary Arterial Hypertension. Patient diagnosed with CREST syndrome and was treated with meloxicam 1x7,5 mg, nifedipin 3x10mg, metotrexate 1x7,5 mg/week, klindamisin 4x300 mg. Topical: Compress nacl 0,9% + gentamisin zalf. After 30 days of treatment showed clinical improvement.
INTRODUCTION

Systemic sclerosis (SSc / Scleroderma) is chronic autoimmune disorder such as connective tissue disorder of unknown etiology, heterogenous clinical manifestations and often progressive course. The distinctive involvement of multiple internal organs, most notably the lungs, gastrointestinal tract, heart, and kidneys. The word scleroderma literally means "hard skin" and describes the most dramatic clinical feature of the disease namely, skin fibrosis. The early stage of the disease, associated with prominent inflammatory features, is followed by the development of widespread functional and structural alterations in multiple vascular beds and progressive visceral organ dysfunction due to fibrosis. The presence of thickened skin (scleroderma) distinguishes SSc from other connective tissue diseases.

Scleroderma cases were first reported by Carlo Curzio in 1753 in Naples that affects women 17 years of age. Relationship scleroderma with Raynaud's Phenomenon, first reported by Maurice Raynaud in 1865. Then in the following year is known that the disease also attacks to the visceral organs. In 1945, Goetz proposes the term progressive systemic sclerosis lesions which describes a broad, both in the skin and visceral organs. In 1964, Winterbauer describe one variant of scleroderma is called CRST syndrome (Calsinosis, Raynaud's Phenomenon (RP), Sclerodactily and Telangiectasias). In 1979, CRST was expanded to CREST by Shulman’s group, also at johns Hopkins, who added esophageal involment to the cardinal manifestations. Incidence 20 new patients per million per year in the United States, 4–5 times more common in women than men. The average age at the time of diagnosis is approximately 30-50 years.

A comprehensive view of the pathogenesis of SSc must take into account the three cardinal features of the disease: (1) vasculopathy, (2) cellular and humoral immunity, and (3) progressive visceral and vascular fibrosis in multiple organs. Autoimmunity and altered endothelial cell function and vascular reactivity may be the earliest manifestations of SSc. Complex interplay between these processes is thought to initiate and then amplify and sustain the fibrotic process.

Diagnostic criteria by The American College of Rheumatology: thickened and symmetric induration of the skin of the fingers proximal to metacarpophalangeal or metatarsophalangeal joints (major criteria) or at least two of the following: sclerodactyly, digital pitting scar, bibasilar pulmonary fibrosis (minor criteria).
Scleroderma can be classified into Two main subsets:

1. **Diffuse cutaneous scleroderma**—rapid development of symmetric skin thickening, starting in the fingers and ascending from distal to proximal extremities, face, and the trunk. At high risk for development of visceral disease early in course.

2. **Limited cutaneous scleroderma**—skin involvement limited to face and extremity distal to elbows; associated with better prognosis; frequently has features of CREST syndrome (calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasias)\(^1,2,3,5,7,9\).

There is no cure for scleroderma, but many of its problems and complications can be treated\(^1,2,3\).

**CASE**

A Female, Mrs DH 45 years came to the H. Adam Malik general hospital Medan on November 2015 with the main complaints digital ulcers that doesn’t healed, along with hard lumps for 1 year. Thickening, tightening of the skin on the hands and feet for 2 years. Fingers blanch when weather and cold air and return to normal after 1 hour when heated for 3 year. Stiffness and painful joints in the hands, feet and hip joint for 2 year, Limitation of motion and mouthfish 1 year.

On status present found compos mentis sensorium, blood pressure 139/77 mmHg, pulse 86 x/minute; regular, respiration 18 x/minute, and temperature 37\(^0\)C. Physical examination found Pursed lip. Digital ulcers and Calcinosis on the digiti II-III manus dextra and digiti III sinistra, digiti II pedis dextra and sinistra. Sclerodactily on fingers and toes. Raynaud’s Phenomenon (+).

The laboratory found Hb 10,7 g/dl, leucocyte 14,790/mm3, platelet count 474,000/mm3. Urea : 38 mg/dl; creatinine: 0.5 mg/dl. Fasting plasma glucose : 70 mg /dl, Na : 143 mEq/l; K : 4,1 mEq/l, CRP qualitative : negative, positive ANA test: 178 (strong >60), Results of histopathological examination of the skin : from skin tissue preparations with chisel-lined epithelium lining the experience hyperkeratosis with shortening reteridge, subepidermis was thickened fibrous connective tissue that contains collagen and consists of the core fibrocyte and fibroblasts, it is also evident exocrine glands and hair follicles, with conclusion : scleroderma. Radiology of thorax we found CTR 56%, with conclusion : cardiomegaly. Radiology on pelvic we found narrow joint space on the femoro acetabulum dextra, with conclusion : OsteoArthritis on right hip joint. Echocardiografi we found Mean
Pulmonary Arterial Pressure 33 mmhg (>25mmhg), with conclusion early Pulmonary Arterial Hypertension.

Patient diagnosed with CREST syndrome and was treated with meloxicam 1x7.5 mg, nifedipin 3x10 mg, metotrexate 1x7.5 mg/week. Klindamisin 4x300 mg. Topical: compress nacl 0.9% + gentamisin zalf. After 30 days of treatment showed clinical improvement.

DISCUSSION

Systemic sclerosis (SSc / scleroderma) is a chronic autoimmune disorder of unknown etiology with characterized by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs, most notably the lungs, gastrointestinal tract, heart, and kidneys. The word scleroderma literally means "hard skin" and describes the most dramatic clinical feature of the disease—namely, skin fibrosis. The early stage of the disease, associated with prominent inflammatory features, is followed by the development of widespread functional and structural alterations in multiple vascular beds and progressive visceral organ dysfunction due to fibrosis.

Two main subsets of Systemic Sclerosis: Limited cutaneous systemic sclerosis (lcSSc) is characterized by skin disease that does not progress proximal to the elbows or knees. A subset of this condition is the CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome. Diffuse cutaneous systemic sclerosis (dcSSc) is characterized by skin thickening that involves areas proximal to the elbows and/or knees.

Clinical Manifestation of scleroderma;

**Skin:** Patients are at risk for the development of rapidly progressive acral and trunk skin thickening and early visceral abnormalities. Skin and visceral changes tend to parallel each other in severity, but not always. Some patients have rapid progression for 2 to 3 years and then arrest of the disorder, allowing for some improvement of the disorder.

**Raynaud phenomenon:** occurs in almost all patients. It usually occurs more than 2 years before skin changes. The vasospasm in the hands can be associated with reduced perfusion to the heart, lungs, kidneys, and gastrointestinal tract. If Raynaud phenomenon is not present but skin findings are suggestive of scleroderma, another disease such as eosinophilic fasciitis should be considered.
Articular: Non deforming symmetric polyarthritis similar to rheumatoid arthritis may precede cutaneous manifestations by 12 months. Patients can have both articular erosions and nonarticular bony resorptive changes of ribs, mandible, radius, ulna, and distal phalangeal tufts which are unique to systemic sclerosis. Up to 60% of patients have “leathery” crepitation of the tendons of the wrist.

Pulmonary: A considerable decrease in diffusing capacity can be present with a normal chest radiograph. Diffuse interstitial fibrosis occurs in approximately 70% of patients and is the most common pulmonary abnormality. There are two main types of significant pulmonary involvement: ILD (Intertitial Lung Disease) and PAH (Pulmonary Arterial Hypertension). Pleuritis (with effusion) is very rare. PAH is more common in patients with CREST variant.

Cardiac: occur in up to 70% of patients. Conduction defects and supraventricular arrhythmias are most common. Pulmonary hypertension with cor pulmonale is the most serious problem.

Gastrointestinal: Esophageal dysfunction is the most frequent gastrointestinal abnormality. It occurs in 90% of patients and often is asymptomatic. Lower esophageal sphincter incompetence with acid reflux may produce esophageal strictures or ulcers. Medications to reduce acid production are important. Reduced esophageal motility may respond to therapy with metoclopramide, cisapride, or erythromycin. Small bowel hypomotility may be associated with pseudo-obstruction, bowel dilatation, bacterial overgrowth, and malabsorption. Treatment with tetracycline may be helpful, but promotility agents are less effective. Colonic dysmotility also occurs, and wide-mouthed diverticuli may be found.

Renal: Renal involvement may result in fulminant hypertension, renal failure, and death if not treated aggressively. Proteinuria, newly diagnosed mild hypertension, microangiopathic hemolytic anemia, vascular changes on renal biopsy, and rapid progression of skin thickening may precede overt clinical findings of renal crisis.

Laboratory Findings: Limited scleroderma is associated with an early rise in ANA levels. The overall sensitivity of ANA in systemic sclerosis is 85%. Anticentromere antibody are present in 82-96% of patients with the CREST varian. Anti topoisomerase I antibody (anti-Scl-70) is found in approximately 25% of patients with scleroderma.

In this case,

Management of systemic scleroderma
1. Counseling and psychosocial support

Patients should know the diagnosis of the disease and systemic problems. Although there
is no drug that is effective and can make symptoms healed and looks normal, but treatment can be done so that the complications of the disease can be prevented and better quality of life. Counseling and psychological support plays a very important in the management of the disease because the disease is long and progressive.

2. Management of the skin and joints
The skin of scleroderma patients often dry and itchy. Patient should be advised not to scratch, do not wear tight shoes and easily cause irritation. Lanolin oily and very useful as well as an ointment to soften the skin. Digiti ulcer should be cleaned carefully with peroxidase and lotion Eusol. Keeping warm limbs and therapy to accelerate healing Raynaud's phenomenon. Arthralgia/arthritis and tenosynovitis treatment by providing a non-steroidal anti-inflammatory (NSAID)s. If pain persists, it can be considered a local steroid injections or small doses of systemic steroids (prednisone <10 mg/day) for a short time. Physiotherapy can be performed in patients with contractures of periarticular fibrosis that causes disability flex and straighten the fingers.

3. Management of Raynaud's phenomenon
Raynaud's phenomenon is a dominant symptom in systemic sclerosis. Avoiding smoking and cold air, as well as keep your body in warm, usually quite effectively cope with Raynaud's phenomenon were mild and moderate. In severe circumstances, such as when accompanied by ulcers on the fingertips or interfere with daily activities, can be attempted use of vasodilators, such as nifedipin, prazosin, or topical nitroglycerin. The use of slow release nifedipine showed good results with a hypotensive effect. In addition, nifedipine also can improve myocardial perfusion in systemic sclerosis. Other drugs that can be tried to cope with Raynaud's phenomenon is iloprost, a prostacyclin analogue. The drug is administered at a dose perdrrip 0,5-2 ng/kg/min, 5-8 hours/day for 6 h (iv) 5-10 days. In addition, to cope with Raynaud's phenomenon, this drug can also be used to treat ulcers on the fingers.

4. Drug Agent
Various classes of drugs that can be given to scleroderma patients are : Antifibrotik Therapy (D-penicillamine, penecilin G). D-Penicillamine, showed good results to tackle skin disorders in systemic scleroderma, although treatment is needed in the long term. In vitro, interferon gamma can inhibit fibroblast proliferation and collagen production.

5. Immunomodulation ( Immunotherapy) : Activation of the immune system plays a role in the onset of disease and organ damage. Immunotherapy in scleroderma include the use of nonselective immunosuppressive drugs (methotrexate (MTX), MMF, azathioprine,
cyclophosphamide) and soon as well as selective immunosuppressive drugs such as immunotherapy by targeting the T cells such as cyclosporine A, sirolimus (rapamycin), antithymocyte globulin (ATG), basiliximab, abatacept, and extracorporeal alfafacept photonunotherapy or phophopheresis (ECP). Immunotherapy by targeting the B cells (rituximab anti-CD20); Intra venous immunoglobulin (IVIG); cell-based immunotherapy of autologous and allogenic hematopoietic namely stem cell transplantation (HSCT), such as anti-TNF biologic immunotherapy-α (infliximab), tyrosine kinase inhibitor (imatinib). Methothrexate (dose : 10-15 mg/week) can reduce the spread of damage to the skin, in the case of scleroderma-myositis and inflammatory arthritis. If the response is not adequate treatment within 3-6 months then consider replacing treatment with MMF (2-3 g/day). Indications are corticosteroids on inflammatory myositis, active fibrosing alveolitis (interstitial lung disease), symptomatic serositis, edematosus phase of skin disorders and arthritis refractory.

6. Management of complication : Patient with early PAH (Pulmonary arteial hypertension) are generally asymptomatic. PAH can be given nifedipine. Gastrointestinal problems such as dysphagia and reflux esophagitis can be treated with H2 blockers such as cimetidine and ranitidine, antacids and cytoprotective drugs. In severe circumstances, may be recommended administration of omeprazole. Practical actions such as preventing eating a lot before bedtime and elevating the head while sleeping to prevent reflux esophagitis helpful. Bowel disease with malabsorption syndrome can be treated with antibiotics are cyclic. Restricting the enterostomy and alimental can be used. ACE-inhibitors may be given to control hypertension and prevent progressive kidney disease1,2,3.

In this case

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Rheumatology Division

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CONCLUSION

We reported a case of CREST syndrome in a female, 45 years old based on clinical features and investigation. Patients given immunosuppressant therapy, then it is recommended for clinical improvement.
DAFTAR PUSTAKA