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Case report
Prikaz slučaja
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LIMITED SCLERODERMA – A CASE REPORT

OGRANIČENA SKLERODERMA – PRIKAZ SLUČAJA

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Summary
Introduction. Systemic sclerosis is a rare autoimmune disorder of the connective tissue, gastrointestinal tract, lungs, kidneys, and musculoskeletal tissue. It predominantly affects women. The localized variant is limited scleroderma. **Case Report**. We present a 64-year-old female patient with the diagnosis of limited scleroderma that has lasted for thirteen years. She had hyperpigmentation, telangiectasias, and progressive skin tightening of the face and fingers. Her blood test was positive for antinuclear antibodies. Sclerodactyly began in the distal phalanx. Tender and painful calcium deposits appeared subcutaneously on the surface of palms and knees, radiographically confirmed. The patient was treated with surgical debridement, vasodilating agents, corticosteroids, diltiazem, sildenafil, nitro paste, antiplatelet drugs, and physical therapy. **Conclusion**. It is necessary to control numerous factors that affect daily functioning, including nutrition, pain therapy, musculoskeletal dysfunctions, and emotional and social aspects caused by deformities. Targeted therapy in the early stages of the disease, before irreversible damage occurs, improves the overall quality of life.
Key words:Scleroderma, Limited; Calcinosis; CREST Syndrome; Autoimmune Diseases; Risk Factors

Sažetak
Uvod. Sistemska skleroza je redak autoimuni poremećaj vezivnog tkiva, gastrointestinalnog trakta, pluća, bubrega i koštano-zglobnoh tkiva. Pretežno obolevaju žene. Lokalizovana varijanta bolesti je ograničena skleroderma. **Prikaz slučaja**. Predstavljamo pacijentkinju starosti 64 godine, sa dijagnozom ograničene skleroderme koja traje 13 godina. Postojale su hiperpigmentacija, teleangiektazije i progresivno zatezanje kože lica i prstiju. Uzorak krvi je bio pozitivan na antinuklearna antitela. Sklerodaktilija je započela na distalnim falangama prstiju. Osetljive i bolne naslage kalcijuma pojavile su se supkutano na površini dlanova i kolena, radiografski potvrđene. Pacijentkinja je lečena hirurškim uklanjanjem depozita, vazodilatatornim agensima, kortikosteroidima, diltiazemom, sildenafilom, nitro-pastom, antitrombocitnim lekovima i fizikalnim terapijama. **Zaključak**. Potrebno je kontrolisati mnogobrojne faktore koji utiču na svakodnevno funkcionisanje, uključujući ishranu, terapiju bola, disfunkciju mišićno-skeletnog sistema, emocionalne i socijalne aspekte uzrokovane deformitetima. Ciljana terapija zahvaćenih organa u ranom stadijumu bolesti, pre nego što nastupe nepovratna oštećenja, poboljšava ukupan kvalitet života.
Ključne reči: ograničena skleroderma; kalcinoza; CREST sindrom; autoimuna oboljenja; faktori rizika

Introduction

Systemic sclerosis is a rare autoimmune connective tissue disorder. The prevalence is estimated at 1/12,500 adults, with a higher incidence among women (female to male ratio around 4:1) [1, 2]. It typically affects various organs, including the skin, gastrointestinal system, lungs, kidneys, skeletal muscle tissue, and pericardium. Systemic sclerosis or scleroderma is a generalized form, whereas limited scleroderma, also known as calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias (CREST) syndrome, is the localized variant [3]. Limited scleroderma may lead to the development of progressive pulmonary arterial hypertension, rarely seen in diffuse scleroderma, with a prevalence of 10% [3]. Prominent findings include the intimal proliferation of small and medium-sized pulmonary arteries. While biliary cirrhosis is uncommon in systemic sclerosis, it may develop in limited scleroderma. Various peripheral nervous system symptoms are associated with direct auto-inflammatory processes, vasculitis, or median neuropathy due to compression [1, 3]. In this report, we present a case of limited scleroderma and provide a summary of current knowledge about its treatment, along with all the criteria for its definition.

Case Report

We present a 64-year-old woman with a diagnosis of limited scleroderma. The first symptoms appeared on the acral areas of the hands thirteen years ago. She visited a primary healthcare physician due to numbness in the fingers and toes upon exposure to cold, which resulted in discoloration of her digits from white to blue. Upon exposure to warmth, her digits became red, painful, swollen, and stiff. After physical examination, the primary healthcare physician found telangiectasia in the skin on the palms, and sclerodactyly, which started in the distal fingers of both hands. Skin thickening was also observed on

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Abbreviations
CREST – calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias

the hands. The laboratory tests showed abnormal results for the following: erythrocyte sedimentation rate of 66, red blood cell count of 3.7 x 10^{12}/L, hemoglobin level of 8.8 g/L, positive antinuclear antibody 1:580 with a centromere pattern, and negative anticentromere antibody. There was no family history of a similar condition, and the patient reported no other serious diseases. According to physical examination and laboratory test results, Raynaud's phenomenon was suspected and a rheumatologist was consulted. During the diagnostic procedures, the rheumatologist found nail fold capillary abnormalities, and no pathologic radiologic findings. As she met at least 3 of the following clinical features: Raynaud's phenomenon, sclerodactyly, and telangiectasia, the diagnosis of limited scleroderma was made by a rheumatologist, three months after consulting the primary healthcare physician. In the first stage of the disease, the patient received anti-inflammatory drugs, vasodilators, hydroxychloroquine, anti-anemic drugs, corticosteroid hand creams, and was advised to wear gloves and warm socks when cold, physical therapy and regular exercise, avoid smoking, stress, and eliminate sympathomimetic medications.

The face was affected five years after the appearance of the first symptoms. The facial skin was tight, thin, and hard, which made it look smaller, and wrinkles appeared around the mouth. A dry mouth caused difficulty smiling, laughing, talking, and chewing food. The patient also developed firm yellowish nodules on the finger joints and had regurgitation after large meals. She also reported difficulty swallowing and heartburn, and additional tests were performed to identify any complications related to the lungs, heart, and gastrointestinal system. Esophageal dysfunction was found using esophagogastroduodenoscopy and it was treated with proton pump inhibitors and prokinetic agents, in addition to the therapy she was already using. At that stage of the disease, she complained about muscle weakness.

In 2019, the patient reported tender and painful subcutaneous calcium deposits with a chalk-like consistency on the palms and knees. The X-ray showed calcinosis of variable opaque densities ranging in size from 10 x 10 to 10 x 15 mm lying superficially within the soft tissues **(Figure 1)**.

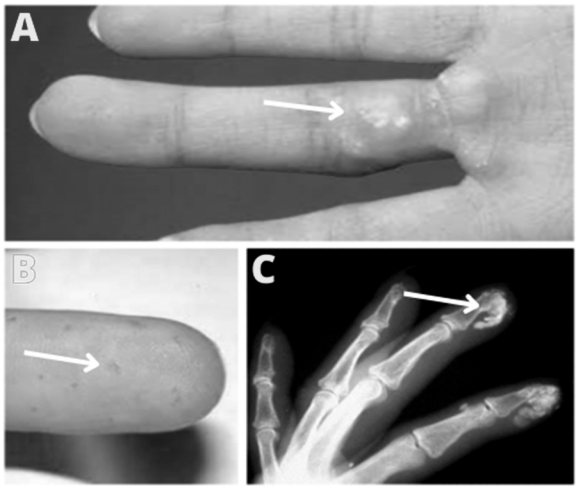

Figure 1. Calcinosis of the right hand (A); Telangiectasias of the left hand (B); Left hand X-ray shows calcification (C)
Slika 1. *(A) Kalcinoza na desnoj šaci; (B) teleangiektazije na levoj šaci; (C) radiografija leve šake prikazuje kalcifikaciju*

The patient underwent surgical debridement due to infection, which was treated with antibiotics. Paraspinal calcifications also occurred, resulting in local pain and radiculopathy. Antinuclear antibodies (1:640) were consistent in the patient's blood, along with mild leukocytosis, normocytic anemia, thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein. The computed tomography did not indicate any lung fibrosis or pulmonary arterial hypertension. The patient received vasodilating agents, corticosteroids, diltiazem, sildenafil, nitro-paste, antiplatelet drugs, proton pump inhibitors, physical therapy, and hand and foot coverings. Regular multidisciplinary clinical follow-ups were necessary, which were coordinated by the primary healthcare physician.

Discussion

We presented a case of limited scleroderma from our clinical practice. Systemic sclerosis, also known as scleroderma, is an uncommon autoimmune disorder affecting connective tissues. Scleroderma can be classified into two main types: diffuse scleroderma

Table 1. CREST Syndrome
Tabela 1. *CREST sindrom*

(**C**) - Calcinosis ***(C)*** *- Kalcinoza*	Calcium deposits in the connective tissues *Depoziti kalcijuma u vezivnom tkivu*
(**R**) - Raynaud's phenomenon ***(R) -*** *Rejnoov fenomen*	Fingers and toes turn white and cold and then blue *Prsti na rukama i nogama postanu beli i hladni, potom modri*
(**E**) - Esophageal dysfunction ***(E) -*** *Disfunkcija jednjaka*	Swallowing difficulties *Poteškoće pri gutanju hrane*
(**S**) - Sclerodactyly/***(S) -*** *Sklerodaktilija*	Thick and tight skin on the fingers/*Debela i zategnuta koža na prstima*
(**T**) - Telangiectasias/***(T) -*** *Teleangiektazije*	Small red spots on the hands and face/*Male crvene mrlje na rukama i licu*

or systemic sclerosis, and localized scleroderma or limited scleroderma, which is characterized by calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias [4]. Scleroderma primarily affects organs such as the skin, gastrointestinal tract, lungs, kidneys, skeletal muscles, and pericardium [1]. Patients with CREST syndrome must meet at least three of the clinical features shown in **Table 1**, according to the American College of Rheumatology classification criteria [5].

In contrast to diffuse scleroderma, limited scleroderma affects only the skin of the extremities and is associated with a gradual and less severe progression of internal organ involvement. Calcinosis is a common complication and 22% of patients develop this condition within the first or second decade after diagnosis [6]. Despite normal calcium metabolism, chronic ischemia can lead to the calcium deposition in inflamed tissues. The subcutaneous tissues and fascia of the hands and feet, as well as the extensor surfaces of the forearms, elbows, and knees, are particularly prone to developing these deposits due to recurrent microtrauma [7]. Although calcific deposits can be asymptomatic, they may be tender and painful and can lead to ulceration, drainage of a chalky substance, and secondary infection. Paraspinal calcifications are rare, but can cause local pain, radiculopathy, and diffuse weakness [8].

Pharmacological treatment methods have been used to treat calcinosis, but there is no effective treatment to date. A variety of drugs such as warfarin, colchicine, probenecid, bisphosphonates, minocycline, salicylates, aluminum hydroxide, and diltiazem have been studied, but their effectiveness is variable [9]. Surgical intervention is necessary for distinct deposits accompanied by extrusion, wound infection, or discomfort. However, asymptomatic deposits should not be excised as they tend to recur.

Raynaud's phenomenon is common in individuals with scleroderma, affecting 96.3% of patients, and it is characterized by excessive vasospastic response to stress or exposure to cold [7]. This phenomenon results in the hands and digits turning cyanotic, pale, and flushed [7]. Esophageal dysfunction is also common, with 90% of cases caused by smooth muscle atrophy in the lower two-thirds of the esophagus. Gastrointestinal reflux caused by esophageal dysfunction can lead to Barrett's esophagus, esophagitis, hemorrhage, and/or strictures [6]. Another hallmark of scleroderma is sclerodactyly, which involves swelling, glossy skin, difficulty bending, and contractures in the fingers [1].

Telangiectasia occurs due to vascular dysfunction, intimal proliferation, thrombosis, and vasospasm. These are caused by abnormal vascular endothelial cells with mononuclear infiltration, disturbances in type 1 T helper and type 2 T helper cells activity, and abnormal fibroblast activity leading to increased collagen deposition [10]. Although biliary cirrhosis is uncommon in systemic sclerosis, it may occur in limited scleroderma. Pulmonary hypertension typically occurs in the absence of interstitial fibrosis (in 3 - 14% of cases) [8]. While seizures and headaches are the most common neurological symptoms in limited scleroderma, involvement of the peripheral and autonomic nervous systems is more common in systemic sclerosis [1].

To diagnose scleroderma, a comprehensive diagnostic approach includes physical examination and additional diagnostic testing. In particular, the presence of anticentromere antibodies is found in a large proportion of patients, ranging from 82 - 96%. However, this test is typically negative in cases of limited scleroderma. Additionally, various nonspecific indicators of inflammation, such as leukocytosis, normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein, may be present and may help to make the diagnosis [11].

In the context of scleroderma, treatment involves various options, such as vasodilating agents, corticosteroids, diltiazem, sildenafil, topical nitroglycerin paste, antiplatelet drugs, physical therapy, and covering in case of Raynaud's phenomenon. However, there is currently no established treatment that can modify the overall course of the disease [1]. Nonetheless, organ-specific treatment can improve the quality of life and survival rate. For instance, in case of progressive pulmonary fibrosis, low doses of corticosteroids along with immunosuppressive agents are typically required. Pulmonary vasodilators are administered in case of pulmonary arterial hypertension. Given that scleroderma is a systemic disease with a variable clinical presentation, a multidisciplinary treatment approach is necessary, including early identification of affected individuals, prompt referral to rehabilitation, and attention to psychological comorbidities such as neuroticism and anxiety, which are closely related to somatization [12, 13].

Conclusion

This case report highlights the significance of a multidisciplinary approach in the management of limited scleroderma. The primary objective of treating limited scleroderma is to reduce the impact of specific organ involvement and enhance the quality of life. Several factors affecting the daily functioning of patients, including pain, musculoskeletal disuse, comorbidities, and emotional issues such as fear, depression, and social isolation caused by physical disfigurement, need to be addressed. Further studies are necessary to gain better understanding of this disease.

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