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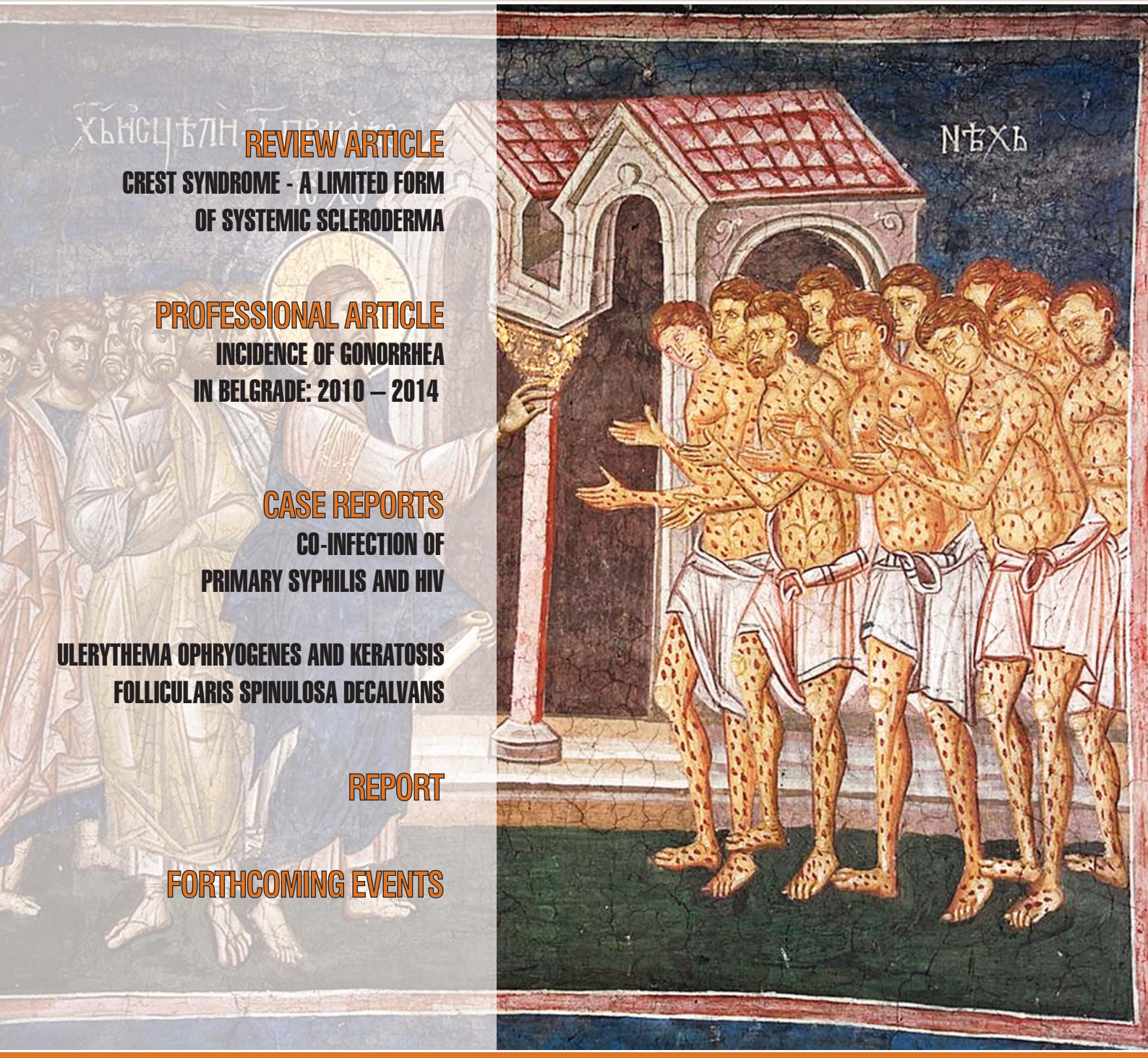



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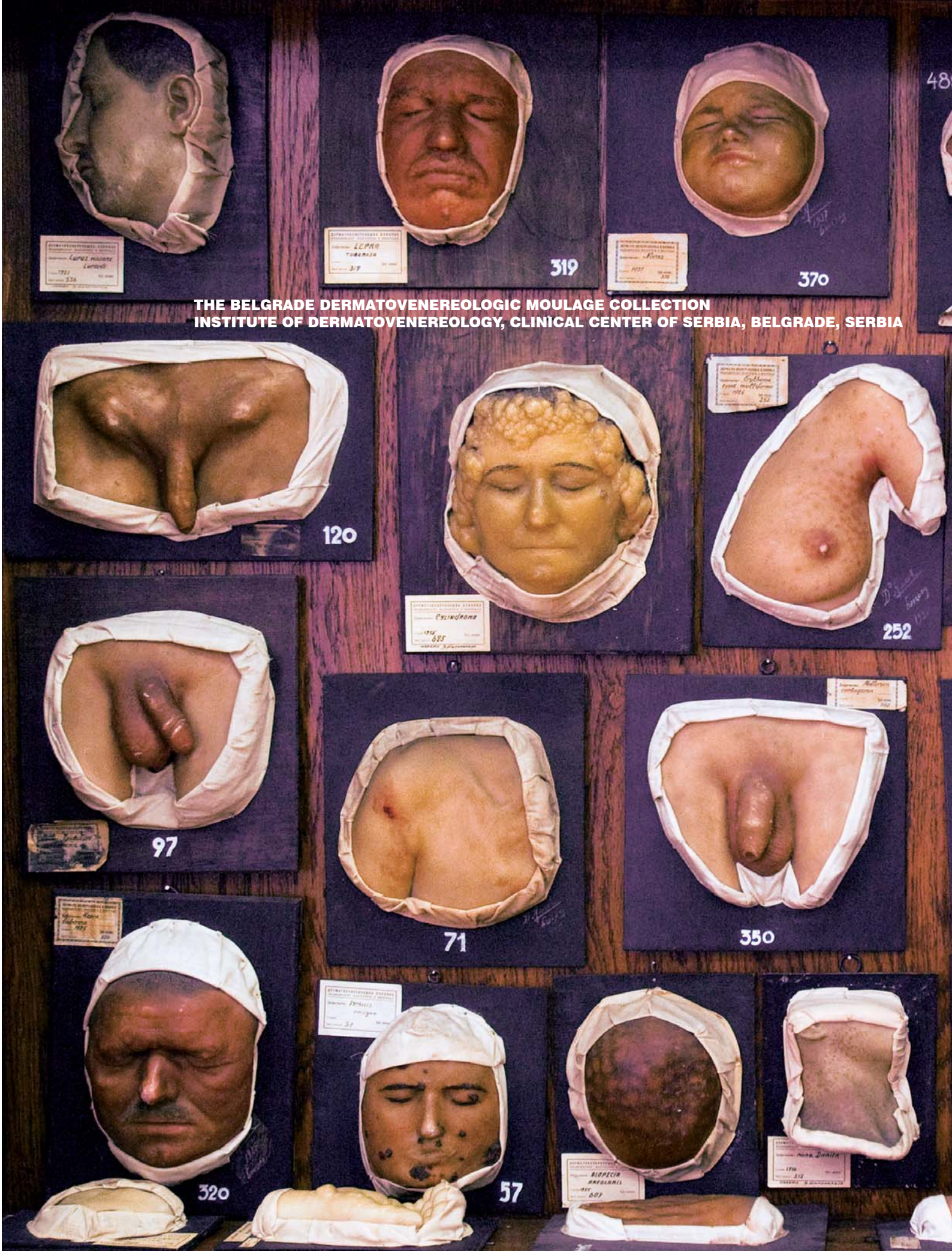


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# CREST Syndrome - a Limited Form of Systemic Scleroderma: a Case Report and Literature Review

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## Abstract

Systemic scleroderma (SSc) is a multisystem disease with microvascular abnormalities, autoimmune disorders, excessive collagen production and deposition, and fibrosis of the skin and internal organs. According to the simplest, though incomplete classification, there are two forms of SSc: diffuse and limited (formerly acrosclerosis). CREST syndrome is a subtype of limited SSc, characterized by: calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. We present a patient with all the features of the CREST syndrome, which appeared at the age of 43 and lasted for 23 years. The patient presented with a gradual development of symptoms during the first ten years, from Raynaud's phenomenon, skin sclerosis, calcinosis, telangiectasia, and esophageal dysmotility. The diagnosis was based on clinical findings and relevant diagnostic procedures. The article presents a literature review on the epidemiology, etiology, pathophysiology, clinical manifestations, various attempts at classification, diagnostic criteria, and therapeutic modalities.
When classifying systemic scleroderma into two main types — diffuse and limited, with CREST syndrome as a variant of the latter, it should be pointed out that both types represent clinical forms of systemic sclerosis, share similar visceral involvement, laboratory abnormalities and course which is variable, as was the case in our patient.

## Key words

Scleroderma, Systemic; CREST Syndrome; Signs and Symptoms; Diagnosis

Systemic scleroderma (SSc) is a multisystem disease with microvascular abnormalities, autoimmune disorders, excessive collagen production and deposition, fibrosis of skin and internal organs, with progressive course and potentially fatal outcome (1, 2, 3, 4).

Due to a wide variety of clinical manifestations, common resemblance or co-occurrence with other connective tissue diseases, attempts to develop an adequate classification have been made for years. In 1962, Tuffanelli and Winkelmann proposed three forms of scleroderma based on skin involvement and severity: 1. acrosclerosis, 2. diffuse scleroderma, and 3. acute diffuse scleroderma (5). In 1978, based on his experience, Barnett suggested three subsets: 1. sclerodactyly; 2. sclerosis limited to the forearms, without trunk involvement; and 3. diffuse skin involvement, including the trunk (6). In 1979, Rodnan and associates made a distinction between diffuse scleroderma and CREST syndrome (7). In 1980, Giordano et al. described four types of systemic sclerosis (SS): 1. no skin involvement (no scleroderma); 2. limited systemic cutaneous sclerosis (limited systemic scleroderma); 3. intermediate systemic cutaneous sclerosis (intermediate systemic scleroderma); 4. diffuse systemic cutaneous sclerosis (diffuse systemic scleroderma) (8). In 1988, LeRoy et al. proposed the simplest classification of systemic sclerosis: diffuse cutaneous SS (diffuse systemic scleroderma), and limited cutaneous SS (limited systemic scleroderma) (9).

In 1980, the Subcommittee for Scleroderma of the American Rheumatism Association (ARA) defined diagnostic and therapeutic criteria for the

 

classification of SSc (10), differentiating acral systemic scleroderma, or sclerodactyly and proximal systemic scleroderma; the single major criterion is scleroderma proximal to the digits, affecting the limbs, face, neck or trunk; or at least two minor criteria such as sclerodactyly or digital pitted scarring or bilateral basal pulmonary fibrosis. In 1996, the Committee of the American Academy of Dermatology proposed a comprehensive classification of cutaneous sclerosis in three large groups: A. primary cutaneous sclerosis, which includes diffuse systemic or limited systemic (CREST syndrome), localized or circumscribed without involvement of internal organs, part of the overlap syndrome (mixed and poorly differentiated connective tissue disease) and eosinophilic faciitis; B. secondary cutaneous sclerosis as a result of GVHD (graft versus host disease), use of medications, intoxication, infection; C. prodromal cutaneous sclerosis syndromes, primarily Raynaud's phenomenon (11). Apart from diffuse and limited systemic cutaneous sclerosis, in 2001, LeRoy and Medsger described also ectopic calcinosis and telangiectasias and limited unclassified prescleroderma, the so-called pre-systemic scleroderma (12). They introduced new criteria, including nailfold capillary microscopic abnormalities and the presence of autoantibodies, in order to establish patients with early limited systemic sclerosis without skin involvement. It is also called SS without skin involvement, visceral sclerosis, or SS sine scleroderma (13, 14).

In 2004, Maricq and Walter selected the following criteria for the classification of systemic sclerosis (SS): 1. sclerodermatous skin involvement; 2. microvascular abnormalities specific to SSc: SD-type nailfold capillary changes and/or CREST-type capillary telangiectasia; 3. presence of anticentromere antibodies (ACA) (14). Based on these criteria they proposed the following classification:

I Diffuse sclerosis (all three criteria)

II Intermediate sclerosis (2 criteria)

III Digital sclerosis (one criterion)

IV Sclerosis without skin involvement (none of the criteria)

V Insufficiently differentiated connective tissue disease with sclerosis (one or none of the criteria)

VI CREST (one or none of the criteria).

In 2007, Walker et al. adapted the LeRoy and Medsger classification which included the following types: limited systemic scleroderma, limited systemic scleroderma with cutaneous involvement, diffuse systemic scleroderma and diffuse fasciitis with eosinophilia (15).

Scleroderma spectrum disorders involve the existence of the following (16):

1. diffuse systemic sclerosis;

2. limited cutaneous systemic sclerosis with CREST syndrome as a variation;

3. systemic sclerosis sine scleroderma;

4. localized scleroderma with linear scleroderma;

5. mixed connective tissue disease with features of systemic sclerosis, polymyositis, and SLE.

6. overlap syndromes: systemic sclerosis plus polymyositis, rheumatoid arthritis, or SLE.

7. scleroderma mimics - amyloidosis, chronic graft-versus-host disease, diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome, nephrogenic fibrosing dermopathy, paraneoplastic syndromes, scleredema, scleromyxedema (papular mucinosis), toxic oil syndrome;

8. undifferentiated connective tissue disease: multiple nonspecific, serologic or clinical abnormalities that do not meet ACR (American College of Rheumatology) criteria for rheumatic disease.

We report a patient with limited systemic scleroderma - CREST syndrome.

## Case Report

A female patient, 66 years of age, first noticed skin changes at the age of 43. They progressed during the following 10 – 15 years, but after that time, they mostly persisted unchanged, with occasional bacterial and fungal secondary infections. The disease lasted for 23 years, and resulted in fatal outcome at the age of 66. In the last eleven years, she was hospitalized several times.

The first symptoms appeared on the acral areas of hands which were cold, turning white, purple then red. At first, the attacks were cold induced, later they became more frequent, regardless of the temperature, involving the toes as well. In the following two years, these were the only symptoms of the disease, but later the fingers got pale, hard, with impaired mobility,

subsequently leading to inability to fully stretch them, which significantly affected activities of daily living. The nails became thin and fragile. The skin of the distal portions of the arms and legs became thinner and tight. The involvement of the face started five years after the appearance of first symptoms; facial skin also became tight, thin and hard, without wrinkles. The face became smaller, wrinkles were prominent around the mouth, whereas dry mouth caused difficulties when smiling, laughing, talking or chewing food. Then, firm yellowish nodules developed on the finger joints, as well as large solid nodules on the shoulders and thighs. At that time, the patient started experiencing difficulties swallowing, heartburn, and regurgitation after large meals. No other organ involvement was reported.

The patient reported no serious illnesses. There was no family history of a similar condition.

*Physical examination*

Upon skin examination, the skin was pale, yellowish in color, thight, smooth, taut, and mask like. The face got smaller, with radial furrows around the mouth, causing the skin to stretch so that the few residual teeth were visible due to gingival retraction. The beaked nose and deep-sunken eyes have contributed to a typical "bird-like" face (Figure 1). The fingers were semiflex, very sclerotic, cold ("Madonna fingers"), tapered at the ends, with shortened distal phalanges, and apparent shortening of thinned nail plates (Figure 1). The dorsal sides of hands presented with small calcifications over the joints, above which the skin was paper thin and pale yellowish in color. Blotchy hyperpigmentation and telangiectasias were also present. The skin of the lower legs and feet exhibited similar characteristics, with pronounced telangiectasias in the form of spots or dark red lacy lines, with cyanosis, hypo- and hyper-pigmentation, and scars, while the nail plates were thickened (Figure 2). The interdigital areas were pesented with madidation and maceration, erythema, erosions and scaling due to secondary fungal infection. Both sides of the gluteal areas were affected by infiltrates with inflamed skin and fluctuation. There

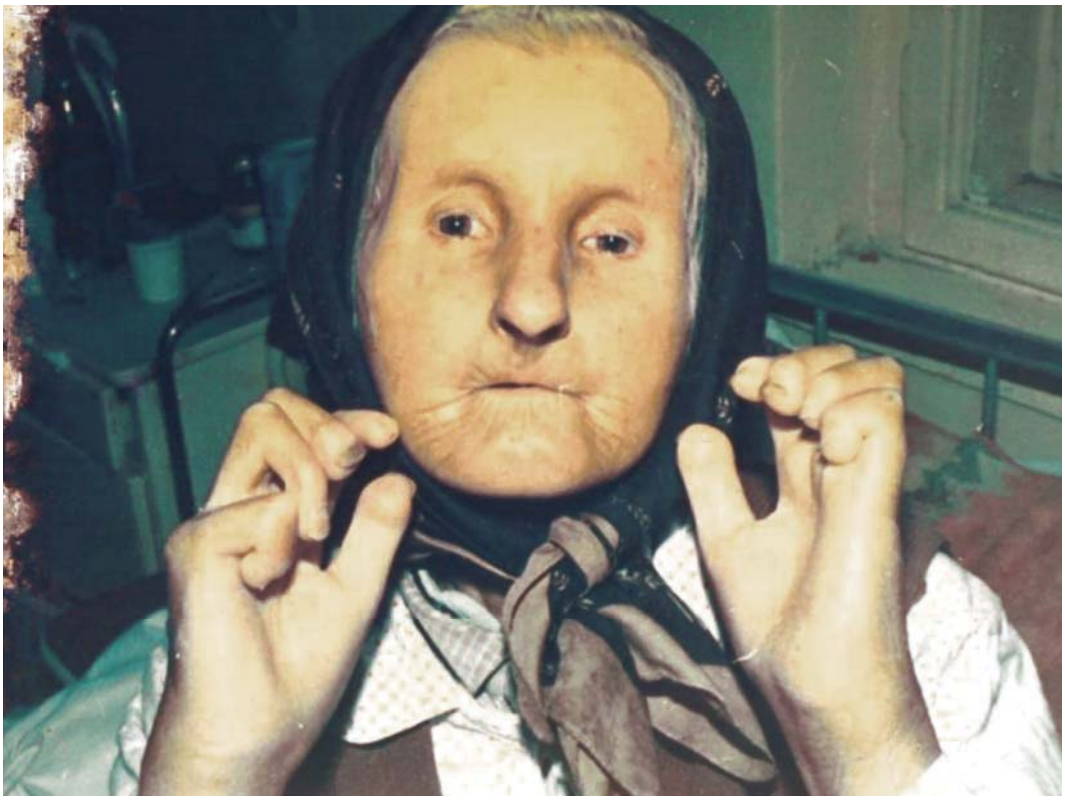

**Figure 1.** The face is tightening; the skin is thin, with radial furrows around the mouth, mask-like and expressionless. The fingers are semiflex, very sclerotic, with shortened distal phalanges, and apparent shortening of thinned nail plates

 

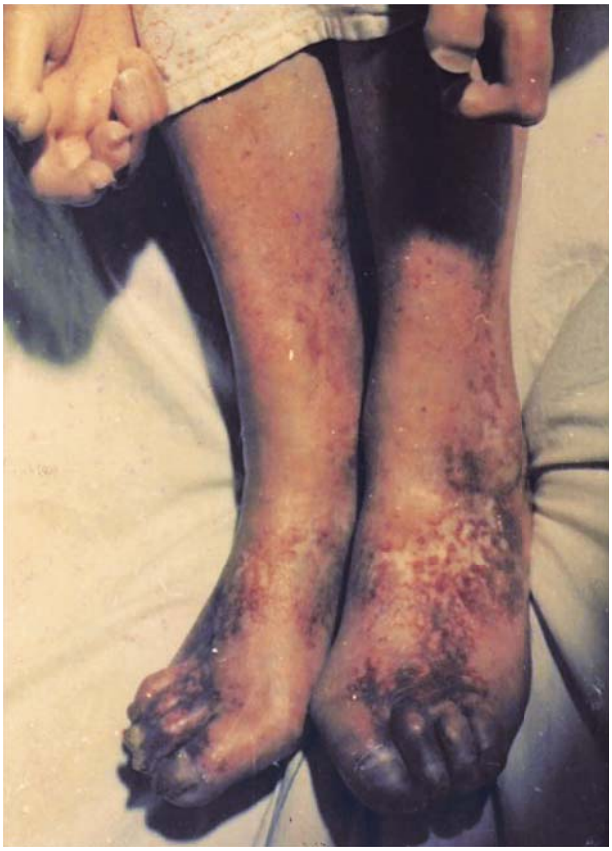

**Figure 2.** The skin of the lower legs and feet is thin, with pronounced telangiectasias in the form of spots or dark red lacy lines, with cyanosis, scars and nail abnormalities

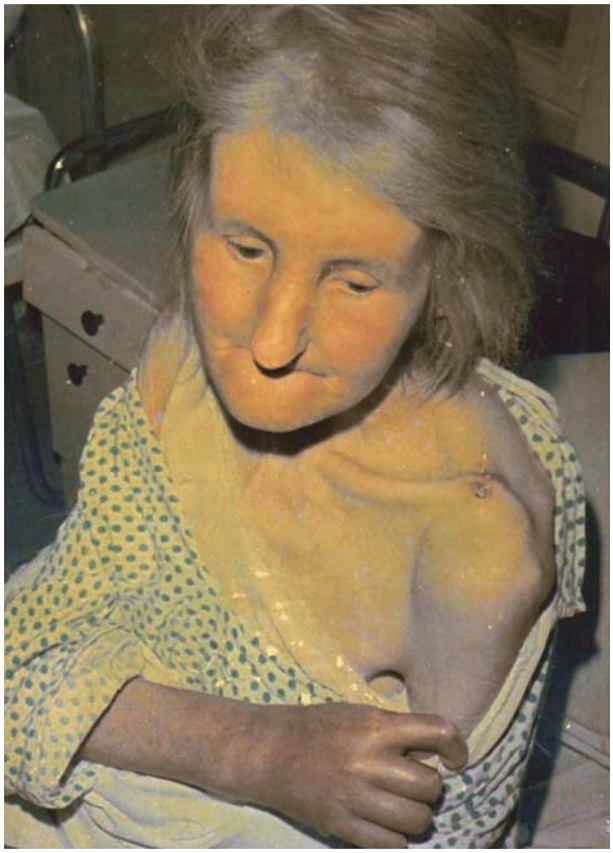

**Figure 3.** Calcifications are present on the left shoulder with a tendency to secretion

was a lesion secreting mucus and blood at pressure or spontaneously, and a chalky white material. After surgical intervention, the pseudofistula was closed, but in the area of the gluteus, indurations in the size of a walnut were palpable. The skin of the lower arms, upper arms and the trunk was affected to a lesser extent. Calcifications were present on the left shoulder with a tendency to secretion (Figure 3).

*Laboratory and other test results*

Laboratory investigations revealed the following abnormal tests: erythrocyte sedimentation rate 78/96, red blood cell count 2,87 x $10^{12}$/L, hemoglobulin 6,91 g/L, urinalysis revealing recurrent hemoglobulinuria, the urinary fractional 17-ketosteroids in 24 h urine - 2,6 mg/24 h (normally 16-18 mg/24 h).

Chest and heart X-ray findings: normal

Pelvis x-ray (2 views): lime salts (calcium apatite) are deposited in the gluteal soft tissues, presenting as grouped oval pinhead- or millet-sized shadows reaching the size of a ”green walnut”; lime salts are also observed in other parts of the pelvis (Figure 4). Esophageal peristalsis: the esophagus is normally positioned, dilated, without peristalsis or visible wrinkles, funnel-shaped in the kardia region, with slow flow of barium suspension (Figure 5).

*Therapy*

The patient received systemic therapy: antibiotics (penicillin, gentamicin), corticosteroids, progesterone, vasodilators (pentoxifylline), griseofulvin, and multi-vitamin preparations; corticosteroids and antimycotics were administered topically. Apart from successful management of the secondary infection, some improvement was achieved by progesterone: the skin was softer, finger mobility was slightly better, and the patient subjectively felt better. However, dissolution of calcifications was not achieved by the applied therapy.

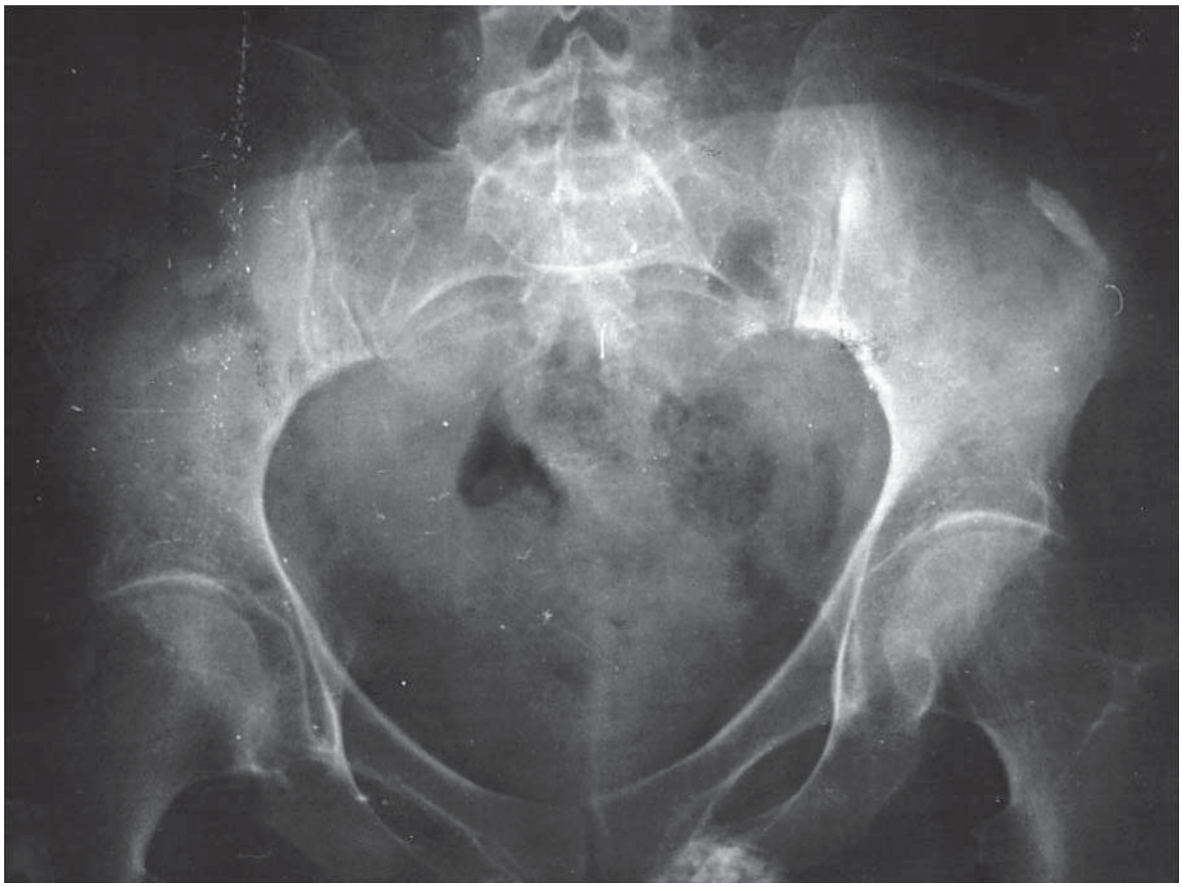

**Figure 4.** Pelvis x-ray revealing oval pinhead- or millet-sized, grouped shadows in the gluteal soft tissues

## Discussion and Literature Review

Systemic sclerosis (SS) is a rare disease that is more common among women than men, with the peak age of onset between 20 and 50 years (17). The true incidence and prevalence of the disease are unknown, mostly due to a small number of published epidemiological studies, a large variability in the clinical manifestations and severity of the disease, the difficulty in applying classification criteria, and the variability in the design and methods used in epidemiological studies (18). A group of French authors analyzed 32 articles published from 1969 to 2006 in which the prevalence of SSc (systemic sclerosis with sclerosis of the skin) (SSc) ranged from 7/million to 489/million and its incidence from 0.6/million/y to 122/million/y (18). The prevalence is higher in the US (276 cases per million adults) and Australia (233 cases per million) than in Japan and Europe (France, 158 per million, and England 88 per million). Higher prevalence was established in Afro Americans (315 cases per million) than in Caucasians (224.7 cases per million) (19). According to various studies, the female to male ratio ranges from 1.1: 1 (20) to 14: 1 (21). Earlier onset of the disease is found in women in regard to men (average age for men 58.9 ± 13.5 years, and 49.2 ± 15.7 years for women (22). SS is rare in children (23).

Systemic scleroderma (SSc) is a SS affecting the skin and a multisystem connective tissue disease of unknown etiology, but it is certainly associated with genetic factors, immune system alterations, and environmental factors (15, 18, 24). Its pathogenesis involves vascular abnormalities resulting in tissue hypoxia, immune responses manifesting with altered T- and B-lymphocyte functions and production of autoantibodies, through fibroblast dysfunction and excessive collagen synthesis (25, 26, 27). A wide variety of hypotheses have been offered to explain the pathogenesis of SSc (25).

 

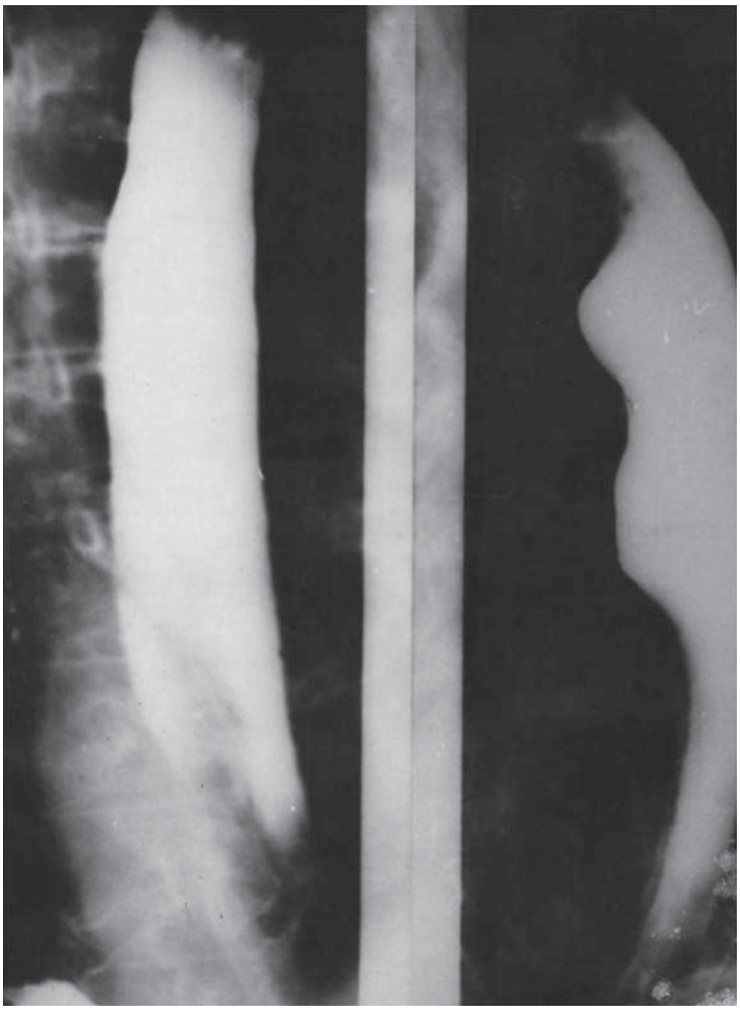

**Figure 5.** The esophagus is dilated, without peristalsis or visible wrinkles, funnel-shaped in the kardia region

Although familial cases of SSc are rare, a family case history is an important factor in the development of the disease (28). Genetic factors clearly influence disease susceptibility as a complex that includes a number of genes and chromosomal loci (24). The HLA (human leukocyte antigen) genes have been implicated in the susceptibility to SSc (29). Multiple genetic patterns in SSc, and various HLA alleles are associated with different clinical and serological aspects of this disease (30).

The immune hypothesis of SSc patho-genesis emphasizes the role of T cell-derived cytokines implicated in the damage of the blood vessels and indirectly tissue hypoxia; they also directly stimulate fibroblasts to increased collagen synthesis. T helper lymphocytes impair humoral immunity and increase in titer of antinuclear antibodies. The immune hypothesis and autoimmune events in the pathogenesis of the SSc is supported by: elevated serum interleukin-2 levels, activated lymphocytes in the biopsy specimens, activated monocytes in the peripheral blood, reduced number of CD8+ T lymphocytes, impaired function of NK (natural killer) cells, presence of various autoantibodies and immune complexes (25).

Some environmental factors may play a role in triggering SSc in persons with genetic predisposition, such as physical trauma (long-term exposure to vibration, burns) (11), viral infections (cytomegalovirus, parvovirus B19, herpes virus) or helicobacter pylori, toxic substances (vinyl chloride, some pesticides, benzene derivatives, silica, trichloroethylene, organic solvents, epoxy resins), and drugs (cocaine, appetite suppressants, penicillamine,

vitamin K, bleomycin, isoniazid) (11, 31, 32). Relations between systemic sclerosis and occupational exposure to certain chemicals as triggers of systemic scleroderma have been investigated, for example in construction workers and miners who work with explosives, but later studies showed this association to be unreliable (33). There are authors who believe that occupational exposure to organic solvents is not significantly associated with systemic scleroderma, and one should be cautious in interpreting the impact of organic solvents and certain chemicals on the development of scleroderma in textile workers (34).
According to the vascular hypothesis of the SS pathogenesis, primary changes affect the blood vessels (intimal thickening and vessel lumen occlusion). Endothelial cells are among the first targets, or primary dysfunctional cells in this disease (35). Precapillar sphincter dilation causes microvascular hypertension, swelling, telangiectasia, and later arteriolar hyperplasia and fibrosis. It is possible that blood vessel insufficiency causes tissue injury, whereas fibrosis is a part of the reparation process. Excessive collagen production results in fibrosis of the skin and internal organs; collagen (types I, III, IV, and VII), fibronectin, glycosaminoglycans, and proteoglycans are deposited in the interstitium and in the intima of small arteries (36). Collagen deposition may be caused by increase in the number of fibroblasts which produce collagen, or increased collagen production in fibroblasts, but also by reduced collagen degradation.

**The acronym CREST** stands for calcinosis, Raynaud's phenomenon (RPh), esophageal dysmotility, sclerodactyly, telangiectasia syndrome, and dates back to the twentieth century: in 1911, Thibierge and Weissenbach described a patient with skin calcinosis, RPh, sclerodactyly and telangiectasia, and named it CRST syndrome (37). In 1964, Winterbauer registered esophageal dysmotility in 4 of his 8 patients with CRST syndrome (38), and in 1973, Frayha et al. proposed the acronym CREST, due to common occurrence of esophageal dysmotility (39). Later, various combinations of these clinical manifestations have been described, including REST syndrome (without calcinosis), CRest, "Pure" CREST (in patients with two or more symptoms of CREST, but not enough criteria for limited or diffuse systemic sclerosis), "Plus" CREST (association with other forms of systemic scleroderma - limited or diffuse, or with other autoimmune diseases) (40). Our patient was diagnosed with CREST syndrome, fulfilling all criteria. Due to common absence of some manifestations, some authors believe it is more correct to speak about limited cutaneous scleroderma, and that presence of two of five manifestations is sufficient (3), however, this is unlikely to be a separate syndrome distinct from systemic sclerosis, but only a subgroup of systemic sclerosis (41).

Calcinosis is one of the typical manifestations of CREST syndrome, but it may occur in all types of scleroderma. Calcinosis occurs in about 25% of patients with limited SSc and it can be associated with problems of poor peripheral circulation, causing local skin irritation, inflammation, ulceration and encouraging secondary infection (42). Calcinosis generally results from dystrophic calcification associated with massive collagen degeneration (43). Cutaneous deposition of calcium salts in the skin occurs in a variety of clinical settings, beginning as a calcium phosphate nidus and progressing to hydroxyapatite crystal formation within a collagen matrix (43). Dystrophic calcification is due to accumulation of calcium apatite crystals, with normal levels of serum calcium, phosphorus, and alkaline phosphatase (44). Calcium deposits develop in the skin, as subcutaneous nodules or massive nodes, mainly in the elbows, knees, fingers and toes, but also in other body areas (45). Sometimes they are visible, sometimes just palpable. The overlying skin is thin and often painful. The lumps may break through the skin and leak a chalky white liquid. Secondary infections and inflammations are not uncommon (26). Our patient presented with multiple calcifications of various localization and size, and at one point she needed surgical intervention.

Raynaud's phenomenon (RPh) causes numbness, pain and color changes in fingers in a large number of patients with limited SSc (46). It was first described by Maurice Raynaud in 1862 (47). It is usually the first and often the only symptom of scleroderma for many years, hence its central role in diagnosis of SSc (45). It is usually triggered by exposure to cold or emotional stress; due to spasm of small blood vessels (capillaries) one or more fingers suddenly turn white, become cold and insensitive (48). After a few minutes or longer, lack of oxygen in the blood causes cyanosis and pain in the fingers, but when the circulation gets normal, hyperemia occurs and the skin gets red (49). Between

 

episodes the patient is symptom free (26). Secondary RPh is typical for collagen and vascular diseases; it is usually asymmetric and may be accompanied by ulcerations or necrosis. Primary RPh affects younger individuals, after stressful events or exposure to cold; changes are symmetrical without ulcerations and necrosis (3).

At the age of 43, our patients presented with RPh symptoms, initially after exposure to cold, and later regardless of environmental factors; for two years it was the only manifestation of the disease.

Esophageal dysmotility: Although patients with SSc present with changes in the entire gastrointestinal tract, esophageal involvement is most common (26). The majority of patients with CREST syndrome demonstrate hypomotility. The esophageal epithelium may show a cobblestone appearance due to pearly white plaques; apart from subepithelium, fibrosis may also affect regions with muscle atrophy (41). Apart from esophageal aperistalsis, spasms and esophageal stricture have rarely been reported. Esophageal manometry and radionuclide transit test are better than radiography in the detection of motor abnormalities (41).

Esophageal dysmotility is usually found in the lower two-thirds of the esophagus and the lower esophageal sphincter, due to smooth muscle atrophy and fibrosis of the lamina propria and submucosa, atrophy and mucosal erosion and disruption of the capillary network (1). Patients often state they must drink liquids to swallow solid food (50). Esophageal reflux is common (16), as well as nausea, vomiting, weight loss, diarrhea, constipation and bleeding (45, 49). It has been pointed that symptoms of esophageal reflux are twice as common as dysphagia (41).

After five years since the beginning of the disease, our patient presented with difficulties in swallowing, heartburn, and regurgitation with large meals.

Sclerodactyly is the most easily recognizable manifestation, but it is not prominent in all patients (50). It is thickening which generally only involves the skin of the fingers (and toes) distal to the metacarpophalangeal joints in CREST syndrome. Sclerodactyly evolves through three phases: the edematous phase, indurative phase, and atrophic phase (26): the edematous phase begins with finger swelling, morning stiffness, and arthralgias; in the second phase the skin becomes thickened, shiny, without wrinkles, erythematous, and itchy; in the last, atrophic phase, the skin becomes fragile and lax, although it looks thicker due to thight connections with the structures underneath (1). The fingertips are pointed, fixed in an acutely flexed position, with ulcerations and calcifications. The distal phalanges are shortened or missing, hands are stiffened into a claw and immovable (48). The nails are dystrophic, dry, striated, deformed. Skin distal to the elbows and knees, but but also of the neck and face may be involved.

Three years after the appearance of RPh, our patient presented with skin changes on her fingers: first edema, then thickening, thinning, accompanied by reduced mobility and fixed flexion. There were also nail changes. Changes on the face and calcifications were registered 5 years after the onset of the disease.

Telangiectasias may occur in all types of SSc. They affect the face and extremities due to dilation of blood vessels on the skin surface, but also on the mucous membranes (lips, digestive tract) (26). The number and locations of telangiectasias increase over time (50). Our patient had numerous telangiectasias and scars on the shins and dorsum of the feet.

**Other symptoms of CREST syndrome** include fatigue, weakness, breathing difficulties, dizziness, ulcerations on the fingers and toes, poor wound healing, dry mouth and eyes, problems with the teeth.

Although the majority of patients may be classified into diffuse or limited SSc, there is a possibility of overlapping clinical symptoms, so all patients are at risk for complications of SSc (51).

Pulmonary arterial hypertension is a significant cause of mortality in SSc (52). The prevalence of pulmonary arterial hypertension in diffuse SSc ranges from 4.9% to 26.7% (53). However, pulmonary arterial hypertension may be a complication of limited SSc as well (54, 55).

Scleroderma renal crisis is a rare but serious complication of SSc (56). It is defined as severe hypertension associated with rapid increase in serum creatinine, with or without microangiopathic hemolytic anemia (57). It occurs in about 20% of patients with diffuse SSc, but it also affects patients with limited SSc and CREST syndrome (58, 59, 60). Regular renal function monitoring is recommended for all patients with SSc. Corticosteroids, especially high doses, represent a risk for scleroderma renal crisis (61).

Primary biliary cirrhosis (PBC) may also be accompanied by CREST syndrome. The association

of these two diseases is explained by a common autoimmune mechanism, and it is considered a distinct entity (PBC-CREST). Along with keratoconjunctivitis sicca, it is known as Raynaud's syndrome. According to Tojo and associates (62), patients with PBC-CREST have milder symptoms than patients with PBC or CREST alone, but have a larger number of esophageal varices. High titers of anti-centromere antibodies (ACA), low titers of anti-mitochondrial antibodies, high prevalence of HLA-DR9 and better prognosis are registered in patients with PBC-CREST. This association is well known in women, but it may also occur in men (63).

Using non-invasive cardiovascular magnetic resonance (CMR) imaging (64), coronary artery abnormalities and myocardial fibrosis can be registered, and all patents with SSc present with multiple fibrotic areas (65). The pathogenesis of the fibrotic lesions in SSc is still unclear. However, a spasm of small coronary arteries (myocardial Raynaud's phenomenon) has been suggested as a possible mechanism (65). Mavrogeni et al. (66), used CMR to evaluate 5 patients with CREST syndrome and 5 patients with SSc. All patients with CREST syndrome presented with coronary artery ectasia, whereas patients with SSc were without cardiac symptoms with normal coronary artery findings, but patchy fibrosis was identified in all of them (66)..

Anemia has also been associated with CREST syndrome (67) as a result of jejunal telangiectasias, with normal colposcopic findings and esophagitis.

Lauritano et al. (68) observed tongue rigidity and some speckled red alternating with white spots on the hard palate and in the vestibule in patients with Sjögren's syndrome and CREST.

CREST syndrome is rarely associated with other malignancies (69). It has been suggested that patients with scleroderma and Barrett's metaplasia are at increased risk of complications, such as strictures or adenocarcinoma, cases of CREST syndrome and lung adenocarcinoma, esophageal carcinoma, and adenocarcinoma of the third portion of the duodenum (41, 69).

Hachulla and Launay (70) reviewed the literature concerning the diagnosis and classification of SSc, describing characteristics of certain forms of the disease. In diffuse cutaneous form of SSc, disease progression is very fast, with a high incidence of renal, cardiac and pulmonary alterations (71). These characteristics also include: RPh episodes with fast skin changes, changes on the trunk and acral parts of the body, presence of tendon friction rubs, early and significant appearance of interstitial lung disease, chronic renal failure with oliguria, diffuse gastrointestinal diseases, with involvement of myocardium, genitourinary and musculoskeletal system, absence of ACA, dilatation of capillaries and nailfold capillary destruction, autoantibodies against Topoisomerase I (Scl 70) (in 30% of patients) (10, 16). The limited cutaneous SSc is characterized by slow progression, and less frequent and later spread on the internal organs. RPh is recorded in the course of several years, skin sclerosis affects the hands, face, legs and forearms (acral parts); there is a significantly lower incidence of pulmonary hypertension, with or without interstitial lung disease, trigeminal neuralgia, calcification and skin telangiectasia, often with ACA (anticentromere antibody that reacts with the kinetocore of metaphase chromosomes) in 40 - 70% (41), dilated nailfold capillaries (10).

**Systemic sclerosis sine scleroderma** (ssSSc) is a rare disorder in which patients develop vascular and fibrotic damage to internal organs, in the absence of cutaneous sclerosis (72). Brazilian authors studied 947 consecutive patients with SSc and 8.3% were classified as ssSSc (73). In this series, patients with ssSSc had a relatively mild type of disease with good prognosis. The disease was characterized by (13): RPh with a peripheral vascular equivalent (digital pitting scars, digital tip ulcers, digital tip gangrene and abnormal nailfold capillaries), positive antinuclear antibodies (ANA), one visceral organ involvement typical of SSc (any one of the following: distal esophageal hypomotility, small bowel hypomotility, pulmonary interstitial fibrosis, pulmonary hypertension, cardiac involvement typical of scleroderma or renal failure consistent with scleroderma renal crisis) and absence of another defined connective tissue or other disease as a cause of signs and symptoms cited above.

**Scleroderma overlap syndromes** mostly include simultaneous occurrence of sclerosis and some autoimmune systemic diseases (polymyositis, systemic lupus erythematosus or rheumatoid arthritis). If only RPh, ulcers, digital pitting ulcers, and ANA are present, with no other signs of systemic disease, it is presystemic scleroderma (1), corresponding with prodromal cutaneous sclerosis syndrome.

 

Rare cases of nodular and keloidal scleroderma have also been described. There are two categories: 1) systemic scleroderma accompanied by generalized distribution of ivory-colored subcutaneous nodules 3-20 mm in diameter, whose histology shows fibromatous changes or fibrinoid necrosis, and 2) localized scleroderma, subcutaneous morphea/ deep morphea/morphea profundus, with localized or generalized nodules; the skin is pigmented or hypopigmented, while most morphea nodules are said to be non-progressive (41). Localized scleroderma is characterized by extensive deposition of collagen with a thickening of the dermis and/or subcutaneous tissue. Unlike systemic sclerosis, it presents without sclerodactyly, RPh, nail changes, telangiectasia and progressive involvement of internal organs (41).

Speaking of patients with SSc, the most common subsets are limited cutaneous (approximately 60% of patients with systemic sclerosis) and diffuse cutaneous (approximately 35% of patients with systemic sclerosis), whereas systemic sclerosis without scleroderma affects about 5% (16). Approximately 15% of patients have pulmonary hypertension, and 10% have overlap syndromes.

**The diagnosis of systemic sclerosis** is based on the following (11, 41):

**A.** Clinical findings: 1) Medical history (on the overall health status, development of the disease and symptoms, exposure to possible precipitating factors, symptoms involving the lungs, heart, gastrointestinal tract, kidneys, muscles, etc.). 2) Clinical examination of the skin and other organs, and diagnostic criteria;

**B**. Diagnostic tests: Erythrocyte sedimentation rate, blood count, biochemical analyses; Skin biopsy; X-ray of the lungs, heart and esophagus; CT scan o the bones (in patients with calcinosis CT should be done when radiography findings are normal); Esophageal manometry and radionuclide transit are better than radiography for showing motor abnormalities; plethysmography, laser Doppler flowmetry, thermography, finger systolic blood pressure are used in the RPh (26); Cardiovascular magnetic resonance imaging is used to detect changes in the coronary arteries and the heart muscle, but major differences between limited and diffuse SSc are not probable (74).

The diagnosis of RPh is made using: plethysmography, laser Doppler flowmetry, thermography, finger systolic blood pressure (26). Serological tests: antinuclear antibodies (ANA) (90% - 95% in limited cutaneous and diffuse cutaneous SSc) (75). Other tests are used depending on the affected organ: pulmonary function tests, chest radiography, electrocardiogram, gastrointestinal motility testing, renal function tests, etc.

**C.** Diagnostic criteria of the American College of Rheumatology (ACR) (9). The patient should fulfill a major criterion or two of the three minor criteria:

I Major criteria - Scleroderma proximal to the digits, affecting limbs, face, neck or trunk - this is a single major criterion.

II Minor criteria;

(a) sclerodactyly

(b) digital pitted scarring

(c) bilateral basal pulmonary fibrosis.

Nadashkevich et al. (76) have proposed nine criteria - ABCDCREST: A. autoantibodies to: centromere proteins, Scl-70 (TOPO I), or anti-fibrillarin; B. bibasilar pulmonary fibrosis; C. contractures of the digital joints or prayer sign; 4. D. dermal thickening proximal to the wrists; 5. C. skin calcinosis; 6. RPh - Raynaud's phenomenon; 7. E. - esophageal distal hypomotility or reflux-esophagitis; 8. S. - sclerodactyly or non-pitting digital edema; 9. T. - telangiectasias. The classification of definite SSc requires at least three of the above criteria. Although presence of topoisomerase 1 (Scl-70) is extremely rare in localized scleroderma, autoantibodies to topoisomerase 11 were found in 70% of patients with localized scleroderma, and 85% of patients with generalized morphea (41).

Classification criteria for systemic sclerosis, published by the American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative (77) in 2013, include 8 criteria validated by a number of points, so that the definite diagnosis of SSc is set if the total score is 9 or more. These are: 1) skin thickening of fingers of both hands extending proximally to the metacarpophalangeal joints (sufficient criterion - 9 points); 2) finger tip lesions, edema - 2 points, sclerodactyly - 4 points; 3) finger lesions, ulcerations - 2 points; finger tip-pitting scars - 3 points; 4) telangiectasias - 2 points; 5) abnormal nailfold capillaries - 2 points; 6) lung involvement, pulmonary arterial hypertension - 2 points; interstitial lung disease - 2 points; 7) RPh - 3 points; 8) scleroderma related antibodies - 3 points.

In recent years a number of authors (78 - 82) is working on the revision of the classification criteria, including a broad range of clinical and laboratory elements that characterize SSc, which should contribute more accurate diagnosis, therapy and prevention of complications of the disease. Nailfold capillary microscopy (NCM) is a method used to assess the degree of capillary dilation (83), being very important for early diagnosis of SSc. NCM has significantly improved the identification of clinical differences (84), and that is why diagnostic sensitivity of ACR criteria may be markedly improved by addition of simple clinical variables, including NCM abnormalities and ACA positivity, as novel minor criteria (83). Capillary patterns may correlate with visceral involvement and capillaroscopy thus has the potential as a screening tool to enable early diagnosis of organ involvement in systemic sclerosis, as well as early therapy and prevention of disease progression (85). This method allows: early diagnosis of systemic sclerosis without skin involvement, differentiation of primary RPh from secondary RPh and follow up of disease progression (86). Today, videocapillaroscopy is most widely used (87). When comparing NCM and dermoscopy, most nailfold capillary images can be classified and assessed with higher accuracy (88).

Serological tests are of great importance in the diagnosis and differential diagnosis, especially related to the presence of antinuclear antibodies (ANA), which are the expression of autoimmune response (35), and clinically are associated with pulmonary and arterial hypertension, and interstitial lung disease; ANA may be present in healthy individuals as well, but in low percentage (89). Anticentromere antibodies (ACA) are found in 40 to 70% of patients with limited cutaneous sclerosis and are associated with calcinosis, RPh, esophageal dysmotility, sclerodactyly, telangiectasia, and pulmonary arterial hypertension; they are found only in 2 to 5% of patients with diffuse scleroderma, when they are associated with digital ulceration or digital loss. ACA findings indicate capillary involvement (90). Anti-topoisomerase I (anti-Scl-70) autoantibodies are found in 20 to 40% of patients with diffuse cutaneous sclerosis, and only 6% with limited cutaneous SSc; they are associated with rapid progression of skin thickening, scleroderma, renal crisis, pulmonary fibrosis, joint, muscle and heart involvement, hypertension and proteinuria (91). Anti-fibrillin-1 antibodies (U1-RNP) indicate a serious involvement of skin and systemic organs with high mortality, whereas anti-nucleolar antibodies indicate a limited form of the disease; however, they can be detected in patients with pulmonary hypertension and pulmonary fibrosis (75). Anti-RNA Polymerase III (Pol 3) antibodies are registered in 10 - 20% of patients with SSc, pointing to a serious disease with scleroderma, renal crisis and association with malignancy (91).

There is a registered association between SSc and various HLA alleles (92). Scleroderma is associated with HLA-DQA1* 0501 and DQB1* 0301 allele in all ethnic groups, DRB1* 1104 in Caucasians and Hispanics, and DRB1* 0804 in African Americans (93). HLA-DRB1 alleles are associated with limited scleroderma (29), and B* 62, DRB1* 11 and DRB1* 07 with diffuse scleroderma (1, 94). Pulmonary fibrosis is associated with HLAB* 62 and HLA Cw* 0602, and pulmonary hypertension with HLAB* 13 and HLAB* 65 (29). There is a correlation between the connective-tissue growth factor (CTGF), and systemic sclerosis, particularly in patients with anti-Scl-70 antibodies and pulmonary fibrosis (95). The presence of certain HLA alleles correlates with the presence of autoantibodies specific for systemic scleroderma (93, 96).

**Differential diagnosis** includes (16, 41): RPh of occupational origin, vibration-induced injuries, other connective tissue diseases or mixed connective tissue diseases (eg, rheumatoid arthritis or systemic lupus erythematosus), undifferentiated connective tissue disease, amyloidosis, paraneoplastic syndrome, and pseudoscleroderma (congenital, metabolic, toxic, chronic graft-versus-host disease).

Despite numerous new findings, there is still no therapeutic algorithm that can significantly change the natural course of the disease. Symptomatic treatment is of great importance (35).

**The therapy** of SSc depends on the segment in the pathogenesis of the disease which is being treated, e.g. changes in the vascular system, increased collagen synthesis, or modified immune reactivity (1). Vasoactive treatment includes: prostacyclin, low molecular weight dextran, stanozolol, nifedipine, captopril, ketanserin and plasmapheresis. Collagen production is affected by: D-penicillamine, pentoxifylline, coagulation factor XIII, cyclofenil,

 

colchicine, griseofulvin, 13-cis retinoic acid. Immune therapy includes: prednisone, cyclophosphamide, azathioprine, cyclosporine.

Hinchcliff and Varga (16) presented a treatment overview of organ specific complications of SSc (16):

Raynaud's phenomenon - α-Adrenergic blockers, angiotensin-II receptor blockers, long-acting calcium channel blockers (dihydropyridines), pentoxifylline (Trental), stellate ganglionic blockades, digital sympathectomy;

skin fibrosis - immunomodulatory drugs (d-penicillamine, mycophenolate mofetil, cyclophosphamide;

gastroesophageal reflux – antacids, histamine H2 blockers, proton pump inhibitors;

intestinal dysmotility or bacterial overgrowth – antibiotics, correction of nutritional deficiencies, promotility agents;

pulmonary fibrosis or alveolitis - immunomodulatory drugs, initial therapy with oral or intravenous cyclophosphamide, maintenance therapy with azathioprine;

pulmonary arterial hypertension – diuretics, endothelin-1 receptor inhibitors (bosentan), oxygen, phosphodiesterase-5 inhibitors (sildenafil), prostacyclin analogues (epoprostenol, treprostinil, iloprost), warfarin (sometimes used in patients with recurrent pulmonary thromboembolic disease);

scleroderma renal crisis – dialysis, short-acting angiotensin-converting enzyme inhibitors.

Manno and Boin (97) gave an overview of immunomodulators which are used in the therapy of SSc including: category, name of the drug, mechanism of action, and recommended doses:

1. nonselective immunosuppressive therapy: cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate;

2. T-cell-targeted immunotherapy: cyclosporine A, antithymocyte globulin, extracorporeal photoimmunotherapy or photopheresis, sirolimus (rapamycin);

3. B-cell-targeted immunotherapy: rituximab;

4. intravenous immunoglobulins;

5. biological immunotherapy: anti-TNF-α agents, infliximab;

6. antifibrotic therapy: CAT-192, imatinib mesylate;

7. cell-based immunotherapy: autologous hematopoietic stem cell transplantation.

In some cases, clinical improvement in patients with SSc is obtained by UVA-1 phototherapy (98).

Meta-analysis was conducted to determine the efficacy of calcium channel blockers for RPh, pointing to a moderate reduction in the frequency and severity of ischemic attacks (99). The following blockers were evaluated: nifedipine, nicardipine, nisoldipine, diltiazem; nifedipine was indicated for RPh, since it significantly reduced the frequency and severity of ischemic attacks with highest therapeutic efficacy (100). Type V phosphodiesterase inhibitor, sildenafil, stimulates accumulation of cyclic guanosine monophosphate, decreasing intracellular calcium concentrations, inducing relaxation of the vascular smooth muscle and consequent dilation (101, 102). Several-week use of sildenafil causes significant reduction in the frequency and severity of RPh (102). A synthetic phosphodiesterase III inhibitor, cilostazol increases conduit vessel diameter in patients with primary and secondary RPh, with a favorable impact on conduit vessel responsiveness to cold in patients with primary RPh without affecting microvascular flow or symptoms (103). Selective alpha-adrenergic receptor blocker acts in the recovery from cold-induced vasospasm in scleroderma patients (104). If topical glyceryl trinitrate is used in the treatment of primary RPh or limited SSc, it may cause endothelium-dependent vasodilator effect (105).

The mechanism of calcinosis formation is not entirely understood, and no effective treatment is available (106). However, low doses of warfarin may be effective in some patients with early and moderate SSc. Minocycline may be effective in the control of calcinosis in systemic sclerosis. The mechanism of action may be mainly through inhibition of matrix metalloproteinases and anti-inflammatory effects (42). Physical therapy of calcinosis includes: extracorporeal shock wave lithotripsy (107), carbon dioxide laser (108), and erbium laser (109). Treatment of finger calcinosis has a wide range of possibilities depending on the extent of calcifications and the involvement of deep structures. From a surgical point of view, simple removal is adequate in minor outpatient cases, whereas radical debridement is required in the major and more painful cases (44). Laser surgery may reduce telangiectasias, and amputation is sometimes necessary in gangrene.

Topical therapy includes (11):

- broad-spectrum topical antibiotics;
- nitroglycerin ointment for ischemic ulcers;
- topical antipruritics;
- emollients.

Other forms of therapy (31, 32):

- patient education on the characteristics of the disease and awareness of urgent problems;
- physiotherapy to promote joint mobility and muscle strength;
- exercises to maintain range of motion (mouth, face and hand stretches);
- avoid tobacco and maintain healthy weight;
- nutritional advice, and supplements if needed;
- for Raynaud's phenomenon: avoid cold and trauma, use warm clothing or heated clothing; For an attack - warm the body, hands and feet, use gentle arm movements or gentle massage to help restore circulation;
- occupational therapists - for adaptations to assist in daily living;
- camouflage products – cosmetics.

Skin protection: Avoid harsh soaps and detergents; reduce bathing frequency (bathe just once a day or every other day, using warm rather than hot water); apply sunscreen and increase moisture levels in your home by using a humidifier;

- practice good oral hygiene.

**The prognosis and course** of the disease indicate that although spontaneous remission is possible, SSc is essentially a chronic disease with progressive course with possible crises due to organ involvement. The patient should be informed about the objective circumstances in terms of clinical manifestations and treatment options, with high commitment of the entire team of doctors and psychotherapy.

## Conclusion

When classifying systemic scleroderma into two groups - diffuse and limited, with CREST syndrome as a variant of the latter, it should be considered that both types represent clinical variants of systemic sclerosis, share similar visceral involvement, laboratory abnormalities and the course which is not invariable, as shown in our patient. We reported a case of a patient with typical features of limited SSc, and all the symptoms of CREST syndrome, in whom the disease lasted for 23 years; therapeutic modalities provided only temporary improvement, eventually resulting in a fatal outcome.

## Abbreviations

SSc – systemic scleroderma
CREST – Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia
SS – systemic sclerosis
ARA - American Rheumatism Association
GVHD - graft versus host disease
ACR - American College of Rheumatology
HLA - human leukocyte antigen
IL - interleukin
NK - natural killer
RPh – Raynaud's phenomenon
PBC - primary biliary cirrhosis
ACA – anti centromere antibodies
Scl 70 - topoisomerase 1
ssSSc - SSc *sine* scleroderma
ANA - antinuclear antibodies
NCM - nailfold capillary microscopy
CTGF - connective-tissue growth factor
TNF - tumor necrosis factor

## References

1. Karadaglić Đ, Pavlović M. Sklerodermija. In: Karadaglć Đ, editor. Dermatologija. Beograd: Vojnoizdavački zavod, Versalpress Beograd; 2000. p. 1721-41.
2. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann Intern Med 2004; 140: 37-50.
3. Fabri M, Hunzelmann N. Differential diagnosis of scleroderma and pseudoscleroderma. J Dtsch Dermatol Ges 2007;5(11):977-84.
4. Mavrogeni S, Bratis C, Manoussakis M. Coronary artery abnormalities in CREST syndrome revealed by cardiovascular magnetic resonance imaging. Can J Cardiol 2011;27:390e5-7.
5. Tuffanelli DL, Winkelman RK. Diffuse systemic scleroderma. A comparison with acrosclerosis. Ann Intern Med 1962;57:198-203.
6. Barnnett AJ. Scleroderma (progressive systemic sclerosis): progress and course based on a personal series of 118 cases. Med J Aust 1978;2:129-34.
7. Rodnan GP, Jablonska S, Medsger TA. Classification and nomenclature of progressive systemic sclerosis (scleroderma). Clin Rheum Dis 1979;5:5-13.
8. Giordano M, Valentini G, Migliaresi S, Picillo U, Vatti M. Different antibody patterns and different prognoses in patient with scleroderma with various extent of skin sclerosis. J Rheumatol 1986;13:911-6.
9. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
10. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.

 

11. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, et al. Guidelines of care for scleroderma and sclerodermoid disorders. J Am Acad Dermatol 1996;35:609-14.
12. LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumtol 2001;28:1573-6.
13. Poormoghim H, Lucas M, Fertig N, Medsger TA, Jr. Systemic sclerosis sine scleroderma: demographic, clinical and serologic features and survival in forty-eight patients. Arthritis Rheum 2000;43:444-51.
14. Maricq HR, Valter I. A working classification of scleroderma spectrum disorders: a proposal and the results of testing on a sample of patients. Clin Exp Rheumatol 2004;22(3 Suppl. 33):S5-13.
15. Walker JG, Pope J, Baron M, LeClercq S, Hudson M, Taillefer S, et al. The development of systemic sclerosis classification criteria. Clin Rheumatol 2007;26:1401-9.
16. Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. Am Fam Psysican 2008;78(8):961-8.
17. Habif TP, Campbell JL, Chapman MS, Dinulos JGH, Zug KA. Skin disease diagnosis and treatment. Philadelphia: Elsevier Mosby; 2005. p. 354-7.
18. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum 2008;37:223-35.
19. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laining TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.
20. Englert H, Joyner J, Bade R, Thompson M, Morris D, Chambers P, et al. Systemic scleroderma: a spatiotemporal clustering. Int Med J 2005;35:228-33.
21. Tamaki T, Mori S, Takehara K. Epidemiological study of patients with systemic sclerosis in Tokyo. Arch Dermatol Res 1991;283:366-71.
22. Alamanos Y, Tsifetaki N, Voulgari PV. Epidemiology of systemic sclerosis in Northwest Greece 1981 to 2002. Semin Arthritis Rheum 2005;34:714-20
23. Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV Jr, et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. J Reumatol 2006;33(5):1004-13.
24. Tan FK. Systemic sclerosis: the susceptible host (genetics and environment). Rheum Dis Clin North Am 2003;29:211-37.
25. Radić M, Martinović Kaliterna D, Fabijanić D, Radić J. Sistemska skleroza- patogeneza, kliničke manifestacije i liječenje. Liječ Vjesn 2010;132:162-8.
26. Yoon JC, Elston DM. CREST syndrome treatment and management. Medscape Drug, Disease and Procedures. [updated 2015 Oct 15; cited 2015 Oct 23]. Available from: http://emedicine.medscape.com/article/1064663-treatment
27. Wollheim FA. Classification of systemic sclerosis. Visions and reality. Rheumatology 2005;44:1212-6.
28. Herrik AL, Worthington A. Genetic epidemiology: systemic sclerosis. Arthritis Res 2002;4:165-8.
29. Gladman DD, Kung TN, Siannis F, Pellett F, Farewell VT, Lee P. HLA markers for susceptibility and expression in scleroderma. J Rheumatol 2005;32(8):1481-7.
30. Del Rio APT, Sachetto Z, Sampaio-Barros PD, Marques-Neto JF, Santos Londe AC, Barros Bertolo M. HLA markers for poor prognosis in systemic sclerosis Brazilian patients. Dis Markers 2013;35(2):73-8.
31. Hartree N, Harding M, Jackson C. Systemic sclerosis (scleroderma). [cited 2015 Oct 1]. Available from: http://patient.info/doctor/systemic-sclerosis-scleroderma
32. Limited scleroderma (CREST syndrome). ). [cited 2015 Oct 1]. Available from: http://www.mayoclinic.org/diseases-conditions/crest-syndrome/basics/definition/con-20031524
33. Maitre A, Hours M, Bonneterre V, Arnaud J, Arslan MT, Carpentier P, et al. Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. J Rheumatol 2004;31(12):2395-401.
34. Bovenzi M, Barbone F, Pisa FE, Betta A, Romeo L, Tonello A, et al. A case-control study of occupational exposures and systemic sclerosis. Int Arch Occup Environ Health 2004;77:10-6.
35. Goodfield MJD, Jones SK, Veale DJ. The connective tissue diseases. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed. London: Wiley-Blackwell; 2010. p. 51.64-51.79.
36. Postiglione L, Montagnani S, Riccio A, Montuori N, Sciorio S, Ladogana P, et al. Enhanced expression of the receptor for granulocyte macrophage colony stimulating factor on dermal fibroblasts from scleroderma patients. J Rheumatol 2002;29(1):94-101.
37. Thibierge G, Weissenbach R. Concretions calcaires sous-cutanées et sclerodermie. Ann Dermatol Syph 1911;4:129-55.
38. Winterbauer RH. Multiple telangiectasia, Raynaud`s phenomenon, sclerodactyly, and subcutanious calcinosis: a syndrome mimicking hereditary hemorrhagic telangiectasia. Bull Johns Hopkins Hosp 1964;114:361-83.
39. Frayha RA, Scarola JA, Hulman LE. Calcinosis in scleroderma: a reevaluation of the CREST syndrome (abstract). Arthritis Rheum 1973;16:542.
40. Ensz S. Kidney (renal) involvement (main meni). International Scleroderma Network; c1998-2015 [cited 2015 Oct 1]. Available from: http://www.sclero.org/scleroderma/symptoms/renal/a-to-z.html
41. Goodfield MJ, Jones SK, Veale DJ. The connective tissue diseases. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. Oxford: Blackwell Publishing; 2010. p. 51.1-51.138.
42. Robertson LP, Marshall RW, Hickling P. Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. Ann Rheum Dis Mar 2003;62(3):267-9.
43. Kawakami T, Soma Y, Mizoguchi M, Saito R. Immunohistochemical analysis of transforming growth factor-beta 3 in calcinosis in a patient with systemic sclerosis and CREST syndrome. Br J Dermatol 2000;143:1097-131.
44. Merlino G, Germano S, Carlucci S. Surgical management of digital calcinosis in CREST syndrome. Aesthetic Plast Surg 2013;37:1214-9.
45. Ngan V. Systemic sclerosis. Derm Net NZ c2003. [updated 2014 Dec 25; cited 2015 Oct 1]. Available from: http://www.dermnetnz.org/immune/systemic-sclerosis.html.
46. Limited scleroderma (CREST syndrome). [cited 2015 Oct 1]. Available from: http://www.medicalgeek.com/disease-syndromes-procedures/15910-limited-scleroderma-crest-syndrome.html.
47. Raynaud M. De l`asphyxie local de la gangrene symetrique des extremites. Paris: L. Leclerc; 1862.
48. Paravina M. Bolesti vezivnog tkiva. In: Paravina M, Spalević

Lj, Stanojević M. Tiodorović J, Binić I, Jovanović D. Dermatovenerologija. Niš: Prosveta; 2006. p. 219-28.
49. Limited scleroderma (CREST syndrome). [cited 2015 Oct 1]. Available from: www.drugs.com/mcd/limited-scleroderma-crest–syndrome
50. CREST Syndrome. [cited 2015 Oct 1]. Available from: http://en.wikipedia.org/ wiki/CREST-syndrome
51. Hachulla E, Coghlan JG. A new era in the management of pulmonary arterial hypertension related to scleroderma: endothelin receptor antagonism. Ann Rheum Dis 2004;63:1009-14.
52. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J 2007;37:485-94.
53. Wigley FM, Lima JA, Mayes M, McLain D, Chapin JL, Ward-Able C. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community- based rheumatologists (the UNCOVER study). Arthritis Rheum 2005;52:2125-32.
54. Chang B, Schachna L, White B, Wigley FM, Wise RA. Natural history of mild-moderate pulmonary hypertension and the risk factors for severe pulmonary hypertension in scleroderma. J Rheumatol 2006;33: 269-74.
55. Cox SR, Walker JG, Coleman M, Rischmueller M, Proudman S, Smith MD, et al. Isolated pulmonary hypertension in scleroderma. Inter Med J 2005;35:28-33.
56. Batal I, Domsic RT, Medsger TA, Bastacky S. Scleroderma renal crisis: a pathology perspective. Int J Rheumatol 2010;2010:543704.
57. Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med 2000;133:600-3.
58. Tarcin O, Tarcin O, Ozcivan M, Aydin H, Tiftikci A. CREST syndrome and Renal involvement. Marmara Med J 2007;20(3):186-9.
59. Sugimoto T, Sanada M, Kashiwagi A. Is scleroderma renal crisis with anti-centromere antibody-positive limited cutaneous systemic sclerosis overlooked in patients with hypertension and or renal dysfunction? Nephrology 2008;13(2): 179-80.
60. Sugimoto T, Soumura M, Soumura M. Scleroderma renal crisis in a patient with anticentromere antibody-positive limited cutaneous systemic sclerosis. Mod Rheumatol 2006;16(5):309-11.
61. Trang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. Rheumatol Int 2012;32(3):645-53.
62. Tojo J, Ohira H, Suzuki T, Takeda I, Shoji I, Kojima T, et al. Clinicolaboratory characteristics of patients with primary biliary cirrhosis associated with CREST symptoms. Hepathol Res 2002;22:187-95.
63. Kouraklis G, Glinavou A, Karatzas G. Primary biliary cirrhosis accompanied by CREST syndrome. South Med J 2002;95(9):1058-9.
64. Mavrogeni S, Manoussakis MN, Karagiorga TS, Douskou M, Panagiotakos D, Bournia V, et al. Detection of coronary artery lesions and myocardial necrosis by magnetic resonance in systemic necrotizing vasculitides. Arthitis Rheum 2009;61:1121-9.
65. Mavrogeni S, Bratis C, Manoussakis M. Coronary artery abnormalities in crest syndrome revealed by cardiovascular magnetic resonance imaging. Can J Cardiol 2011; 27:390e5-7.
66. Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Campolis C, et al. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed-enhanced magnetic resonance imaging study. Arthritis Rheum 2007;56:3827-36.
67. Lachter J, Suissa A, Schiff E, Rosner I. Anemia in CREST syndrome. Isr Med Assoc J 2003:5:449.
68. Lauritano D, Bussolati A, Baldoni M, Leonida A. Scleroderma and CREST syndrome: a case report in dentistry. Minerva Stomatol 2011;60(9):443-65.
69. Anastasopoulos G, Marinis A, Konstantinidis C, Theodosopoulos T, Fragulidis G, Vassiliou I. Adenocarcinoma of the third portion of the duodenum in a man with CREST syndrome. World J Surg Oncol 2008;6:106.
70. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. Clin Rev Allergy Immunol 2011;40:78-83.
71. Haustein UF. Scleroderma and pseudo-scleroderma: uncommon presentations. Clin Dermatol 2005;23:480-90.
72. Mayes MD, Ho KT. Understanding and managing scleroderma. Scleroderma foundation. [cited 2015 Oct 1]. Available from: http://www.scleroderma.org/site/DocServer/UandM.pdf?docID=326
73. Marangoni RG, Rocha LF, Del Rio AP, Yoshinari NH, Marquez-Neto JF, Sampaio-Barros PD. Systemic sclerosis sine scleroderma: distinct features in a large Brazilian cohort. Rheumatology 2013;52:1520-4.
74. Hachulla AL, Launay D, Gaxotte V, de Groote P, Lamblin N, Devos P, et al. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. Ann Rheum Dis 2009:68:1878-84.
75. Lyons R, Narain S, Nichols C, Satoh M, Reeves WH. Effective use of autoantibody tests in the diagnosis of systemic autoimmune disease. Ann N Y Acad Sci 2005;1050:217-28.
76. Nadashkevich O, Davis P, Fritzler MJ. A proposal of criteria for the classification of systemic sclerosis. Med Sci Monit 2004;10(11):CR615-21.
77. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 Classification criteria for systemic sclerosis: an American college of rheumatology / European league against rheumatism collaborative initiative. Artritis Rheumat 2013;65(11):2737-47.
78. Fransen J, Johnson SR, van den Hoogen F, Baron M, Allanore Y, Carreira PE, et al. Items for developing Revised Classification Criteria in systemic sclerosis: results of a consensus exercise. Arthritis Care Res (Hoboken) 2012;64(3):351-7.
79. Johnson SR, Fransen J, Khanna D, Baron M, van den Hogen F, Medsger TA Jr, et al. Validation of potential classification criteria for systemic sclerosis. Arthritis Care Res (Hoboken) 2012;64(3):358-67.
80. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirjak L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign suspicion of systemic sclerosis Ann Rheum Dis 2014;73(12):2087-93.
81. Muller-Ladner U, Tyndall A, Czirjak L, Denton C, Matucci-Cerinic M, EUSTAR centres. Ten years EULAR Scleroderma Research and Trial (EUSTAR): what has been achieved? Ann Rheum Dis 2014;73(2):324-7.
82. Khanna D, Furst DE, Allanore Y, Bae S, Bodukam V, Clements PJ, et al. Twenty-two points to consider for clinical trials in systemic sclerosis, based on EULAR standards. Rheumatology

 

2015;54:144-51.
83. Lonzetti LS, Joyal F, Raynauld JP, Roussin A, Goulet JR, Rich E, et al. Updating The American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. Arthritis Rheum 2001;44(3):735-8.
84. Cutolo M, Matucci Cerinic M. Nailfold capillaroscopy and classification criteria for systemic sclerosis. Clin Exp Rheumatol 2007;25:663-5.
85. Jung P, Trautinger F. Capillaroscopy. J Dtsch Dermatol Ges 2013;11:731-6.
86. Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C. Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. A future tool for the analysis of microvascular heart involvement? Rheumatology (Oxford) 2006;45(Suppl 4):iv43-6.
87. Baron M, Bell M, Bookman A, Buchignani M, Dunne J, Hudson M, et al. Office capillaroscopy in systemic sclerosis. Clin Rheumatol 2007;26:1268-74.
88. Hughes M, Moore T, O`Leary N, Tracey A, Ennis H, Dinsdale G, et al. A study comparing videocapillaroscopy and dermoscopy in the assessment of nailfold capillaries in patients with systemic sclerosis – spectrum disorders. Rheumatology 2015;54(8):1435-42.
89. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008;58(12):3902-12.
90. Larche M. What`s new in Scleroderma. [cited 2015 Oct 1]. Available from: http://static1.squarespace.com/static/5280f5e9e4b0c046bfaad504/t/52decb0ee4b0fb2ead9eb0ba/1390332686069/Whats+new+in+Scleroderma+8th+Jan+2014.pdf.
91. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 2005;35:35-42.
92. Karp DR, Marthandan N, Marsh SG, Ahn C, Arnett FC, Deluca DS, et al. Novel sequence feature variant type analysis of the HLA genetic association in systemic sclerosis. Hum Mol Genet 2009;19(4):707-19.
93. Arnett FC, Gourh P, Shete S, Ahn CW, Honey RE, Agarwal SK, et al. Major histocompability complex (MHC) class II alleles, haplotypes and epitopes which confer susceptibility or protection in systemic sclerosis: analyses in 1300 Caucasian, African-American and Hispanic cases and 1000 controls. Ann Rheum Dis 2010;69(5):822-7.
94. Loubiere LS, Lambert NC, Madeleine MM, Porter AJ, Mullarkey ME, Pang JM, et al. HLA allelic variants encoding DR11 in diffuse and limited systemic sclerosis in Caucasian women. Rheumatology 2005;44(3):318-22.
95. Fonseca C, Lindahl GE, Ponticos M, Sestini P, Renzoni EA, Holmes AM, et al. A polymorphism in the CTGF promoter region associated with systemic sclerosis. N Engl J Med 2007;357:1210-20.
96. Beretta L, Rueda B, Marchini M, Santaniello A, Simeon CP, Fonollosa V, et al. Analysis of class II human leucocyte antigens in Italian and Spanish systemic sclerosis. Rheumatology 2012;51(1):52-9.
97. Manno R, Boin F. Immunotherapy of systemic sclerosis. Immunotherapy 2010;2(6):863-78.
98. Morita A, Kobayashi K, Isomura I, Tsuji T, Krutman J. Ultraviolet A1 (340-400 nm) phototherapy for scleroderma in systemic sclerosis. J Am Acad Dermatol 2000; 43:670-4.
99. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud`s phenomenon: a meta-analysis. Rheumathology 2005;44:145-50.
100. Goundry B, Bell L, Langtree M, Moorthy A, BMJ. Diagnosis and management of Raynaud`s phenomenon. BMJ 2012;344:e 289.
101. Rybalkin SD, Yan C, Bornfeldt K, Beavo J. Cyclic phosphodiesterases and regulation of smooth muscle function. Circ Res 2003;93:280-91.
102. Gore J, Silver R. Oral sildenafil for the treatment of Raynaud`s phenomenon and digital ulcers secondary to systemic sclerosis. Ann Rheum Dis 2005;64:1387.
103. Rajagopalan S, Pfenninger D, Somers E, Kehrer C, Chakrabarti A, Mukherjee D, et al. Effects of Cilostazol in patients with Raynaud`s syndrome. Am J Cardiol 2003;92:1310-5.
104. Wise RA, Wigley FM, White B, Leatherman G, Zhong J, Krasa H, et al. Efficacy and tolerability of a selective alpha(2c)-adrenergic receptor blocker in recovery from cold-induced vasospasm in scleroderma patients: a single-center, double-blind, placebo-controlled, randomized crossover study. Arthritis Rheum 2004;50(12):3994-4001.
105. Anderson ME, Moore TL, Hollis S, Jayson MIV, King TA, Herrick AL. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud`s phenomenon and systemic sclerosis. Rheumatology (Oxford) 2002;41:324-8.
106. Cukierman T, Elinav E, Korem M, Chajek- Shaul T. Low dose warfarin treatment for calcinosis in patients with systemic sclerosis. Ann Rheum Dis 2004;63:1341-3.
107. Sparsa A, Lesaux N, Kessler E, Bonnetblanc JM, Blaise S, Lebrun-Ly V, et al. Treatment of cutaneous calcinosis in CREST syndrome by extracorporeal shock wave lithotripsy. J Am Acad Dermatol 2005;53:S263-5.
108. Chamberlain AJ, Walker NP. Successful palliation and significant remission of cutanous calcinosis in CREST syndrome with carbon dioxide laser. Dermatol Surg 2003;29:968-70.
109. Saddic N, Miller JJ, Miller OF 3rd, Clarke JT. Surgical debridement painful fingertip calcinosis cutis in CREST syndrome. Arch Dermatol 2009;145:212-3.

# CREST sindrom - ograničena varijanta sistemske skleroderme: prikaz slučaja i pregled literature


## Sažetak

Uvod. Sistemska skleroderma (SSc) je multisistemska bolest sa mikrovaskularnim abnormalnostima, autoimunskim poremećajima, pojačanom produkcijom i depozicijom kolagena i fibrozom kože i visceralnih organa. U osnovi radi se o sistemskoj sklerozi (SS) u kojoj skleroza zahvata i kožu. Prema najjednostavnijoj, mada ne i kompletnoj klasifikaciji, registruju se dve forme SSc: difuzna SSc i limitirana (raniji naziv akralna) SSc. Podtip limitirane SSc je CREST sindrom, čije su karakteristike: kalcinoza, Rejnoov fenomen (RF), ezofagealni dismotilitet, sklerodaktilija i teleangiektazije.

Prikaz slučaja. Prikazana je bolesnica sa sa tipičnom kliničkom slikom limitirane SSc i svim elementima CREST sindroma, kod koje je bolest počela u njenoj 43. godini i trajala 23 godine, sa postepenim razvojem bolesti u prvih desetak godina, počev od Rejnoovog fenomena, skleroze kože, kalcifikacija, telangiektazija do dismotiliteta ezofagusa. Primenjivana terapija je dovodila do privremenih poboljšanja, da bi konačno rezultirala smrtnim ishodom.

Dijagnoza je postavljena na osnovu kliničke slike i relevantnih dijagnostičkih procedura.

Diskusija. Akronim CREST potiče iz XX veka: Tibijerž (*Thibierge*) i Vajsenbah (Weissenbach) 1911. godine opisali su bolesnika sa kalcinozom kože, RF, sklerodaktilijom i telangiektazijama i bolest označili kao CRST sindrom. Vinterbauer (*Winterbauer*), kod četiri od svojih osam bolesnika sa CRST sindromom, 1964. godine registrovao je i dismotilitet jednjaka, a Freja (*Frayha*) i saradnici su 1973. godine, zbog česte pojave dismoliliteta jednjaka predložili akronim CREST. Dalje su opisivane razne kombinacije ovih kliničkih manifestacija, pa se govorilo o REST sindromu (bez kalcinoze), CRest, „Pure“ CREST (kada pacijent ima dva ili više simptoma CREST, ali nema dovoljno kriterijuma ni za limitiranu ni za difuznu sistemsku sklerozu), „Plus“ CREST (udruženost sa drugim formama sistemske skleroderme – limitiranom ili difuznom ili sa drugim autoimunskim bolestima). Kod naše pacijentkinje je postavljena dijagnozu CREST sindroma, sa ispunjenjem svih kriterijuma. Iako pojedini autori, zbog čestog odsustva pojedinih od naznačenih karakteristika bolesti smatraju da je ispravnije govoriti o limitiranoj kutanoj sklerodermi, te da je za dijagnozu dovoljno prisustvo dve od pet karakteristika, sindrom ne možemo odvojiti od sistemske skleroderme odnosno sistemske skleroze.

Kriterijumi za klasifikaciju sistemske skleroze koje je 2013. objavio Američki koledž za reumatologiju i Zajednička inicijativa Evropske lige protiv reumatizma (*American College of Rheumatology (ACR)/ European League Against Rheumatism Collaborative Initiative*), obuhvata 8 kriterijuma koji su vrednovani određenim brojem poena, tako da se definitivna dijagnoza SSc može postaviti ako je ukupan skor 9 ili više. To su: 1. zadebljanje prstiju obeju ruku proksimalno od metakarpofalangealnih zglobova (dovoljan kriterijum – 9 bodova); 2. zadebljanje prstiju, otok – 2 poena, sklerodktilija – 4 poena; 3 lezije prstiju, ulceracije – 2 poena, ispod ravni kože – 3 poena; 4. telangiektazije – 2 poena; 5. abnormalni kapilari nokatnog zaslona – 2 poena; 6. zahvaćenost pluća: pulmonalna arterijska hipertenzija – 2 poena, intersticijalna plućna bolest – 2 poena; 7. RF – 3 poena; 8. autoantitela tipična za sklerodermu (ACA anticentromerna, ili Scl-70 antitopomeraza 1 (TOPO I), ili anti-fibrillarin) – 3 poena.

U novije vreme veliki broj autora radi na reviziji klasifikacije I kriterijuma uvodeći širok dijapazon elemenata koji su klinički i laboratorijski karakteristični za SSc, što će svakako doprineti preciznojoj dijagnostici, terapiji i prevenciji komplikacija bolesti. Kapilarna mikroskopija zaslona nokatne ploče (engl. *nailfold capillary microsopy* - NCM) je metoda kojom se određuje stepen kapilarne dilatacije, što je vrlo važno za ranu dijagnozu SSc. Kako kapilarne promene mogu da koreliraju sa visceralnim zahvatanjem, kapilaroskopija omogućava ranu dijagnozu organskih promena, što ima za rezultat rani početak terapije i prevenciju progresije i oštećenja organa. Ovom metodom se omogućava rana dijagnostika sistemske skleroze bez zahvatanja kože, kao i razlikovanje primarnog od sekundarnog


 

RF i registrovanje progresije bolesti. Danas je najviše u upotrebi video-kapilaroskop. Ukoliko NCM poredimo sa dermoskopijom, snimci dobijeni pomoću NCM se mogu klasifikovati i mogu se ozbiljnije procenjivatii.

I pored brojnih novih saznanja, još uvek ne postoji terapijski algoritam koji može bitno promeniti prirodni tok bolesti. Od izuzetnog značaja je simptomatsko lečenje pacijenata. Lečenje SSc se planira zavisno od segmenta u patogenezi bolesti na koji se želi delovati, npr. na promene u vaskularnom sistemu, ili na povećanu sintezu kolagena ili izmenjenu imunsku reaktivnost. Za vazoaktivno lečenje primenjuju se: prostaciklin, niskomolekulski dekstran, stanozolol, nifedipin, kaptopril, ketanserin i plazmafereza. Na produkciju kolagena deluju: D-penicilinamin, pentoksifilin, faktor koagulacije XIII, ciklofenil, kolhicin, griseofulvin, 13-cis retinoična kiselina. Za imunsku terapiju koriste se: prednizon, ciklofosfamid, azatioprim, ciklosporin.

Hinhklif (*Hinchcliff*) i Varga su dali pregled lečenja organ-specifičnih komplikacija kod SSc:

- Rejnoov fenomen – alfa adrenergični blokatori, blokatori angiotenzin II receptora, dugodelujući (*long-acting*) blokatori kalcijumovih kanala (dihidropiridini), pentoksifilin (trental), blokade stelatnih gangliona, digitalna simpaktetomija;
- fibroza kože – imunomodulatorni lekovi (d-penicilinamin, mikofenolat mofetil, ciklofosfamid;
- gastro-ezofagealni refluks – antacidi, H2 antihistaminici, inhibitori protonske pumpe;
- intestinalni dismotilitet ili bakterijska infekcija – antibiotici, korekcija nutricione deficijencije, promotilitentni agensi;
- pulmonalna fibroza ili alveolitis – imunomodulatori, inicijalna terapija sa oralnim ili intravenoznim ciklofosfamidom, terapija održavanja – azatioprin;
- pulmonalna arterijska hipertenzija – diuretici, inhibitori endotelin-1 receptora (bosentan), kiseonik, inhibitori fosfodiesteraze-5 (sildenafil), analozi prostaciklina (epoprostenol, treptostanil, iloprost), warfarin (kod rekurentne pulmonalne tromboembolične bolesti);
- sklerodermna reanalna kriza – dijaliza, kratkodelujući inhibitori angiotenzin-konvertujućeg enzima;

Mano (*Manno*) i Boin su dali pregled imunomodultora koji se primenjuju kod SSc prema kategorijama, nazivu leka, mehanizmu dejstva i preporučenim dozama:

- neselektivna imunoterapija – ciklofosfamid, mikofenolat mofetil, azatioprin, metotreksat;
- T-ćelijska ciljana imunoterapija – ciklosporin A, antitimocitni globulin, ekstrakorporalna fotofereza, sirolimus (rapamicin);
- B-ćelijska ciljana imunoterapija - rituksimab;
- intravenozni imunoglobulini;
- biološka imunoterapija - inhibitori TNF alfa, infiksimab;
- antifibrotična terapija - CAT-192, imatinib mesilat;
- ćelijski bazirana (*cell-based*) imunotrapija - transplantacija autolognih i alogenih stem ćelija.

Kliničko poboljšanje kod bolesnika sa SSc dobijeno je u pojedinim slučajevima primenom fototerapije UVA 1 zracima.

Zaključak. Podelom sistemske skleroderme u dve grupe oboljenja, grupu difuzne i grupu limitirane skleroderme, sa CREST sindromom kao pripadnikom limitirane skleroderme, mora se imati na umu da obe grupe obuhvataju različite kliničke varijante sistemske skleroze, koje zahvataju iste organe, dovode do istih laboratorijskih odstupanja i pokazuju tok koji nije nepromenljiv, što je prikazano i u slučaju opisanom u ovom radu. Prikazana je bolesnica sa tipičnom kliničkom slikom limitirane sistemske skleroze i svim simptomima CREST sindroma, kod koje je bolest trajala 23 godine, a primenjivana terapija je dovodila do privremenih poboljšanja, da bi konačno rezultirala smrtnim ishodom.

## Ključne reči

Sistemska skleroderma; CREST sindrom; Znaci i simptomi; Dijagnoza; Prikazi slučajeva; Pregled literature

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# The Incidence of Gonorrhea in Belgrade in the Period 2010 - 2014

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## Abstract

The World Health Organization (WHO) estimated that in 2008 there were 106.1 million newly registered cases of gonorrhea among adults worldwide. Of these cases, 3.4 million were in the WHO European Region. In the European Union and European Economic Area, the overall incidence of reported cases was 15.3 per 100.000 population in 2012; the highest rate (45.4 per 100.000) was observed in the United Kingdom, while low rates (<5 per 100.000) were generally reported in the Central and Eastern Europe. In 2012, low incidence of gonorrhea (1.49/100.000) was reported in Serbia, as well.

The purpose of this study was to report on the epidemiology of gonorrhea in a Belgrade population (about 1.5 million inhabitants) during the period 2010 - 2014, and to discuss data on gonorrhea rates in the European Union.

In Serbia it is mandatory to report gonorrhea, and all reports of culture-proved gonorrhea are sent to the City Institute for Public Health in Belgrade. These reports were used as the source for data analysis of gonorrhea incidence. Incidence rates were calculated using data from the 2011 population census in Serbia for Belgrade population. Age-adjusted annual incidence rates were carried out by a direct method using the "world population" as a standard.

During the 2010 - 2014 period, the average gonorrhea incidence in Belgrade population was 9.2 per 100.000 in men, and 1.9 per 100.000 in women. The incidence was highest in men and women aged 20 - 29 years. In all age groups gonorrhea incidence was higher in men than in women, the average male/female ratio being 4.8. In both sexes, the incidence of gonorrhea was highest in persons who had never married, with secondary education and unemployed. Out of 357 men with gonorrhea, 92 (25.77%) were self-reported homosexuals.

## Key words

Gonorrhea; Incidence; Age Distribution; Sex Distribution; Homosexuality, Male; Sexual Behavior

Gonorrhea is a sexually transmitted disease caused by the gram-negative bacterium *Neisseria gonorrhoeae*. Infection predominantly involves the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctiva. It is commonly transmitted through sexual contact (i.e. genital-genital, genital-anorectal, oro-genital or oro-anal) or vertically from mother to infant.

The World Health Organization (WHO) estimated that in 2008 there were 106.1 million new cases of gonorrhea among adults worldwide (1). Of these, 3.4 million were in the WHO European Region. In the European Union and European Economic Area, the overall incidence of reported cases was 15.3 per 100.000 people in 2012. The highest rates were observed in the United Kingdom (45.4 per 100.000), while low rates (<5 per 100.000) were generally reported in the Central and Eastern Europe. In 2012, there was a low reported incidence of gonorrhea in Serbia (1.49/100.000), as well.

The purpose of this study was to report on the epidemiology of gonorrhea in Belgrade (about 1.5 million inhabitants) during the period 2010 - 2014, and to discuss the data in the light of changes in gonorrhea incidence in the European Union.

 

## Material and methods

Reporting of gonorrhea is required in Serbia, and in Belgrade all reports of laboratory proven cases of gonorrhea are sent to the City Institute for Public Health. These reports were used as the source of information on gonorrhea incidence.

Gonorrhea incidence rates were based on data from the 2011 Serbian census for Belgrade population. Age-adjustment of annual incidence rates was carried out using a direct method of "world population" as a standard (4).

## Results

A total of 438 gonorrhea cases, 357 males and 81 females, were newly registered at the City Institute for Public Health in Belgrade during 2010 - 2014. The incidence in males ranged from 4.8 to 14.0 per 100.000, the average incidence being 9.2 per 100.000. In females, the incidence ranged from 0.3 to 3.1 per 100.000, and the average incidence was 1.9 per 100.000 (Figure 1). The age-adjusted average incidence was 9.4 per 100.000 in males and 2.2 per 100.000 in females.

The incidence of gonorrhea in Belgrade was highest in men and women aged 20 - 29 years. In both sexes the lowest incidence was in persons aged 50 and over, and in children ≤19 years of age. In all age groups, gonorrhea incidence was higher in men than in women. The male/female ratio ranged from 2.4 to 6.5, the average ratio being 4.8 (Table 1).

In both sexes gonorrhea incidence was highest in persons who had never married, with secondary education, and unemployed (Table 2). Out of 357 men with gonorrhea, 92 (25.77%) were self-reported homosexuals.

## Discussion

A dramatically decreasing trend of gonorrhea incidence in Belgrade was observed in the last two decades of the XX century (53 per 100.000 in 1988 and 8 per 100.000 in 2000) (5, 6). The incidence of gonorrhea in Belgrade continued to decline in the first decade of the new millennium, when it was under 5 per 100.000 inhabitants (6). However, since 2011, the incidence has increased from 2.47 per 100.000 in 2010 to 8.25 in 2013, and 7.17 per 100.000 in 2014.

A similar pattern of gonorrhea incidence in the new millennium was also observed in the European Union. A decreasing trend of gonorrhea incidence during the first decade (the rate was 16.6 per 100.000 in 2003, and 9.65 per 100.000 in 2008), was followed by an increase (2). Since 2008, the rate of gonorrhea

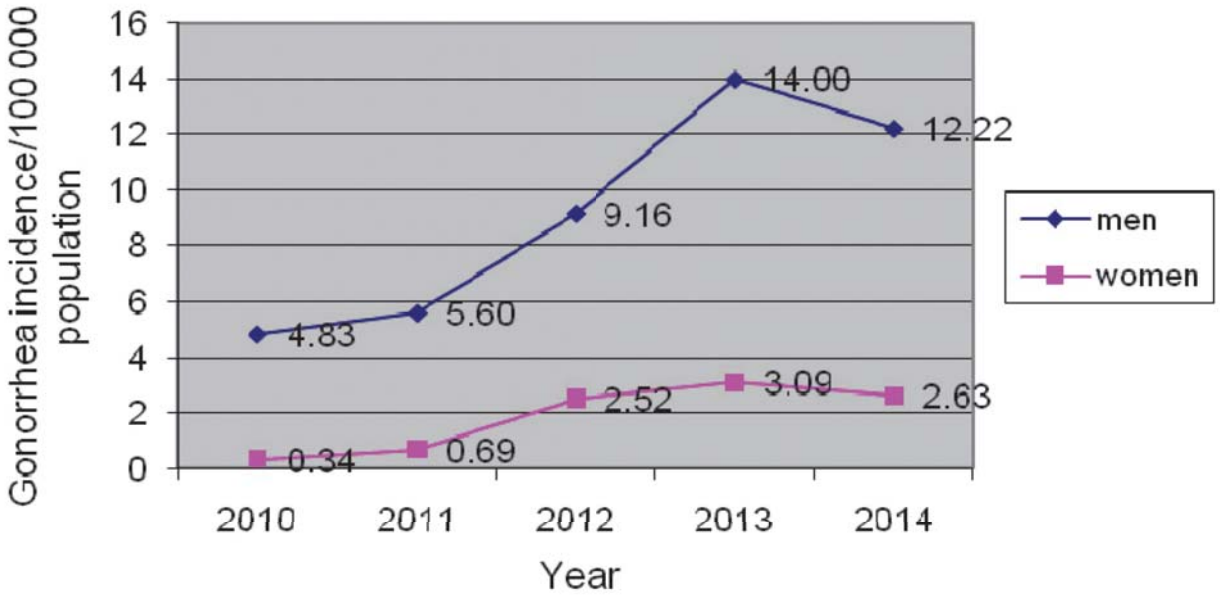


**Figure 1.** Sex distribution of gonorrhea incidence in Belgrade in 2010 - 2014

Table 1. Total number of gonorrhea cases and average incidence (per100.000) distributed by age, sex, and male to female ratio, Belgrade 2010 - 2014

| Age group | Men | | Women | | Sex ratio |
|---|---|---|---|---|---|
| | Number of cases | Average incidence | Number of cases | Average incidence | Male/female |
| ≤19 | 18 | 2.2 | 7 | 0.9 | 2.4 |
| 20-29 | 148 | 26.9 | 40 | 7.1 | 3.8 |
| 30-39 | 124 | 19.8 | 21 | 3.2 | 6.2 |
| 40-49 | 37 | 7.1 | 6 | 1.1 | 6.5 |
| 50+ | 30 | 2.1 | 7 | 0.4 | 5.3 |
| Total | 357 | 9.1 | 81 | 1.9 | 4.8 |

increased by 62%: from 10 to 16 per 100.000 in 2012. The trend of gonorrhea in the European Union varies among countries. Countries which reported high rates in the 1990, such as Bulgaria, Romania and the Czech Republic, reported a decreasing or stable trend. However, other countries (e.g. Denmark, Lithuania, Ireland and the United Kingdom) reported an increasing incidence, especially since 2008 (2).

In 2012, the highest rates were observed in the United Kingdom (45.4/100.000), Latvia (29.4/100.000), Ireland (24.2/100.000) and Estonia (15.7/100.000), and the lowest (≤1.5/100 000) in Bulgaria, Croatia, Luxembourg, Portugal and Serbia (2, 3).

There is no clear explanation for the declining trends of gonorrhea in Belgrade during the last two decades of the XX century, but it may reflect changes in healthcare systems, including more private offices, and therefore substantially increased number of unreported infections. Also, the increasing number of private pharmacies has allowed antibiotics without prescriptions and self-treatment, which may mask the infection and the diagnosis. The decreasing trend of gonorrhea incidence in 1990s could also be, at least partly, explained by the changes in sexual behavior in response to the AIDS epidemic, especially among men who have sex with men (MSM). The change in sexual behavior is characterized by reduction in the number of partners and safer sexual practice (7).

As already stated, the recent increase of gonorrhea incidence in Belgrade during 2010 - 2014 is similar to that seen in many other European countries. In Europe, it may partially be attributed to increased use of more sensitive diagnostic tests, such as Nucleic Acid Amplification Tests (NAATs) and changes in testing policies including testing at multiple anatomical sites (e.g. rectum, pharynx) among MSM (8). At the same time, more successful antiretroviral therapy has decreased the concern about HIV infection, and high risk behavior increased again especially among homosexual men (9).

The increase of gonorrhea incidence in Belgrade may be explained by the fact that the first Counseling Department for Sexually Transmitted Diseases at the City Institute for Skin and Venereal diseases in Belgrade was established in 2008, which is intended for patients without referral by their GP. The Department is friendly to vulnerable groups (MSM, patients who live with HIV, sex workers) and partner notifications are more effective. At the same time, because of unfavorable economic conditions, the number of patients who can afford private physicians has decreased as well as the number of unreported cases. During 2010 – 2014, the majority of registered

 

Table 2. Total number of gonorrhea cases and average incidence (per 100.000), distributed by marital status, education and working status, Belgrade 2010 - 2014

| Characteristic | Men | | Women | |
|---|---|---|---|---|
| | Total number of cases | Average incidence | Total number of cases | Average incidence |
| Marital status | | | | |
| Never married | 286 | 24.6 | 56 | 5.4 |
| Married | 63 | 3.4 | 23 | 1.2 |
| Divorced | 8 | 5.1 | 2 | 0.7 |
| Education | | | | |
| ≤ Elementary | 46 | 9.2 | 16 | 1.8 |
| Secondary | 282 | 14.9 | 61 | 3.3 |
| High | 29 | 4.5 | 4 | 0.5 |
| Working status | | | | |
| Employed | 156 | 10.0 | 41 | 2.9 |
| Unemployed | 133 | 38.1 | 24 | 8.1 |
| Student | 60 | 17.7 | 15 | 4.0 |
| Retired | 8 | 1.0 | 1 | 0.1 |

gonorrhea cases in Belgrade (95%) came right to the City Institute for Skin and Venereal Diseases.

The only laboratory test for the diagnosis of gonorrhea that is used in the afore-named Department is direct microscopy of Gram- or methylene blue stained smear. Microscopy has good sensitivity (≥95%) and specificity in symptomatic men with urethral discharge, but poor sensitivity in asymptomatic men and in endocervical infections (≤55%) or in rectal infections (≤40%). However, microscopy is not recommended for identification of pharyngeal infection (10, 11). Cultures appropriate for endocervical, urethral, rectal and pharyngeal specimens have not routinely been performed due to technical limitations. NAATs is a diagnostic tool for gonorrhea which is not available in public healthcare services in Serbia, and this method is more sensitive than culture, offering testing on a wider range of different types of specimens. Moreover, it is less demanding in specimen's quality, transportation and storage of specimens (12).

A higher incidence of gonorrhea in men than in women in Belgrade and in European Union (2), may be explained by differences in the sexual behavior of men and women, and by sex differences in clinical manifestations of the disease. It is well known that homosexual men are more vulnerable to sexually transmitted infections, including gonorrhea. More

than ¼ of men with gonorrhea in Belgrade are self-reported homosexuals. Men who have sex with men account for 38% of cases reported in 2012 in the European Union (2).

In the present study, the highest incidence of gonorrhea among men and women, was established in the age group 20 - 29, which is in line with results from the European Union (2). The association of young age with higher gonorrhea incidence rate may be explained by age-related sexual behavior and biological characteristics of the host-pathogen interactions (13).

According to our results, in both sexes gonorrhea infection was most frequent in persons who had never married, with secondary education, and were unemployed. Low education level, young age and low socioeconomic status were found to be positively related to gonococcal infection (14).

The critical feature of this analysis is data accuracy, since the number of gonorrhea cases in Belgrade could have been underestimated for several reasons: there is a possibility that some patients did not visit a physician, which some physicians did not report all cases, and that diagnosis of gonorrhea sometimes failed because of the lack of adequate laboratory feasibilities.

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## Abbreviations

WHO - World Health Organization
AIDS - acquired immunodeficiency syndrome
MSM - men who have sex with men
NAATs - nucleic acid amplification tests
HIV - human immunodeficiency virus

## References

1. World Health Organization. Global incidence and prevalence of selected curable STI-2008. Geneva: World Health Organization; 2008 [cited 2015 Jul 4]. Available from: http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf
2. European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2012. Stockholm: ECDC; 2014. p. 15-22.
3. Institute of Public Health of Serbia „Dr Milan Jovanovic Batut“. Center for Disease Control and Prevention: Report of infectious diseases in the Republic of Serbia in 2014. Belgrade: Institute of Public Health of Serbia „Dr Milan Jovanovic Batut“; 2015. p. 75-84.
4. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO Standard, GPE Discussion Paper Series: No.31. Geneva: EIP/GPE/EBD, World Health Organization; 2001 [cited 2015 Jul 4]. Available from: http://www.who.int/healthinfo/paper31.pdf
5. Bjekić M, Vlajinac H, Šipetić S, Kocev N. Trends of gonorrhoea and early syphilis in Belgrade, 1985-1999. Sex Transm Infect 2001;77:387-8.
6. Center for Disease Control and Prevention. Report of infectious diseases in Belgrade in 2010. Belgrade: City Institute of Public Health of Belgrade; 2010. p. 49.
7. Johnson AM, Gill ON. Evidence for recent changes in sexual behaviour in homosexual men in England and Wells. Philos Trans R Soc Lond B Biol Sci 1989;325:153-61.
8. Schachter J, Moncada J, Liska S, Shayevich C, Klausner JD. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections in the oropharynx and rectum in men who have sex with men. Sex Transm Dis 2008;35:637-42.
9. Katz MH, Schwarcz SK, Kellogg TA, Klausner JD, Dilley JW, Gibson S, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. Am J Public Health 2002;92:388-94.
10. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med 1996;72:422-6.
11. Barlow D, Phillips I. Gonorrhoea in women. Diagnostic, clinical and laboratory aspects. Lancet 1978;1(8067):761-4.
12. Whiley DM, Garland SM, Hartnett G, Lum G, Smith DW, Tabrizi SN, et al. Exploring ‘best practice’ for nucleic acid detection of Neisseria gonorrhoeae. Sex Health 2008;5:17-23.
13. Hook EW, Reichart CA, Upchurch DM, Ray P, Celentano D, Quinn TC. Comparative behavioral epidemiology of gonococcal and chlamydial infections among patients attending a Baltimore, Maryland, Sexually transmitted disease clinic. Am J Epidemiol 1992;136:662-72.
14. Bjekić M, Vlajinac H, Šipetić S, Marinković J. Risk factors for gonorrhoea: case-control study. Genitourin Med 1997;73:518-21.

 

# Incidencija gonoreje u Beogradu u periodu 2010–2014.godine

## Sažetak

Uvod. Svetska zdravstvena organizacija procenila je da je globalno u 2008. godini bilo 106,1 milion novoregistrovanih slučajeva gonoreje kod odraslih, od kojih su 3,4 miliona bili u evropskom regionu Svetske zdravstvene organizacije. U Evropskoj uniji i evropskom ekonomskom regionu, u 2012. godini ukupna učestalost prijavljenih slučajeva gonoreje iznosila je 15,3 na 100 000 stanovnika. Najviša incidencija od 45,4 na 100 000 utvrđena je u Velikoj Britaniji, dok su najniže stope (< 5 na 100 000) bile u Centralnoj i Istočnoj Evropi. U Srbiji je stopa u 2012. godini takođe bila niska i iznosila je 1,49.

Cilj. ovog rada bio je da se u Beogradu, glavnom gradu Srbije koji broji oko 1,5 miliona stanovnika, prati kretanje godišnje stope u periodu 2010–2014. godine i da se dobijeni podaci porede sa kretanjem stope u Evropskoj uniji u istom periodu.

Materijal i metode. Prijavljivanje svakog novo-otkrivenog slučaja gonoreje u Srbiji je zakonska obaveza. U Beogradu se svi slučajevi laboratorijski potvrđene gonoreje prijavljuju Gradskom zavodu za javno zdravlje, te su ovi izveštaji korišćeni kao izvor podataka. Za izračunavanje incidencije korišćeni su podaci za beogradsko stanovništvo iz popisa stanovništva Srbije iz 2011. godine. Standardizacija godišnjih stopa po starosnom dobu vršena je direktnom metodom uz *svetsku populaciju* kao standard.

Rezultati. U periodu od 2010. do 2014. godine prosečna incidencija gonoreje u beogradskoj populaciji iznosila je 9,2 na 100 000 stanovnika za muškarce i 1,9 na 100 000 stanovnika za žene. Kod oba pola incidencija je bila najveća u starosnom dobu od 20 do 29 godina. U svim uzrasnim grupama, incidencija gonoreje bila je veća za muškarce nego za žene i prosečan odnos među polovima bio je 4,8 u „korist" muškaraca. Među pripadnicima oba pola, infekcija je bila češća kod neoženjenih/neudatih lica, osoba sa srednjom stručnom spremom i kod nezaposlenih. Od ukupno 387 muškaraca obolelih od gonoreje 92 (25,77%) su bili muškarci koji imaju seksualne odnose sa muškarcima.

Diskusija. Dramatični pad učestalosti gonoreje u Beogradu zabeležen je tokom poslednje dve decenije prošlog veka, stopa od 53, koliko je iznosila 1988. godine, pala je na 8 u 2000. godini. Isti trend nastavljen je i u prvoj deceniji novog milenijuma, kada je stopa iznosila 5. Međutim, od 2011. godine, učestalost se povećava i stopa raste od 2,47 koliko je iznosila u 2010. godini do 8,25 u 2013. i 7,17 u 2014. godini.

Sličan trend incidencije gonoreje utvrđen je u novom milenijumu i u Evropskoj uniji: tokom prve decenije stopa pada sa 16,6 koliko je iznosila u 2003. godini na 9,65 u 2008. godini, da bi potom počela da raste, pa je od 2008. do 2014. godine zabeležen porast za 62%, sa 10 na 16 koliko je iznosila stopa u 2012. godini.

Ne postoji jasno objašnjenje za trend pada učestalosti gonoreje u Beogradu tokom poslednje dve decenije dvadesetog veka, ali on može odražavati promene u zdravstvenim sistemima, uključujući privatizaciju u zdravstvu, a samim tim i značajno veći broj neprijavljenih infekcija. Takođe, sve je bio veći broj privatnih apoteka u kojima je kupovina antibiotika bila dozvoljena bez lekarskog recepta, što je istovremeno otvorilo mogućnost tzv. samolečenja i „maskiranja" infekcije, tj. dijagnoze. Takođe, usledile su promene u seksualnom ponašanju kao odgovor na epidemiju AIDS-a, naročito među muškarcima koji su imali seks sa muškarcima (MSM). Promena u seksualnom ponašanju podrazumevala je smanjenje broja partnera i usvajanje bezbednije seksualne prakse.

Kao što je već navedeno, nedavni porast incidencije gonoreje u Beogradu tokom 2010–2014. godine sličan je onom koji je registrovan u mnogim drugim evropskim zemljama. On se u Evropi može delom pripisati povećanju upotrebe senzitivnijih dijagnostičkih testova, kao što su test-amplifikacije nukleinske kiseline (NAATs) i uzorkovanje materijala sa više različitih anatomskih regija (npr. rektum, ždrelo) kad MSM. Istovremeno na drugoj strani, zahvaljujući sve efikasnijoj antiretrovirusnoj terapiji smanjivao se strah od infekcije HIV-om i učestalost seksualnog ponašanja sa visokim rizikom za prenošenje seksualno-prenosivih oboljenja ponovo je rasla, posebno među homoseksualcima. Povećanje incidencije gonoreje u Beogradu može se pripisati

i činjenici da je od 2008. godine, počelo da radi prvo novoosnovano Savetovalište pri Odeljenju za seksualno prenosive bolesti u Gradskom zavodu za kožne i venerične bolesti u Beogradu, gde su pacijenti imali mogućnost pregleda bez uputa svog lekara. Odeljenje je prijateljski orijentisano ka ugroženom stanovništvu (MSM, pacijenti koji žive sa HIV-om, seksualne radnice), tako da je i broj onih koji su prijavljivali partnerstvo rastao. Istovremeno, zbog nepovoljne ekonomske situacije, broj pacijenata koji su mogli da priušte posetu privatnim lekarima je smanjen i samim tim verovatno je to jedan od razloga što se smanjio i broj neprijavljenih slučajeva. Većina registrovanih slučajeva gonoreje u Beogradu (95%) tokom 2010–2014. godine je iz Gradskog zavoda za kožne i venerične bolesti.

Veća učestalost gonoreje kod muškaraca nego kod žena u Beogradu i u Evropskoj uniji, može se objasniti razlikama u seksualnom ponašanju i u kliničkim manifestacijama oboljenja koje postoje između žena i muškaraca. Poznato je da kod muškaraca homoseksualaca postoji povišen rizik za nastanak seksualno prenosivih infekcija, uključujući i gonoreju. Više od četvrtine muškaraca sa gonorejom u Beogradu deklarisalo se kao homoseksualac. Muškarci koji imaju seks sa muškarcima čine čak 38% svih slučajeva gonoreje prijavljenih u 2012. godini u Evropskoj uniji. U ovoj studiji je najviša stopa gonoreje kod muškaraca i žena utvrđena u starosnoj grupi 20–29 godina, što je u skladu sa rezultatima dobijenim iz Evropske unije. Pojava viših stopa kod mlađih starosnih grupa može se objasniti većom slobodom seksualnog ponašanja kod mlađih osoba i biološkim razlikama koje utiču na ishod infekcije. Prema našim rezultatima, kod oba pola gonoreja je bila najčešća kod osoba koje nikada nisu bile u braku, koje su imale srednju školsku spremu i koje su bile nezaposlene. Poznato je da nizak nivo obrazovanja, mlađe životno doba i nizak socio-ekonomski status predstavljaju faktore rizika za nastanak gonokokne infekcije.

Zaključak. Slabost ove analize se odnosi se na preciznost podataka, s obzirom na potcenjen broj slučajeva gonoreje u Beogradu za šta postoji nekoliko mogućih razloga: postoji mogućnost da izvestan broj inficiranih nije posetio lekara, da neki lekari ne prijavljuju sve slučajeve i da dijagnoza gonoreje ponekad nije uspešna zbog nedostatka adekvatnih laboratorijskih mogućnosti.

**Ključne reči**: Gonoreja; Incidencija; Starosna struktura; Polna struktura; Homoseksualnost kod muškaraca; Seksualno ponašanje

 

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# Co-infection of Primary Syphilis and HIV after a Single Exposure - a Case Report

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## Abstract

Human immunodeficiency virus type 1- infected patients with syphilis are among the most important transmitters of HIV-1 infection due to biological effects of genital ulcerations, and aggravation due to their continued risky behavior. The association between primary syphilis and acute HIV-1 co-infection is not well documented, and reports on isolated cases are raising special interest and indicate that this double primary co-infection may occur. We present a case of a 31-year-old man with no past medical history who presented with fever, papular rash on the face which lasted for a few days, and a single genital ulcer. He was diagnosed with primary syphilis and primary HIV-1 infection after a single exposure with an infected female sex worker. Male-to-female HIV transmission during vaginal intercourse is significantly more likely than female-to-male HIV transmission. However, high prevalence of sexually transmitted diseases among female sex workers contributed to high HIV transmission probability, as in our case.
As far as the available world literature is concerned, this is the first case of co-infection of primary syphilis and HIV.

## Key words

Syphilis; Syphilis, Cutaneous; Syphilis Serodiagnosis; Sexually Transmitted Diseases; HIV; Disease Transmission, Infectious; Case Reports

Syphilis is one of the most prevalent infections in people living with HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome). According to a recent research which estimated the prevalence of sexually transmitted infections (STI) in this group, the reported rates of syphilis co-infection in HIV-infected individuals range from 1%–21% in North America to 2%–43% in Europe (1). An increased prevalence of syphilis all over the world has been reported in the past 10 years, particularly after the introduction of highly active antiretroviral therapy (HAART) for AIDS in 1996, which was followed by increase in unsafe anal sex in men who have sex with men (MSM) (2). In addition, sporadic unconnected outbreaks of heterosexually transmitted syphilis associated with commercial sex workers, migration, and partner swapping have been documented (3).

Currently, syphilis and HIV go hand in hand, since they affect similar subgroups, facilitate the acquisition of each other, and may aggravate the clinical course of both diseases. The main way of transmission is among high risk groups, such as men who have sex with men, sex workers and drug users (4).

## Case report

A 31-year-old man of Asian origin was admitted with a week history of small painful ulcers of the soft palate, tongue erythema and a single well defined firm, painless ulcer on the penis with adjacent inguinal lymphadenopathy. He also had multiple erythematous facial papules. On admission he was febrile, dehydrated, with a cachectic appearance. He received oral antibiotics and antivirals in the last 24 hours with no improvement.

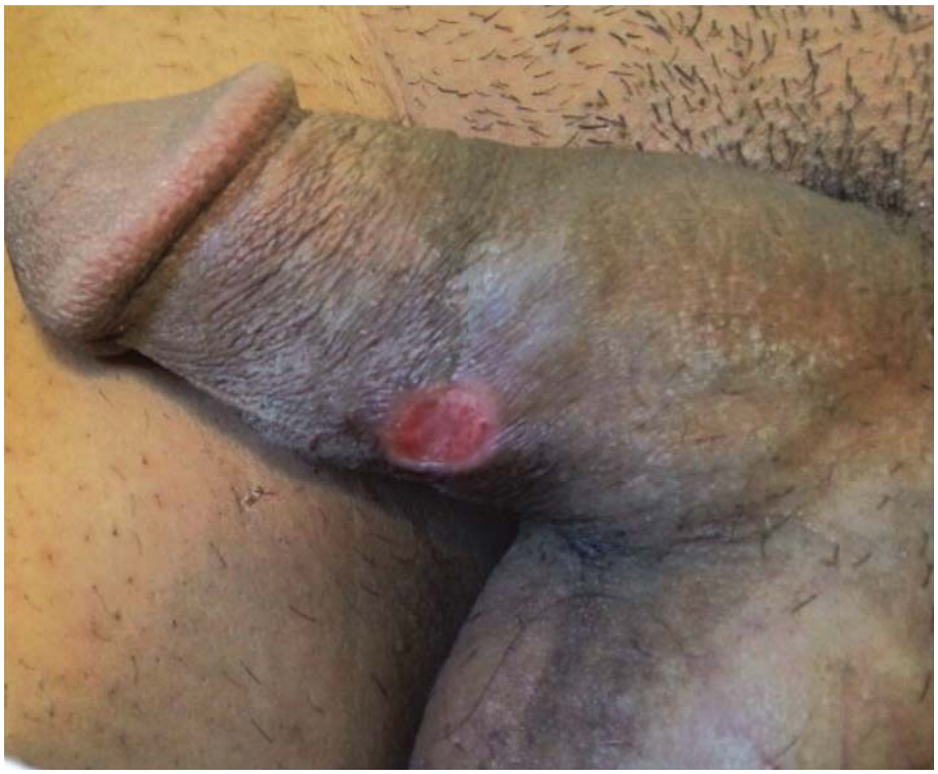

**Figure 1.** Penile lesion on admission

The patient had no significant medical history; he reported no history of recent travel, medication or illicit drug use. He had a single unprotected sexual intercourse (oral and vaginal sex) with a female illegal sex worker about 4 weeks before the onset of lesions. He claimed he did not have sex in the past three years.

Laboratory tests showed negative direct microscopy findings from the penile lesion for *Treponema pallidum*, a weakly positive VDRL test (Venereal Disease Research Laboratory), positive *T. Pallidum* enzyme immunoassay (EIA) for IgM and IgG and positive test results for *Treponema pallidum* particle agglutination (TP-PA) (Fujirebio, Belgium) with a titer 1 : 2560, indicating syphilis infection. Routine ELISA HIV antibody test (Vironostika, France) was positive, but Western-blot (Fujirebio, Belgium) which is the gold standard for the detection of antibodies to HIV-1 was negative, while lymphocytopenia with a CD4/CD8 ratio of 0.124 raised suspicion of an overlap between primary HIV and syphilis infection. The patient was successfully treated for syphilis with 2,4 millions of intramuscular benzathine penicillin G. On a follow up visit after a month of treatment, VDRL test was negative, Western-blot turned out to be strongly positive; CD4 T lymphocyte count was 406 cells/mm$^3$ of blood (normally 500 - 1,200), with a high total viral load of 140.000/ml of blood. Clinically, the genital ulcer resolved after a week of treatment, leaving an area of hyperpigmentation, and facial papules also disappeared within 3 weeks. The patient was diagnosed with primary co-infection of syphilis and HIV.

## Discussion

A striking increase in the prevalence of concomitant human immunodeficiency virus (HIV) infection and syphilis, observed by clinicians and public health workers over the past decade, has renewed interest in the subject. The aforementioned differences in the prevalence of syphilis in HIV-infected individuals within different studies may be due to sampling, study design, diagnostic tests, or potentially temporal factors (5). Concomitant syphilis and HIV infection are particularly common among men who have

 

sex with men (MSM) and sex workers (6). Several studies have reported the rate of HIV and syphilis co-infection as high as 50% (7, 8). Moreover, in a crosssectional study conducted among HIV infected patients who attended the AIDS Outpatient Clinic in Victoria (Brazil), the prevalence of syphilis infection turned to be high as well, while syphilis infection was independently associated with male gender, history of male to male sex, current use of antiretroviral therapy, and history of syphilis infection (5). Nevertheless, to the best of our knowledge, there has been no report published in the world literature on primary co-infection of both syphilis and HIV after a single exposure.

Both syphilis and HIV typically present with primary lesions/symptoms between 2 to 6 weeks after exposure to *Treponema pallidum* and HIV-1, respectively. Although syphilis presentation in patients with HIV is largely similar to that in patients without HIV, differences in disease manifestation may be present (9, 10). Syphilis usually takes a more malignant course, although asymptomatic primary syphilis can also been seen (4). Serologic tests for syphilis in HIV-infected persons may be modified as well, showing extremely high titers, as in our patient.

Acute HIV (AHI) infection, with a duration of a few weeks to two months, is the earliest stage of HIV disease, when plasma HIV viremia can be detected, but before HIV antibodies can be measured (11-13). Forty to ninety percents of newly-infected persons may present with a clinical picture that represents a diagnostic challenge, usually described as "the worst flu ever" or "acute retroviral syndrome" (ARS) (13). Nonspecific symptoms called ARS or"primary HIV infection", are the body's natural response to the HIV infection and include fever, fatigue, pharyngitis, weight loss, night sweats, lymphadenopathy, myalgias, joint pain, headache, nausea and diarrhea. Rash or mucocutaneous ulcers can also be present (11). More specific symptoms, such as photophobia, and retro-orbital pain may develop as well. Development of the classic mononucleosis-like symptoms coincides with high level viremia, as in our patient, and may last several days up to several weeks. Initial viremia has been reported to be as early as 4–11 days, while clinically detectable viremia may be more delayed (12). Leukopenia and/or thrombocytopenia, also seen in our patient, are frequently recovered and support the diagnosis. Formation of HIV-1–specific antibodies marks seroconversion; antibodies are generally detectable by week 3–12, most frequently 4 - 6 weeks after infection, although the window period may last up to 6 – 12 months (12).

The diagnosis of acute HIV infection (AHI) becomes rather difficult concerning the fact that routine HIV antibody tests (rapid HIV test or conventional enzyme immunoassay EIA, or Western blot) will typically remain negative at the time of peak viremia and the onset of symptoms. Thus, additional virus-specific diagnostic tests with a window period 1 – 4 weeks after exposure, such as viral load tests also called PCR (polymerase chain reaction) tests for plasma HIV load (HIV plasma RNA), or HIV p24 antigen assay (ELISA) are needed to detect HIV infection prior to the appearance of antibodies. The results of a viral load test are described as the number of copies of HIV RNA in a millilitre of blood. HIV p24 is a major protein that is part of HIV and is detectable 2 – 3 weeks after infection – before antibodies are produced, but not really afterwards – and p24 levels only stay high for the next 1 – 2 months. Assays that measure plasma HIV-1 load are more preferable because sensitivity of p24 antigen assay is time dependent, and p24 antigenemia may wane during AHI (12). Routine detection of HIV-1 plasma RNA by PCR is not currently approved by the US Food and Drug Administration for diagnosing HIV-1 infection unless history of recent high risk exposure (e.g. condom break with a known HIV-positive partner) and symptoms consistent with HIV seroconversion (fever, extreme tiredness, heavy "flu-like" illness etc.) are present, as in our patient (12). If it is positive, it must be confirmed with another test, either Western blot or antibody test that differentiates HIV-1 and HIV-2. Since EIA detects antibodies to HIV-1 and HIV-2, a routine confirmatory Western blot which is specific to HIV-1 is needed. When present alone, the HIV antibody test is considered to be indeterminate. This situation is frequently seen during seroconversion and should prompt correlation with the HIV-1 plasma RNA level, which was done in our patient. The diagnosis of primary HIV infection, also termed AHI, in our patient was based on the positive plasma HIV RNA test in conjunction with a indeterminate

HIV antibody test, followed by a confirmatory Western blot at a subsequent point in time (13). On the other hand, the diagnosis of primary syphilis is easier, since sensitivity of the nontreponemal VDRL and rapid plasma reagin (RPR) tests are estimated to be 78 - 86% and treponemal tests such as fluuorescent treponemal antibody absorption (FTA-ABS) and TP-PA tests show a sensitivity of 84% for detecting primary syphilis (14).

All genital ulcer diseases, particularly syphilis, represent an important risk factor for the acquisition of HIV infection (15-17). Moreover, HIV-infected patients with syphilis may be among the most important transmitters of HIV infection due to continuous risky behavior, as well as biologic effects of genital ulcerations. Furthermore, in uncircumcised males, as in our patient, trauma and subsequently sexually transmitted infections are more likely to happen during intercourse on the area of highly vascular frenulum. Thus, circumcision can be considered an effective intervention for reducing HIV transmission by reducing the synergy that normally exists between HIV and other sexually transmitted infections (18).

Male-to-female HIV transmission during vaginal intercourse is significantly more likely than female-to-male HIV transmission (19). However, high prevalence of sexually transmitted diseases among female sex workers contributes to high HIV transmission probability, like in our case.

HIV-infected patients diagnosed with syphilis do not have specific regimens and should be treated for syphilis with the same regimens as non-HIV-infected patients. Our patient was treated in accordance with the recommended regimen for the treatment of primary and secondary syphilis in adults: a single dose 2.4 million units benzathine penicillin G, i.m. (4).

After antiretroviral therapy was introduced, most clinicians agreed that HIV-positive patients with low CD4 counts should be treated, but no consensus was gained as to whether to treat patients with high CD4 counts. The only consensus was on treating patients with advanced immunosuppression (CD4 counts less than 350/μl) (20). The newest World Health Organization Guidelines (dated September 30, 2015) recommend offering antiretroviral therapy (ART) to everyone living with HIV, at any CD4 cell count to reduce the risk of disease progression and for prevention of HIV transmission (21).

This report reviews a previously healthy male patient with primary syphilis and HIV-1, emphasing the importance of testing all persons with a new diagnosis of HIV for syphilis, and vice versa (22, 23). Additionally, it highlights the fact that syphilis agent may enhance the transmission of HIV. Aggressive control of genital ulcer diseases may offer one very feasible approach to reducing transmission of HIV infection.

## Conclusion

As far as the world literature available to us is concerned, this is the first case of co-infection of primary syphilis and HIV.

## Abbreviations

HIV - human immunodeficiency virus
AIDS - acquired immune deficiency syndrome
STI - sexually transmitted infections
HAART - highly active antiretroviral therapy
MSM - men who have sex with men
VDRL - Venereal Disease Research Laboratory
EIA - *T. Pallidum* enzyme immunoassay
TP-PA - *Treponema pallidum* particle agglutination
ELISA - enzyme-linked immunosorbent assay
AHI - acute HIV infection
PCR - polymerase chain reaction
RNA - ribonucleic acid
FTA-ABS - fluuorescent treponemal antibody absorption

## References

1. Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. Sex Transm Infect 2011;87:183–90.
2. Bjekić M, Šipetić S. An outbreak of early syphilis in patients registered at the City institute for skin and venereal diseases in Belgrade from 2010 to 2012: a case series of 86 patients. Serbian Journal of Dermatology and Venereology 2013;5(2):65-71.
3. Waugh M. Sexually transmitted infections: points of interest for 2006. Skinmed 2006;5(2):87–9.
4. Karp G, Schlaeffer F, Jotkowitz A, Riesenberg K. Syphilis and HIV co-infection. Eur J Intern Med 2009;20:9–13.
5. Callegari FM, Pinto-Neto LF, Medeiros CJ, Scopel CB, Page K, Miranda AE. Syphilis and HIV co-infection in patients

 

who attend an AIDS outpatient clinic in Vitoria, Brazil. AIDS Behav 2014;18 Suppl 1:S104-9
6. Gao L, Zhang L, Jin Q. Meta-analysis: prevalence of HIV infection and syphilis among MSM in China. Sex Transm Infect 2009;85:354-8.
7. Paz-Bailey G, Meyers A, Blank S, Brown J, Rubin S, Braxton J, et al. A case-control study of syphilis among men who have sex with men in New York City: association with HIV infection. Sex Transm Dis 2004;31:581-7.
8. Wong W, Chew JK, Kent CK, Klausner JD. Risk factors for early syphilis among gay and bisexual men seen in an STD Clinic: San Francisco, 2002-2003. Sex Transm Dis 2005;32:458-63.
9. Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004;18:2075-9.
10. Abdul Wahab A, Rahman MM, Mohammad M, Hussin S. Case series of syphilis and HIV co-infections. Pak J Med Sci 2013;29:856-8.
11. Von Mollendorf C. Acute HIV: what is new and do we treat. South Afr J HIV Med 2009;10:17-21.
12. Kassutto S, Rosenberg ES. Primary HIV type 1 infection. Clin Infect Dis 2004;38:1447-53.
13. Dubrow R, Sikkema KJ, Mayer KH, Bruce RD, Julian P, Rodriguez I, et al. Diagnosis of acute HIV infection in Connecticut. Conn Med 2009;73(6):325–31.
14. Calonge N. Screening for syphilis infection: recommendation statement. Ann Fam Med 2004;2:362-5.
15. Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. JAMA 1988;260:1429-33.
16. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. Sex Transm Dis 2006;33:143-8.
17. Adolf R, Bercht F, Aronis ML, Lunardi LW, Schechter M, Sprinz E. Prevalence and risk factors associated with syphilis in a cohort of HIV positive individuals in Brazil. AIDS Care 2012;24:252-8.
18. Szabo R, Short RV. How does male circumcision protect against HIV infection? BMJ 2000;320(7249):1592-4.
19. Mastro TD, Satten GA, Nopkesorn T, Sangkharomya S, Longini IM Jr. Probability of female-to-male transmission of HIV-1 in Thailand. Lancet 1994;343(8891):204-7.
20. Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. Lancet 2000;355(9221):2147–52.
21. World Health Organization. Guidelines: HIV. [cited 2015 Oct 27]. Available from: http://www.who.int/hiv/pub/guidelines/en/
22. Zetola NM, Klausner JD. Syphilis and HIV infection: an update. Clin Infect Dis 2007;44:1222-8.
23. Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis 2004;4:456-66.

# Sifilis i HIV u primarnoj koinfekciji – prikaz slučaja

## Sažetak

Uvod. Sifilis predstavlja jednu od prevalentnijih infekcija među ljudima koji su inficirani virusom humane imunodeficijencije (engl. *human immunodeficiency virus* – HIV) i/ili žive sa sindromom stečene imunodeficijencije (engl. *acquired immune deficiency syndrome* – AIDS). Prevalencija koinfekcije uzročnikom sifilisa kreće se 1–21% u Severnoj Americi, a 2–43% u Evropi. Značajan porast učestalosti infekcije uzročnikom sifilisa registrovan je tokom poslednjih 10 godina u celom svetu, naročito posle uvođenja 1996. godine visoko aktivne retroviralne terapije za lečenje AIDS (engl. *highly active antiretroviral therapy* – HAART) i sve učestalijim upražnjavanjem nezaštićenog analnog seksa među muškarcima koji imaju seksualne odnose sa muškarcima (MSM). Štaviše, porastao je i broj slučajeva sifilisa nastao heteroseksualnim prenošenjem sa profesionalnih seksualnih radnika, promiskuitetnim ponašanjem i migracijama.

Prikaz slučaja. Tridesetjednogodišnji muškarac azijskog porekla, primljen je na bolničko lečenje zbog pojave bolnih ulceracija na mekom nepcu praćenih crvenilom jezika i jednog jasno ograničenog bezbolnog ulkusa sa tvrdim ivicama na penisu koji je pratila regionalna limfadenopatija. Po anamnestičkim podacima, promene su trajale nedelju dana. Istovremeno, na prijemu, pacijent je na licu imao multiple eritematozne papule, bio je febrilan, dehidriran i kahektičnog izgleda. Tokom 24 h pred prijem u bolnicu, započeo je uzimanje antibiotika, ali se stanje nije poboljšavalo uključujući i febrilnost.

Pacijent je negirao postojanje ozbiljnijih zdravstvenih problema u prošlosti, putovanja ili uzimanje lekova u poslednjem vremenskom periodu. Istakao je da je imao samo jedan nezaštićen seksualni odnos oralnim i vaginalnim putem sa ilegalnom seksualnom profesionalnom radnicom četiri nedelje pre pojave promena. Insistirao je na podatku da nije imao nijedan seksualni odnos tokom prethodne tri godine.

Relevantna laboratorijska ispitivanja su dala sledeće

rezultate: negativan direktni mikroskopski pregled brisa uzetog sa ivica ulkusa na penisu na prisustvo *Treponema pallidum*; slabo pozitivan VDRL test (engl. *Venereal Disease Research Laboratory*); pozitivan *Treponema pallidum* IgM i IgG EIA test (engl. *enzyme immunoassay*); pozitivan *Treponema pallidum* TP-PA aglutinacioni test (engl. *Treponema pallidum particle agglutination assay*) u titru 1/2 560, čime je dokazano prisustvo sifilistične infekcije; pozitivan rutinski ELISA (engl. *enzyme linked immunoassay*) test za dokazivanje prisustva antitela na HIV; negativan vestern blot test; prisustvo limfocitopenije sa CD4/CD8 odnosom 0,124 što je pobudilo sumnju na preklapanje primarne HIV infekcije sa primarnom sifilističnom infekcijom.

Pacijent je uspešno lečen jednom intramuskularno primenjenom dozom benzatin penicilina G od 2,4 milliona i.j. Na kontrolnom pregledu mesec dana kasnije dobijeni su sledeći rezultati: negativan VDRL test; vestern-blot test jako pozitivan; broj CD4+ T-llimfocita 406 ćelija/mm$^3$ krvi (referalno 500–1 200 ćelija/mm$^3$); PCR sa visokim brojem 140 000 virusnih kopija/ml krvi. Ulkus na penisu je saniran nakon sedam dana od primenjene terapije, ostavljajući rezidualnu hiperpigmentaciju, dok su se papule na licu povukle nakon tri nedelje.

Kod pacijenta je postavljena dijagnoza primarne koinfekcije sifilisom i HIV-om na osnovu anamneze, kliničke slike i toka oboljenja kao i hronologije pozitivnih rezultata laboratorijskih ispitivanja.

Diskusija. S obzirom na to da od oba oboljenja obolevaju osobe unutar istih rizičnih populacija, da pospešuju međusoban razvoj i da mogu pogoršati kliničku sliku i tok jedno drugom, može se reći da u današnje vreme sifilis i HIV „idu“ paralelnim putem. Glavni put prenošenja sifilisa je unutar visoko rizičnih grupa koje čine muškarci koji imaju seks sa muškarcima, seksualne radnice i osobe sa bolestima zavisnosti. U najvećem broju slučajeva, kod osoba inficiranih HIV-om sifilis poprima maligniji tok, ali se mogu javiti i asimptomatski slučajevi primarnog sifilisa. Rezultati seroloških testova koji se koriste za postavljanje dijagnoze sifilisa kod HIV inficiranih osoba, takođe mogu biti modifikovani, kao što je to bio slučaj i kod pacijenta prikazanog u ovom radu.

Akutna HIV infekcija koja traje od nekoliko nedelja do dva meseca (u ovom vremenskom periodu u plazmi inficirane osobe može se dokazati HIV viremija ali ne i antitela protiv virusa), predstavlja najraniji stadijum HIV oboljenja. Oko 40–90% novoinficiranih osoba HIV-om može u tom periodu razviti kliničku sliku koja sama po sebi predstavlja dijagnostički izazov, a opisuje se kao „akutni retrovirusni sindrom“ ili „primarna HIV infekcija“. U ovom stadijumu oboljenja, razvijaju se kod inficiranih osoba nespecifični znaci simptomi i klinički znaci koji predstavljaju izraz prirodne odbrane organizma od virusne infekcije: groznica, febrilnost, malaksalost, glavobolja, gušobolja, muka, povraćanje, dijareja, gubitak telesne težine, noćno znojenje, limfadenopatija, mijalgija, artralgije, ali i osipi po koži i mukokutane ulceracije. Specifičniji znaci mogu takođe biti prisutni i to u vidu fotofobije i retroorbitalnog bola. Razvoj klasičnih simptoma sličnih monomukleozi korelira sa visokim nivoom viremije kao što je to bio slučaj kod našeg pacijenta. Početna viremija može nastupiti već 4–11 dana od infekcije, dok se još laboratorijski ne može dokazati. Leukopenija i trombocitopenija, dokazana i kod našeg pacijenta, javlja se često i može olakšati dijagnozu. Formiranje HIV-1 specifičnih antitela označava serokonverziju i njihovo prisustvo može se dokazati 3–12 a najčešće 4–6 nedelja nakon infekcije, iako period prozora može trajati i 6–12 meseci.

Dijagnoza akutne HIV infekcije (AHI) otežava činjenica da rutiski testovi za dokazivanje HIV antitela kao što je EIA test ili vestern blot, ostaju negativni u vreme najveće viremije i početka prvih simptoma. Zato je potrebno u dijagnostički postupak uključiti virus-specifične dijagnostičke testove čiji periodi prozora traju 1–4 nedelje posle infekcije, sa ciljem dokazivanja HIV infekcije pre pojave antitela u serumu: PCR (engl. *polymerase chain reaction*) za određivanje HIV- RNA u plazmi tj. broja kopija HIV-RNA u mililitru krvi; HIV p24 *antigen assay* (ELISA). HIV p24 je glavni virusni protein koji se može dokazati 2-3 nedelje nakon infekcije – pre pojave antitela, ali ne i kasnije, s obzirom da njegov nivo ostaje visok samo u toku sledeća 1-2 meseca. Određivanje broja kopija HIV-RNA u mililitru krvi ima veću dijagnostičku vrednost, zato što je osetljivost p24 antigenskog testa zavisna od vremena: p24 antigenemija može nestati za vreme AHI.

Rutinsku detekciju HIV-1 RNA u plazmi nije odobrila FDA (*US Food and Drug Administration*) za dijagnozu HIV-1 infekcije osim u onim slučajevima

 

u kojima postoje anamnezni podaci o skorašnjoj visoko rizičnoj ekspoziciji (npr. nezaštićeni seksualni odnos sa HIV pozitivnim partnerom), i/ili simptomi kompatibilni sa HIV serokonverzijom (temperatura, groznica, ekstremni umor, odnosno jače izraženi „akutni retrovirusni sindrom"), kao što je bilo i kod našeg pacijenta. Ukoliko je test pozitivan, mora biti potvrđen drugim testom, kojim se diferencira HIV-1 od HIV-2, npr. vestern blot testom. S obzirom da EIA detektuje antitela na HIV-1 i HIV-2, rutinski test kojim potvrđujemo HIV infekciju jeste vestern blot. Kada je jedini pozitivan test EIA, kojim se određuju antitela, tada ga smatramo indeterminantnim. Ovo se često sreće za vreme serokoinverzije i promptno nameće potrebu za uključivanjem HIV-1 RNA u plazmi, što je i učinjeno kod našeg pacijenta.

Dijagnoza primarne HIV infekcije poznate i pod nazivom akutna HIV infekcija (AHI) postavljena je kod našeg pacijenta na osnovu pozitivnog nalaza HIV RNA u plazmi, u kombinaciji sa indeterminantnim EIA testom, koji su kasnije (hronološki sekvencionirano) potvrđeni vestern blot testom. Na drugoj strani, postavljanje dijagnoze primarnog sifilisa je značajno jednostavnije, s obzirom da se senzitivnost netroponemskih testova VDRL i RPR (engl. *rapid plasma regain*) kreće u rasponu 78–86%, a da senzitivnost treponemskih testova FTA-ABS (*fluuorescent treponemal antibody absorption*) i TP-PA iznosi oko 84% kada se radi o dijagnozi primarnog sifilisa.

Sve seksualno prenosive infekcije koje se manifestuju genitalnim ulceracijama, a naročito se to odnosi na sifilis, predstavljaju veoma značajan faktor rizika za prenošenje HIV infekcije. HIV inficirane osobe istovremeno obolele od sifilisa, s obzirom na kontinuirano rizično ponašanje i biološki potencijal genitalnih ulceracija, predstavljaju najvažnije prenosioce HIV infekcije. Štaviše, kod necirkumciziranih muškaraca, kao što je bio i naš pacijent, trauma za vreme seksualnog odnosa i veoma dobra vaskularizovanost frenuluma još više pospešuju prenos infekcije.

Prenos HIV infekcije sa muškarca na ženu za vreme vaginalnog odnosa je značajno češći nego sa žene na muškarca. Ipak, visoka prevalencija STI među profesionalnim seksualnim radnicama doprinosi visokom riziku od prenošenja HIV infekcije, kao što je to bio slučaj kod našeg pacijenta.

Pacijente inficirane HIV-om kod kojih je dijagnostikovan sifilis treba lečiti po istom režimu kao i neinficirane HIV pacijente: lečenje sprovedeno sa benzatin penicilinom G 2,4 miliona jedinica, intramuskularno u jednoj dozi, po predloženom režimu za lečenje primarnog i sekundarnog sifilisa.

Posle uvođenja antiretroviralne terapije, većina kliničara se složila da pacijente ificirane HIV-om, koji imaju mali broj CD4+ limfocita u krvi, treba lečiti, ali konsenzus nije postignut oko stava da li lečenje treba započeti sa velikim brojem ovih ćelija. Jedini konsenzus koji je postignut jeste da treba lečiti pacijente sa uznapredovalom imunosupresijom (CD4 manji od 350/μl). Najnoviji vodič Svetske zdravstvene organizacije (engl. *World Health Organization guidelines dated September 30, 2015*) podrazumeva da je antiretroviralna terapija potrebna svim osobama koje su inficirane virusom nezavisno od broja CD4+ limfocita. Na ovaj način smanjuje se progresija bolesti i rizik od transmisije.

Primarna HIV infekcija u koinfekciji sa primarnim sifilisom kod prethodno zdrave osobe, nastala nakon heteroseksualnog odnosa, ističe značaj testiranja na *Treponema pallidum* kod svih osoba sveže inficiranih HIV-om. Istovremeno ovaj slučaj potkrepljuje činjenicu da sifilis pospešuje transmisiju HIV infekcije i da samo agresivnom kontrolom svih oboljenja koja se manifestuju genitalnim ulceracijama možemo ući u borbu za smanjanje prenošenja HIV infekcije.

Zaključak. Na osnovu podataka iz nama dostupne svetske literature, ovo bi bio prvi objavljeni slučaj sifilisa i virusa humane imunodeficijencije u primarnoj koinfekciji.

## Ključne reči

Sifilis; Kutani sifilis; Serodijagnouza sifilisa; Seksualno prenosive bolesti; HIV; Transmisija infektivnih bolesti; Prikazi slučajeva

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# Overlap Between Ulerythema Ophryogenes and Keratosis Follicularis Spinulosa Decalvans: a Case Report

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## Abstract

Ulerythema ophryogenes and keratosis follicularis spinulosa decalvans are rare folliculocentric keratotic disorders, from the group of follicular genokeratoses, characterized by keratosis pilaris atrophicans: follicular keratotic papules, sometimes with surrounding erythema, which eventually result in fibrosis, atrophy, progressive scarring and permanent hair loss. Ulerythema ophryogenes begins at birth or soon thereafter; it involves the lateral eyebrows, spreads medially and eventually affects the entire eyebrows, cheeks, and less frequently, forehead and asjecebt scalp. Involvement of the scalp has apparently not been reported in cases in which the eyebrows were predominantly involved. In addition to sporadic cases, ulerythema ophryogenes has been reported among relatives. Keratosis follicularis spinulosa decalvans is also a genetically heterogeneous syndrome which begins in infancy or childhood by involving hair bearing skin, especially the scalp; rarely it is confined to the face involving only eyebrows and eyelashes, but affects predominantly the scalp, leading to severe progressive cicatricial alopecia. Both conditions tend to progress until puberty.

The authors present a case of an otherwise healthy 19-year-old male patient, with absence of lateral eyebrows since childhood, which spread symmetrically and medially, until puberty affecting the entire eyebrows, whereas the eyelashes were completely spared. On examination, skin findings on the face, trunk and extremities pointed to ulerythema ophryogenes: apart from hair loss, the lateral eyebrows were highly erythematous; a great number of disseminated follicular, slightly keratotic papules (keratosis pilaris) pin- or match-head sized, were seen on the trunk, extensor surface of the arms and legs, as well as the buttock, and on palpation the skin felt like a “nutmeg grater”. However, follicle-based erythematous papules (focal patchy alopecia) were found not only along the eyebrows but also partly in the parietal capillitium forming focal patchy alopecia, which is a finding characteristic for keratosis follicularis spinulosa decalvans; the histopathological analysis of the biopsy specimens taken from the parietal capillitium has confirmed the clinical diagnosis.

Cytogenetic analysis showed no karyotypic abnormalities. Family history showed that the patient’s mother and maternal grandfather also suffered from hair loss especially of the lateral eyebrows.

This paper presents an overlap between two rare follicular genokeratoses in a young male with a positive family history, who presented with ulerythema ophryogenes involving not only the eyebrows, but also the scalp, in the form of parietal, focal cicatricial patchy alopecia.

## Key words

Eyebrows; Facial Dermatoses; Keratosis; Hair Diseases; Erythema; Skin Diseases, Genetic; Chromosomes, Human, X; Darier Disease

Ulerythema ophryogenes (UO) and keratosis follicularis spinulosa decalvans (KFSD) are rare folliculocentric keratotic disorders, from the group of follicular genokeratoses, characterized by keratosis pilaris atrophicans (KPA): follicular keratotic papules, sometimes with surrounding erythema, which eventually result in fibrosis, atrophy, progressive scarring and permanent hair loss (1, 2, 3). UO begins

 

at birth or soon thereafter; it involves the lateral eyebrows, spreads medially and eventually affects the entire eyebrows, cheeks, and, less frequently extends to the adjacent scalp. Involvement of the scalp has apparently not been reported in cases in which the eyebrows were predominantly involved (4). In addition to sporadic cases, UO has been reported among relatives; it is assumed that in these cases it is transmitted through autosomal dominant inheritance pattern with variable penetrance (1, 2).

Keratosis follicularis spinulosa decalvans (KFSD) is also a genetically heterogeneous syndrome characterized also with KPA, but contrary to UO, which particularly and initially, to a greater or lesser extent, affects the eyebrow areas, KFSD usually begins in late infancy or childhood by affecting hair bearing skin, especially the scalp; it is rarely confined to the face involving only eyebrows and eyelashes, but affects predominantly the scalp, leading to severe progressive cicatricial alopecia (2, 3, 5); an X-linked inheritance has been proposed with random lyonization, because men are more severely affected than women (2). In both conditions progression usually stops after puberty (2, 3), and they may show overlapping features and inconclusive, non-diagnostic histopathology (2, 4).

The authors present an overlap between two rare follicular genokeratoses in a young male with a positive family history, who presented with UO involving not only the eyebrows, but also the scalp, in the form of parietal, focal cicatricial patchy alopecia.

## Case report

A 19-year-old, otherwise healthy male student, was referred for dermatologic examination due to numerous slightly itchy follicular hyperkeratotic papules surrounded by an erythematous halo, that were confined to the inflamed skin of the parietal scalp and followed by hair loss. The patient had a history of lateral eyebrow loss since infancy, and subsequent development of follicle-based hyperkeratotic papules, 1 - 2 mm in diameter, on the trunk and dorsal aspects of the limbs. The family history showed that the patient's mother and maternal grandfather also suffered from hair loss especially of the ateral eyebrows.

On examination, findings indicated UO: apart from lateral eyebrow loss, the eyelashes were completely spared; the skin of the face was highly erythematous; a great number of disseminated follicular, slightly keratotic papules, pin- or match-head sized, were seen on the capillitium, eyebrows, cheeks, trunk, extensor surface of the arms and legs, as well as the buttocks, and on palpation the skin felt like a "nutmeg grater" (Figures 1, 2); follicle-based erythematous papules were found not only along the eyebrows and cheeks, but also partly in the parietal capillitium, with atrophy and alopecia (Figures 3, 4, 5).

*Histopathological analysis* of the biopsy specimens taken from an area of hair loss on the parietal capillitium, which included follicule-based erythematous papules, revealed dilated hair follicles filled with keratin, infundibular atrophy, perifollicular lymphocytic infiltrates and finally, fibrosis (Figure 6 and 7).

*Karyotype:* in 11 examined metaphases, 46 XY karyotype was found, without fragile chromosomal sites.

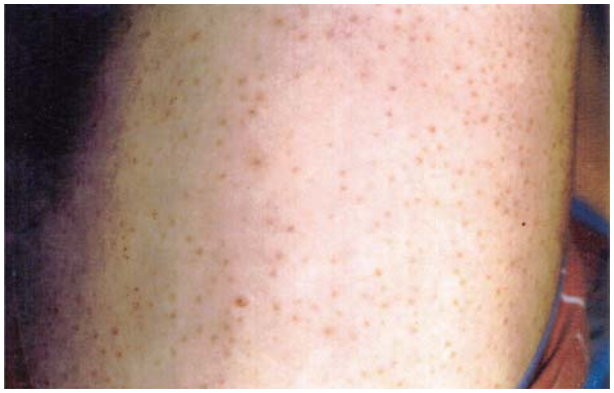

**Figure 1.** Disseminated follicular, slightly keratotic papules, pin- or match-head sized, on the extensor surface of the arms

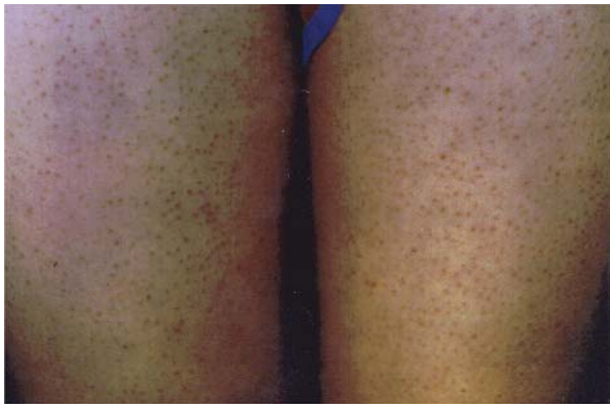

**Figure 2.** Disseminated follicular, slightly keratotic papules, pin- or match-head sized, on the extensor surface of the arms

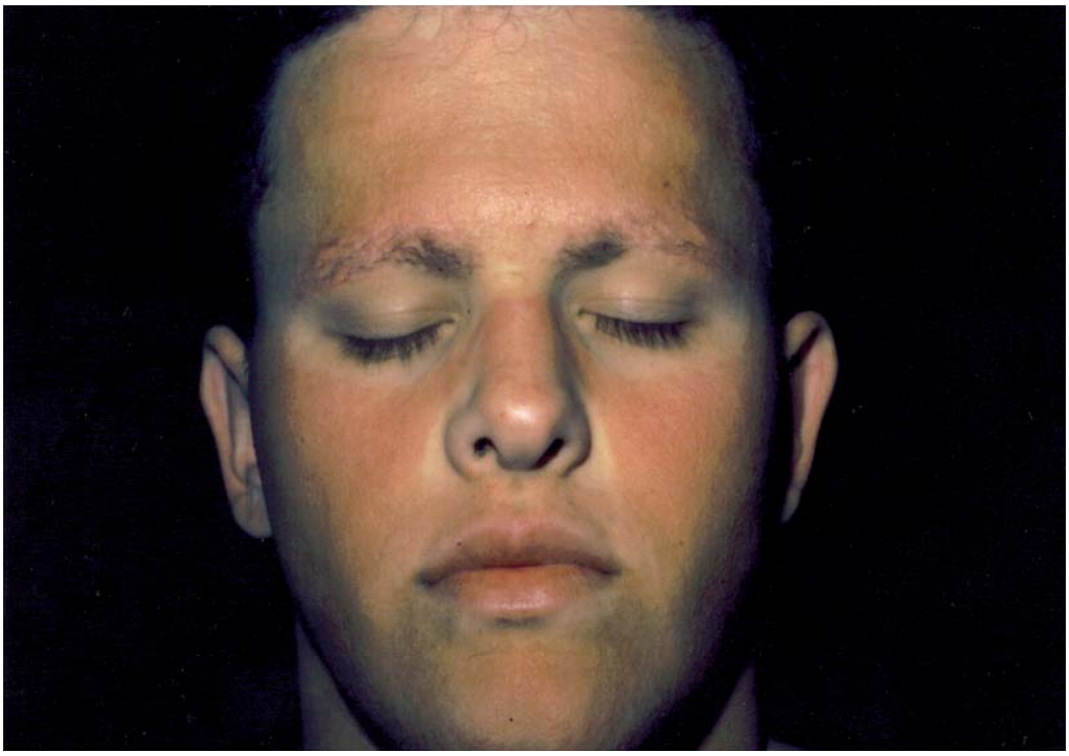

**Figure 3.** Erythema of the face

*Dermatoglyphic findings*: normal, unremarkable.

*Diagnosis* of UO/KPSD overlap was based on history, clinical presentation, course of the disease, and histopathological findings of the biopsy specimens taken from an area of hair loss on the capillitium: changes began in early infancy, predominantly affected the lateral third of the eyebrows, eyelashes were spared, KP was present on the trunk and dorsal aspects of the limbs, whereas around puberty the patient presented with patchy changes on the parietal capillitium, with follicular keratotic-erythematous papules and atrophy, in the form of parietal, focal cicatricial patchy alopecia.

*Therapy* included oral doxycycline, 100 mg per day, for initial control of the inflammatory component, combined with a topical steroid, and 2% salicylic acid in 20% urea cream.

## Discussion

Keratosis pilaris atrophicans (KPA) is clinically characterized by keratotic follicular papules followed by atrophy, scarring and permanent hair loss. If the pathological process affects hair follicles on the scalp, it results in diffuse scarring alopecia. Keratosis pilaris (KP) is often present on the trunk and extremities; sometimes it may be associated with conditions such as ichthyosis vulgaris and xerosis (1, 2).

Although in cases where signs of the syndrome are incomplete or not clearly expressed, KPA is not easily differentiated from KP, one should take into account that KP (either isolated or associated with atopic dermatitis, vulgar ichthyosis or other ectodermal disorders), causes no follicular destruction, atrophy, scarring or changes on the face and scalp characterized by KPA associated with follicular syndrome with inflammation and atrophy. While hyperkeratosis in KP is limited to the openings of hair follicles, in KPA it involves the infundibulum and isthmus—and with hypergranulosis represent the first visible histopathological features. Follicular hyperkeratosis cannot be considered the only cause of acute inflammatory changes in the hair follicles (accompanied by simultaneous accumulation of neutrophils and development of intracellular edema in the interfollicular epidermis and papillary dermis), perifollicular arrangement of collagen fibers, accumulation of mucin and mononuclear cells in the

 

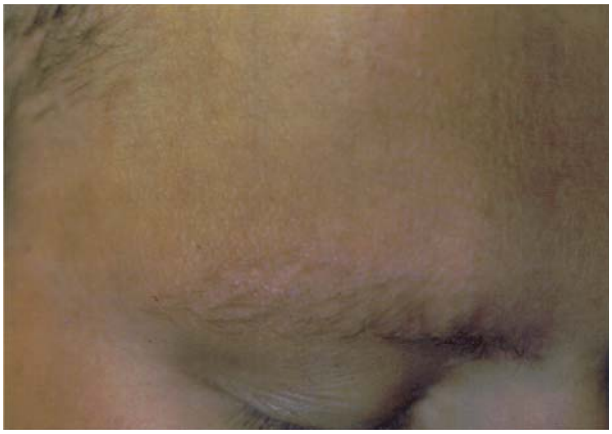

**Figure 4.** Lateral eyebrow loss, the eyelashes completely spared

final phase of the follicular destruction; it is supposed that unknown etiological factors lead to release of cytokines from follicular keratinocytes, which then induce hyperkeratosis and inflammatory changes (2, 6).

Numerous syndromes characterized by KPA have been described. As these syndromes have overlapping features and non-diagnostic histology, as in our case, some authors believe that they represent different stages in the development of the same process (ie. KPA), and that by distribution of changes, severity of inflammation, and the degree of atrophy, they can be classified into one of three existing groups: 1) keratosis pilaris atrophicans faciei (KPAF); 2) atrophoderma vermiculatum (AV); and 3) keratosis follicularis spinulosa decalvans (KFSD) (7). Moreover, AV (synonyms: atrophoderma reticulatum; folliculitis erythematosa reticulata; English - honeycomb atrophy; French - Acne vermoulant) is characterized by symmetrical, preauricular small follicular erythematous papules which are quickly followed by atrophic scars and small, pit-like, atrophic areas, irregular in shape and bounded by narrow ridges, giving the cheeks a worm-eaten appearance and may represent an end stage of the preceding two diseases. Another group of authors argues that the KPAF, KFSD, AV and folliculitis spinulosa decalvans (FAD), described by Van Ouch in 1992 (8), are four clearly distinct clinical entities characterized by the presence of keratosis pilaris atrophicans (2, 9). Thus, atrophoderma vermiculatum, as a clearly distinct clinical and pathomorphological entity, may be associated with various syndromes and multiple anomalies, reviewed by Schaller and associates (10).

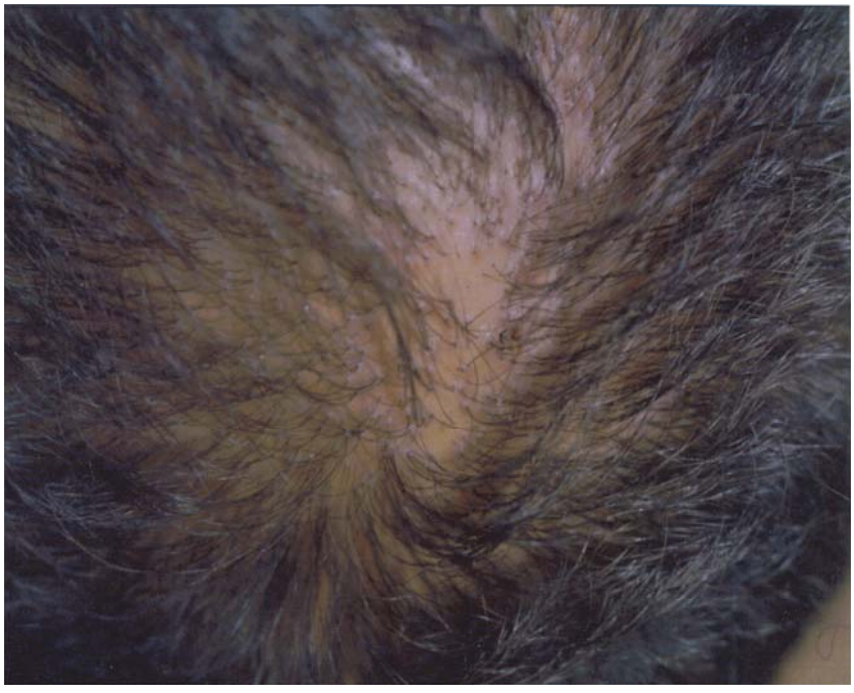

**Figure 5.** Follicle-based erythematous papules in the parietal capillitium, with scalp showing atrophy and patchy alopecia

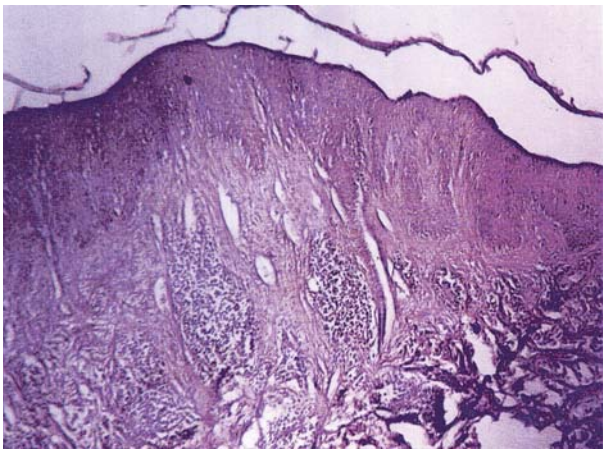

**Figure 6.** The epidermis is moderately hyperkeratotic, with elongation of rete ridges; some hair follicles are dilated, some show fibrous scarring, surrounded with chronic mononuclear cell infiltrates

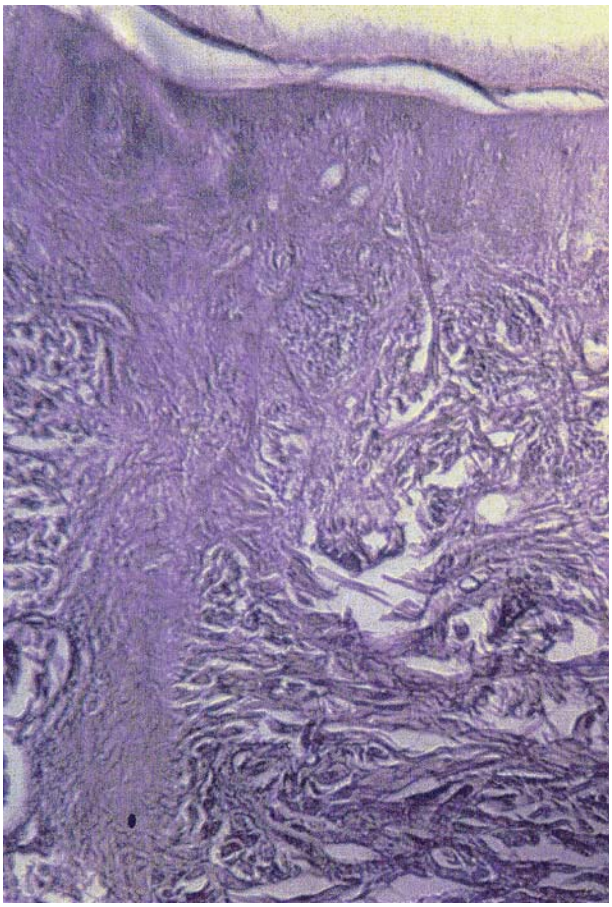

**Figure 7.** The follicular epithelium has been replaced by fibrous connective tissue; sebaceous glands are missing, and sweat glands are spared

keratosis rubra pilaris faciei atrophicans, folliculitis rubra) is derived from the Greek words: *ule* which means a scar, and *ophrys* which means eyebrow (3). UO was first described by Erasmus Wilson in 1878 (13). As mentioned previously, scalp involvement with scaring alopecia has not been reported in UO, particularly not in cases where eyebrows were predominantly affected, like in our case. However, there are reports on diagnosed UO cases with alopecia of the scalp; in order to improve diagnostic accuracy, such cases should be reclassified into one of aforementioned conditions (in which alopecia may occur) (4). KFSD initially appears morphologically in relation to KPAF, but with a more extensive pattern of involvement (5). The scaring alopecia in KFSD may be localized or extensive, involving eyebrows and eyelashes (madarosis) as well as the scalp; however, alopecia is typically patchy, such as in our patient, since the process usually does not affect the entire scalp (2). Other features include facial erythema, which was also present in our patient; photophobia, ophthalmitis, and palmar–plantar keratoderma, may also be present, and although characteristic, these features are not pathognomonic for the disease (2, 3). KFSD was originally described by Lameris in 1905, under the name ichthyosis follicularis (IF) (14); the term keratosis follicularis spinulosa decalvans was created by Siemens, in 1926, when he described some individuals from a Bavarian family with keratosis follicularis spinulosa decalvans (15). Most affected families with KFSD show X-linked inheritance: it was found that the gene responsible for KFSD is located on chromosome Xp22.13 - p22.2, mapped between AFM291wf5 and AFM316yf5 (2). Aten and associates investigated patients with KFSD and confirmed mutation in the MBTPS2 gene; it has been established that this mutation decreases the activity of the enzyme involved in the metabolism of cholesterol and the barrier function of the epidermis (16).

The histopathological findings of KFSD depend on the stage of the disease and site of biopsy. Skin biopsies taken from the thorax and extremities show filiform follicular hyperkeratosis, while those taken from the scalp and eyebrows go through four stages: 1) acute or inflammatory stage, where dilated hair follicles are filled with keratin and dystrophic root; follicular epithelium in the isthmus and infundibulum

 

show acanthosis, hypergranulosis, hyperkeratosis, in some cases concomitant accumulation of neutrophils and intracellular edema in the hyperkeratotic interfollicular epidermis and papillary dermis; 2) stage with perifollicular accumulation of mononuclear cells, scarce infiltrates containing predominantly lymphocytes and plasma cells, followed by accumulation of perifollicular mucin and thickened collagen fibers, extending parallel with the follicular wall; 3) stage of hair follicle destruction with more or less pronounced granulomatous inflammatory response and increased accumulation of plasma and giant cells ("around the foreign body") directed towards so-called "bare" hair in the dermis and the remaining parts of disintegrated follicles; 4) the final stage which cannot be distinguished from pseudopelade; hair follicles are replaced by fibrous streamers (stelae) (2). These stages were compatible with the findings obtained from the biopsy specimens taken from the parietal scalp with alopecia in our patient.

Apart from histopathology, clinical history and course of the disease, differential diagnosis of certain conditions was helpful in establishing the final diagnosis. The later included the following: 1. lolliculitis spinulosa decalvans is characterized by persisting inflammation, exacerbation with pustular elements at puberty, when spontaneous improvement occurs in most patients with KFSD; 2. lichen planopilaris is characterized by atrophic scarring on the scalp, dominated by complete absence of follicular openings; adjacent hair follicles at the periphery of lesions, as well as residual hair follicles within the lesions are surrounded by erythematous perifollicular macula and scales; the edge of the area affected by alopeciashows acuminate keratotic plugs; 3. lichen spinulosus has a predilection for acral areas unlike keratosis pilaris. The horny spine that is characteristic of lichen spinulosus can be removed, leaving behind a tiny funnel-like orifice in the papule, whereas an entire individual lesion can be removed with the plug in keratosis pilaris; 4. Ichthyosis follicularis is present at birth, and is characterized by nonscarring alopecia; histopathologically, unlike KFSD, it presents without fibrosis; 5. Keratosis pilaris atrophicans (KPA) syndrome (keratosis pilaris, alopecia, photophobia or IF, alopecia and photophobia) is also due to mutations on MBTPS2 gene on chromosome Xp21.2 - p22.2, so it can be assumed that KAP syndrome and KFSD represent overlap within the spectrum of phenotypes of the same genetic disorder, but alopecia in KAP syndrome is always nonscarring, unlike in KFSD (17).

In most cases the process resolves by puberty, but the consequences are permanent. The therapy is symptomatic, and there is no specific effective treatment: retinoids (isotretinoin, acitretin) should be used only during the active phase of the disease, which means in the early childhood. Hair loss is permanent, and treatment in the chronic phase, ie. after puberty, which is by far the most common case, only alleviates the existing hyperkeratotic changes. Antibiotic treatment should be carried out only in periods of acute exacerbation, which is manifested by erythema and scarce pustules on the scalp. Biopsy specimens may show *Staphylococcus aureus*, and the treatment should be carried out according to the antibiogram. Topical steroids and keratolytics may partially improve the symptoms, but after cessation of therapy, the benefits are lost. Tretinoin (0.1% cream once daily), may induce or aggravate the existing erythema, that can be avoided by concomitant use of corticosteroid creams (once or twice a day), or topicalretinoic acid 0.025% on alternate days for the scalp at night. Hair removal with a long-pulse Q-switched ruby laser has been found to be useful in progressive orrecalcitrant KFSD. Atrophic lesions may be treated with dermabrasion and/or application of collagen implants, now considered to be the most successful treatment modality. Ablative laser skin resurfacing is done using ultrapulse CO2 or YAG (yttrium aluminum garnet) laser (2). A significant erythema reduction is achieved by using 585 nm pulsed dye laser (18).

## Conclusion

The authors present an overlap between two rare follicular genokeratoses in a young male with a positive family history, who presented with ulerythema ophryogenes involving not only the eyebrows, but also the scalp, in the form of parietal, focal cicatricial patchy alopecia.

## Abbreviations

UO - ulerythema ophryogenes
KFSD - keratosis follicularis spinulosa decalvans
KPA - keratosis pilaris atrophicans

AV - atrophoderma vermiculatum
FSD - folliculitis spinulosa decalvans
IF - ichthyosis follicularis
KAP - keratosis pilaris, alopecia, photophobia
YAG - yttrium aluminium garnet
PDL - pulsed dye laser (585 nm)

**References**


1. Judge MR, McLean WH, Munro CS. Disorders of keratinization. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. Oxford: Blackwell Publishing Ltd; 2010. p. 19.1-19.122.
2. Mirmirani P, Rogers M. Keratosis pilaris and other inflammatory follicular keratotic syndromes. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill; 2008. p. 749-53.
3. Arnold AW, Buechner SA. Keratosis pilaris and keratosis pilaris atrophicans faciei. J Dtsch Dermatol Ges 2006;4:319–23.
4. Messenger AG, de Berker DA, Sinclair RD. Disorders of hair. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. Oxford: Blackwell Publishing Ltd; 2010. p. 66.1-66.100.
5. Khumalo NP, Loo WJ, Hollowood IS, Salvary I, Graham RM, Dawber RPR. Keratosis pilaris atrophicans in mother and daughter. J Eur Acad Dermatol Venereol 2002;16:387-400.
6. Sequeira FF, Jayaseelan E. Keratosis follicularis spinulosa decalvans in a female. Indian J Dermatol Venereol Leprol 2011;77:325-7.
7. Di Lernia V, Ricci C. Folliculitis spinulosa decalvans: an uncommon entity within the keratosis pilaris atrophicans spectrum. Pediatr Dermatol 2006;23(3):255–8.
8. Van Osch LD, Oranje AP, Keukens FM, van Voorst Vader PC, Veldman E. Keratosis follicularis spinulosa decalvans: a family study of a seven male cases and female carriers. J Med Genet 1992;29:36–40.
9. Callaway SR, Lesher JL Jr. Keratosis pilaris atrophicans: case series and review. Pediatr Dermatol 2004;21:14-7.
10. Schaller J, Rytina E, Rutten A, Hendricks C, Ha T, Requena L. Sweat duct proliferation associated with aggregates of elastic tissue and atrophodermia vermiculata: a simulator of microcystic adnexal carcinoma. Report of two cases. J Cutan Pathol 2010:37:1002–9.
11. Guidry JA, Rees A, Chan AJ, Shuja F, Hsu S. Ulerythema ophryogenes and Noonan syndrome. Dermatol Online J 2013;19(2):14.
12. Liakou AI, Esteves De Carvalho AV, Nazarenko LP. Trias of keratosis pilaris, ulerythema ophryogenes and 18p monosomy: Zouboulis syndrome. J Dermatol 2014;41:371–6.
13. Wilson E. Lectures on dermatology. London: J & A. Churchill; 1878.
14. Lameris HJ. Ichthyosis follicularis. Ned Tijdschr Geneeskd 1905;41:1524.
15. Siemens HW. Keratosis follicularis spinulosa decalvans. Arch Dermatol Syphilol 1926;151:384–7.
16. Aten E, Brasz LC, Bornholdt D, Hooijkaas IB, Porteous ME, Sybert VP, et al. Keratosis follicularis spinulosa decalvans is caused by mutations in MBTPS2. Hum Mutat 2010;31:1125-33.
17. Oeffner F, Martinez F, Schaffer J, Salhi A, Monfort S, Oltra S, et al. Intronic mutations affecting splicing of MBTPS2 cause ichthyosis follicularis, alopecia and photophobia (IFAP) syndrome. Exp Dermatol 2011;20:445–56.
18. Alcantara Gonzalez J, Boixeda P, Truchuelo Dıez MT, Fleta Asın B. Keratosis pilaris rubra and keratosis pilaris atrophicans faciei treated with pulsed dye laser: report of 10 cases. J Eur Acad Dermatol Venereol 2011;25:710–4.


# *Ulerythema ophryogenes* i *keratosis follicularis spinulosa decalvans* – prikaz slučaja

## Sažetak


*Ulerythema ophryogenes* (UO) i *keratosis follicularis spinulosa decalvans* (KFSD) predstavljaju retke folikulocentrične keratotične poremećaje, koji pripadaju grupi folikularnih genokeratoza, u kojima dominira *keratosis pilaris atrophicans* (KPA): folikularno smeštene keratotične papule okružene manje ili više izraženim eritemom koje vremenom zamenjuje fibroza, atrofija, progresivno ožiljavanje i trajni gubitak dlake. Proces kod *ulerythema ophryogenes* započinje u prvim mesecima života i zahvata lateralne strane obrva, širi se medijalno, može zahvatiti obrve u celini i znatno ređe proširiti se na čelo i susedni deo kapilicijuma. Zahvatanje kapilicijuma nije karakteristično za *ulerythema ophryogenes*, naročito ne za slučajeve u kojima kliničkom slikom dominiraju promene na obrvama. Pored sporadičnih slučajeva, opisana je i pojava *ulerythema ophryogenes* među srodnicima, pretpostavlja se da se u ovim slučajevima bolest prenosi autozomno dominantno sa varijabilnom penetracijom.

*Keratosis follicularis spinulosa decalvans* takođe je heterogeni genetski sindrom za koji je karakteristična *keratosis pilaris atrophicans*, ali za razliku od *ulerythema ophryogenes* koji od samog početka zahvata manje ili više obrve, *keratosis follicularis spinulosa decalvans* obično započinje kasnije, u ranom detinjstvu i karakteristično zahvata kapilicijum, dovodeći u težim oblicima do progresivne ožiljne alopecije. Pretpostavlja se da se


 

nasleđuje vezano za X-hromozom sa randominiziranom lajonizacijom, s obzirom da se bolest ispoljava sa znatno težim znacima kod osoba muškog pola u odnosu na žene. Kod *ulerythema ophryogenes* i *keratosis follicularis spinulosa decalvans* evolucija bolesti se u najvećem broju slučajeva zaustavlja u vreme puberteta, klinički znaci se međusobno mogu preklapati i biti istovremeno prisutni kod jednog istog pacijenta, a rezultati patohistološke analize ostati bez diferencijalno-dijagnostičkog značaja.

Autori prikazuju overlap dve retke folikularne genokeratoze.

Prikaz slučaja. Devetnaestogodišnji mladić, inače dobrog zdravstvenog stanja, upućen je na pregled dermatologu zbog pojave brojnih folikularnih hiperkeratotičnih papula okruženih eritematoznim haloom u parijetalnom delu kosmatog dela glave. Promene su bile praćene blagim osećajem svraba, skoncentrisane na jednom relativno jasno ograničenom ovalnom polju na kome je dlaka nedostajala a koža pokazivala znake inflamacije. Pacijent je dao podatak da su mu spoljašnji delovi obrva nedostajali od najrananijih meseci života, a da su mu se kasnije na trupu i ekstremitetima počeli javljati čvrsti, orožali čvorići veličine čiodine glavice 1-2 mm u prečniku.

Analizom pedigrea se došlo do podatka da su spoljašnji delovi obrva nedostajali kod pacijentove majke i njenog oca.

Prilikom objektivnog pregleda, nalaz je ukazivao na *ulerythema ophryogenes*: pored nedostatka dlaka, u lateralnim polovinama, obrva trepavice su bile potpuno pošteđene; koža je bila izrazito eritematozna; na kapilicijumu, obrvama, obrazima, na trupu i pretežno na ekstenzornim stranama ruku i nogu kao i na gluteusima, bio je prisutan veći broj diseminovanih folikularno smeštenih i lako keratotičnih papula veličine glavice čiode do šibice, koje su na palpaciju odavale utisak „trenice“ (slike 1 i 2); duž obrva, obraza i na parijetalnom kapilicijumu nalazile su se folikularne eritematozne papule smeštene na eritematoznoj koži sa atrofijom i alopecijom (slike 3–5).

Patohistološka analiza isečka uzetog sa alopecijskog polja na parijetalnom kapilicijumu koji je obuhvatio i folikularno smeštene eritematozne papule, pokazala je proširene otvore dlačnih folikula ispunjene keratinom, atrofiju infundibularnog dela folikuluma i perifolikularni limfocitni infiltrat (slike 6 i 7).

Dijagnoza *ulerythema ophryogenes*/*follicularis spinulosa decalvans* overlap je postavljena na osnovu anamneze kliničke slike, toka oboljenja i patohistološkog nalaza u isečku kože uzete sa regije koju je zahvatila alopecija u parijetalnom kapilicijumu: promene započele u prvim mesecima života, dominantno zahvatile lateralne trećine obrva, trepavice ostale očuvane; po trupu prisutna KP; u vreme puberteta pojavila se jasno ograničena solitarna promena na kapilicijumu sa folikularnim keratotično-eritematoznim papulama, atrofijom, u formi parijetalne, fokalne ožiljne alopecije.

Inicijalno je u terapiju uveden doksiciklin u dozi od 100 mg dnevno sa ciljem kontrole inflamacije, u kombinaciji sa topijskim kortikosteroidnim preparatom, 2% salicilnom kiselinom i kremom sa 20% uree.

Diskusija. *Keratosis pilaris atrophicans* klinički se manifestuje folikularno smeštenim keratotičnim papulama koje postepeno zamenjuju znaci atrofije, ožiljavanje i trajni gubitak dlake. Ukoliko su patološkim procesom zahvaćeni dlačni folikuli u kapilicijumu, nastaje difuzna ožiljna alopecija. *Keratosis pilaris* često je prisutna na trupu i ekstremitetima; Iako se u slučajevima u kojima su znaci sindroma nepotpuni ili nedovoljno jasno izraženi *keratosis pilaris atrophicans* teško razlikuje od k*eratosis pilaris*, treba znati da *keratosis pilaris* (bilo izolovana ili udružena sa atopijskim dermatitisom, vulgarnom ihtiozom ili drugim ektodermnim poremećajima) ne izaziva destrukciju folikula, atrofiju, ožiljavanje, niti promene na licu i poglavini koje karakterišu *keratosis pilaris atrophicans* u sastavu folikularnih sindroma sa inflamacijom i atrofijom. Hiperkeratoza kod *keratosis pilaris* ograničena je na otvore dlačnih folikula, dok u *keratosis pilaris atrophicans* ona zahvata infundibulum i istmus i, uz hipergranulozu, predstavlja prvu vidljivu patohistološku promenu. Folikularna hiperkeratoza se ne može smatrati jedinim uzrokom akutnih zapaljenskih promena u folikulu (praćenih istovremenim nakupljanjem neutrofila i razvojem intercelularnog edema u interfolikularnom epidermisu i papilarnom dermisu), zatim perifolikularnog umnožavanja kolagenih vlakana, nakupljanja mucina i mononuklearnih ćelija i u završnoj fazi destrukcijom dlačnog folikula: pretpostavlja se da za sada nepoznati etiološki faktor dovodi do oslobađanja citokina iz folikularnih keratinocita i da oslobođeni citokini izazivaju hiperkeratozu i inflamacijske promene koje potom slede.

Opisani su brojni sindromi koje karakteriše prisustvo *keratosis pilaris atrophicans*. S obzirom da ovi sindromi imaju overlapping features and non-diagnostic histology as in our case, neki autori smatraju da oni predstavljaju različite faze u razvoju jednog istog procesa (tj. *keratosis pilaris atrophicans*), a da se na osnovu distribucije promena, jačine inflamacije i stepena nastale atrofije, oni mogu svrstati u jednu od tri postojeće grupe koje

čine: 1) *keratosis pilaris atrophicans faciei* – KPAF (*sinonim ulerythema ophriogenes* – UO); 2) *atrophoderma vermiculatum* (AV); i 3) *keratosis follicularis spinulosa decalvans* (KFSD). Štaviše, AV (sinonimi: *atrophoderma reticulatum*; *folliculitis ulerythematosa reticulata*; engl. *honeycomb atrophy*; franc. *acne vermoulant*), za koju su karakteristične simetrične, preaurikularno lokalizovane, male folikularno smeštene eritematozne papule koje brzo zamenjuju atrofisana ožiljna polja i mnogobrojna gusto raspoređena rupičasta, okruglasta ovalna ili nepravilna ulegnuća razdvojena uskim sjajnim beličastim tračcima, koja daju obolelim obrazima izgled drveta izjedenog crvima, može predstavljati završni stadijum prethodna dva oboljenja. Druga grupa autora zastupa stav da KPAF, KFSD, AV i *folliculitis spinulosa decalvans* (FSD) predstavljaju četiri jasno odvojena klinička entiteta koje zajednički karakteriše prisustvo *keratosis pilaris atrophicans*. KPAF se smatra markerom za određene sindrome, kao što je npr. *Zouboulis* sy. za koji je karakteristično prisustvo trijasa: KP, KPAF i 18p monosomija.

Naziv *ulerythema ophryogenes* (UO), (sinonimi: *keratosis pilaris atrophicans faciei*, *keratosis rubra pilaris faciei atrophicans*, *folliculitis rubra*) potiče od grčke reči *ule,* što na engleskom znači *scar*, i od grčke reči *ophrys* što na engleskom znači *eyebrow*. *Ulerythema ophryogenes* prvi je opisao Erazmus Vilson (*Erasmus Wilson*) 1878. godine. Kao što je to ranije istaknuto, zahvatanje kapilicijuma nije karakteristično za UO, naročito ne za slučajeve u kojima kliničkom slikom dominiraju promene na obrvama. Zato treba korigovati dijagnozu u onim slučajevima *ulerythema ophryogenes* u kojima se javila alopecija. *Keratosis follicularis spinulosa decalvans* i *ulerythema ophryogenes* mogu u samom početku izazvati slične morfološke promene, ali je tok oboljenja u KFSD znatno progresivniji i teži. Ožiljna alopecija koja se javlja u KFSD može biti lokalizovana ili opsežnija, sa zahvatanjem obrva, trepavica (*madarosis*) i naročito kapilicijuma; karakteristično je da alopecijom bude obuhvaćen ograničen deo kapilicijuma kao što je to bio slučaj kod našeg pacijenta sa parijetalnom fokalnom cikatricijelnom alopecijom. Na licu može kao u našem slučaju, biti prisutan eritem; fotofobija, oftalmitis, palmo-plantarna keratodermija mogu biti prisutni u pojedinim slučajevima ali nisu osobine patognomonične za oboljenje. *Keratosis follicularis spinulosa decalvans* se prenosi u vezi sa X-hromozomom: utvrđeno je da se gen odgovoran za nastanak oboljenja nalazi na Xp 22.13 - p22.2 i to na mestu koje je na hromozomskoj mapi označeno od AFM291wf5 do AFM316yf5. Ispitivanjima koje je vršio Aten sa saradnicima, kod osoba obolelih od KFSD dokazano je prisustvo mutacija u MBTPS2 genu; utvrđeno je da navedena mutacija izaziva smanjenje aktivnosti enzima uključenog u metabolizam holesterola i barijernu funkciju epidermisa. Patohistološki nalaz u KFSD zavisi od trajanja oboljenja i od mesta sa kog je uzeta biopsija. Promene *keratosis pilaris u* isečku kože uzete s trupa ili ekstremiteta pokazuju filiformnu folikularnu hiperkeratozu), dok one u koži obrva i kapilicijuma prolaze kroz četiri razvojne faze: 1) u akutnoj ili inflamacijskoj fazi, dilatirani dlačni folikuli ispunjeni su keratinom i distrofisanim dlakama, folikularni epitel u istmusu i infundibulumu pokazuje akantozu, hipergranulozu, hiperkeratozu, a u pojedinim slučajevima istovremeno nakupljanje neutrofila i intercelularni edem u hiperkeratotičnom interfolikularnom epidermisu i papilarnom dermisu; 2) u fazi perifolikularnog nakupljanja mononuklearnih ćelija, stvaranje oskudnih infiltrata sastavljenih pretežno od limfocita i manjeg broja plazmocita, praćeno je perifolikularnim nakupljanjem mucina i zadebljalih kolagenskih vlakana koja se protežu paralelno sa zidom folikula; 3) fazu destrukcije dlačnih folikula prati manje ili više izražena granulomatozna inflamacijska reakcija s većim nakupljanjem plazma ćelija i džinovskih ćelija tipa „oko stranog tela“ usmerenih na tzv. „gole“ dlake u dermisu i na preostale delove dezintegrisanih folikula; 4) u završnoj fazi koja se ne može razlikovati od one kod pseudopelade, dlačne folikule zamenjuju fibrozni stubovi tzv. stelae. These were compatibile with the finding obtained from the biopsy taken from the parietal alopecic scalp in our patient.

Diferencijalna dijagnoza ima često dijagnostički značaj i podrazumeva isključivanje sledećeg: 1. za folliculitis spinulosa decalvans karakteristična je značajno izraženija inflamacija, pogoršanje i pojava pustula u kapilicijumu u periodu puberteta, kada kod najvećeg broja obolelih s keratosis follicularis spinulosa decalvans započinje spontano poboljšanje; 2. za lichen planopilaris karakteristične su atrofične ožiljne plaže na kapilicijumu na kojima dominira potpuno odsustvo, tj. gubitak folikularnih otvora; susedni dlačni folikuli po obodu lezija kao i rezidualni dlačni folikuli unutar same lezije okruženi su perifolikularnim eritematoznim makulama i skvamama, po ivicama delova zahvaćenih alopecijom, vidljivi su akuminirani keratotični čepovi; 3. lichen spinulosus pokazuje predilekciju za akralnu lokalizaciju za razliku od keratosis pilaris. Orožali sadržaj koji je po

 

svom izgledu karakterističan za lichen spinulosus može se lako odstraniti, pri čemu na njegovom mestu na papuli zaostaje prostor nalik na levak, dok kod KP zajedno sa keratinskim čepom biva odstranjena lezija u celini; 4. ichthyosis follicularis (IF) je prisutna na rođenju, karakteriše je neožiljna alopecija, u patohistološkom nalazu za razliku od keratosis follicularis spinulosa decalvans nema fibroze; 5. KAP sindrom (keratosis pilaris, alopecia, photophobia s. IF, alopecia i fotofobija) takođe je posledica mutacija u MBTPS2 genu na hromozomu Xp22, pa se može pretpostaviti da KAP sindrom i keratosis follicularis spinulosa decalvans predstavljaju overlap unutar spektra fenotipova jednog istog genetskog poremećaja ali je alopecija u KAP sindromu za razliku od keratosis follicularis spinulosa decalvans uvek neožiljna.

Proces se u najvećem broju slučajeva zaustavlja tokom puberteta ali su posledice trajne. Lečenje je isključivo simptomatsko, specifična terapija ne postoji: retinoide (izotretinoin, acitretin) treba primenjivati samo u vreme aktivne faze oboljenja, što znači u ranom detinjstvu. Gubitak kose, odnosno dlaka je trajan, i svako lečenje u hroničnoj, stacionarnoj fazi, tj. posle puberteta, što je do sada bio najčešći slučaj, može samo ublažiti postojeće hiperkeratotične promene. Lečenje antibioticima treba sprovoditi samo u periodima akutnog pogoršanja, koje se kod manjeg broja obolelih manifestuje pojavom eritema i malog broja pustula na koži poglavine. Iz brisa promena može se izolovati *Staphyloccocus aureus*, a lečenje treba sprovesti prema antibiogramu. Lokalna primena keratolitika i kortikosteroida dovodi samo do delimičnog poboljšanja, a po prestanku lečenja njihov efekat se gubi. Tretinoin (0,1% krem jedanput dnevno), može izazvati na koži pojavu ili pogoršanje već postojećeg eritema, što se može izbeći istovremenom primenom kortikosteroidnih kremova (jedanput do dvaput dnevno), ili 0,025% retinoične kiseline na kapilicijum alternativno svake druge noći. Uklanjanje dlaka uz pomoć rubi lasera (engl. *long-pulse non-Qswitched ruby laser*) pokazalo se efikasno u rekalcitrantnim progresivnim slučajevima KFSD. Atrofične promene mogu se lečiti dermobrazijom i/ili primenom kolagenih implantata što se danas smatra najuspešnijim metodom lečenja, a za izravnavanje površine kože mogu se primeniti ultrapulsni $CO_2$ ili YAG (*yttrium aluminium garnet*) laser. Značajno smanjenje eritema se može postići pomoću PDL lasera (engl. *pulsed dye laser at 585 nm*).

Zaključak. Autori su prikazali overlap dve retke folikularne genokeratoze u slučaju mlade osobe muškog pola sa pozitivnom porodičnom anamnezom, kod koje je *erythema ophryogenes,* pored obrva, zahvatio i poglavinu u formi *parietal*, *focal patchy cicatricial alopecia*.

## Ključne reči

Obrve; Dermatoze lica; Keratoza; Bolesti dlake; Eritem; Genetske kožne bolesti; Humani hromozom X; Darierova bolest

# A Report on the 2nd Congress of the Montenegrin Association of Dermatovenereologists, Pržno, 2015

The 2nd Congress of the Montenegrin Association of Dermatovenereologists (MADV) with International Participation was held at the Congress Center of the *Hotel Maestral*, Pržno, 26 - 29 May, 2015.

The President of the Congress was Dr. Predrag Štilet, and the President of the Scientific Committee was Prof. Miloš Pavlović.

This event brought together outstanding dermatovenereologists from many countries. More than 50 lectures were held in sessions on psoriasis, dermato-oncology, urticaria, dermatitis, autoimmune diseases, skin aging, free topics, and satellite symposia.

Lecturers from Serbia, in order of appearance, were as follows: Mirjana Milinković (A Proposal for the Clinical Workup of Patients with Psoriasis), Svetlana Popadić (Genetic Markers of Inflammation in Patients with Psoriasis), Milomir Gačević (Impact of VEGF on the Melanoma Spread), Danijela Dobrosavljević (Dermoscopy: Old and New Possibilities for Dermatologists), Mirjana Popadić (Diagnostic Significance of Dermoscopic Features for Basal Cell Carcinoma), Ljiljana Medenica (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis), Miloš

**Figure 1.** The Opening Ceremony (the front row, from right to left): Prof. Dr. Miloš Pavlović (Chairman of the Scientific Committee), Prim. Dr. Đoko Jočić (President of the Medical Chamber of Montenegro), His Excellency Dr. Johann Froehlich (Austrian Ambassador in Montenegro), Mr. Zoran Dojčinović (Consul of the Republic of Serbia in Montenegro), Prof. Dr. Rene Gonzalez (Denver, USA), Ms. Rita Gonzalez (Denver, USA), and dermatologists Dr. Bojan Spasic and Dr. Zoran Golušin (Novi Sad, Serbia)

 


**Figure 2.** Miloš Nikolić (Serbia) and Predrag Štilet on the Opening Ceremony

**Figure 3.** Ivana Binić (Serbia) and Predrag Štilet on the Opening Ceremony

**Figure 4.** Masked Ball

Nikolić (ANCA-Associated Vasculitis, Idiopathic and Drug-Induced: What are the Differences?), Marina Jovanović (Contact Sensibilization in Patients with Chronic Urticaria), Ivana Binić (Selection of Patients for Aesthetic Procedures), Marija Balković (FUE Method - Special Indications), Vesna Karanikolić (Risk Factors Related to the Prolonged Time of a Venous Leg Ulcer to Heal with Compression Treatment), Vesna Ignjatović Stojiljković (Mesotherapy and Androgenetic Alopecia), Bojana Spasić (Extramammary Paget Disease: a Case Report) and Milica Stepanović (Balneotherapy for Psoriasis: Experiences in Prolom Banja).

The guests from abroad, together with the members of the Scientific and Organizing Committees and other participants, enjoyed in the Casino of the *Hotel Maestral,* as well as in the beauty of the sea coast of Montenegro.

The masked ball and gala dinner took place in *Hotel Maestral* in Pržno on 28th May, 2015. All together, it was a successful congress with a significant contribution to the scientific field of dermatology.

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# FORTHCOMING EVENTS

Dermatology and Venereology Events 2015/2016

| DATE | MEETINGS, CONGRESSES, SYMPOSIA | ABSTRACT SUBMISSION DEADLINE | MORE INFORMATION AT |
|---|---|---|---|
| 1-4 October, 2015 | 36th Annual Meeting of the International Society for Dermatologic Surgery, Seoul, Korea | 31 July 2015 | www.isdsworld.com |
| 7-11 October, 2015 | 24th EADV Congress Copenhagen, Denmark | 19 April 2015 | www.eadvcopenhagen2015.org |
| 9-12 October, 2015 | 7th Trends in Medical Mycology Lisbon, Portugal | 1 June 2015 | www.timm2015.org |
| 16 October, 2015 | Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia | No abstract submission | www.sld.org.rs |
| 28-31 October, 2015 | 11th EADO Congress Marseille, France | 7 June 2015 | www.eado-melanomacenters-marseille2015.com |
| 5-7 November, 2015 | 18th Belgrade Dermatology Days Belgrade, Serbia | 15 September 2015 | www.udvs.org |
| 18-21 November, 2015 | 9th World Congress for Hair Research, Miami, Florida, USA | 26 May 2015 | www.hair2015.org |
| 3-5 December, 2015 | 16th Congress of the Slovak Society of Cosmetic Dermatology Zilina, Slovakia | 30 September 2015 | www.ssedk.sk |
| 11-12 December, 2015 | Congress of the Association of Serbian Cosmetic and Aesthetic Dermatology, Belgrade, Serbia | No abstract submission | www.asked.rs |
| 28-30 January, 2016 | 4th European School of Dermato-Oncology, Berlin, Germany | No abstract submission | www.dermato-oncology2016.org |
| 28-31 January, 2016 | IMCAS World Congress Paris, France | 28 December 2015 | www.imcas.com |
| 26-27 February, 2016 | 4th Symposium on Diagnosis and Treatment of Fungal Diseases Belgrade, Serbia | 20 December 2015 | www.dtfd.org |
| 7-8 April, 2016 | 1st Regional Congress on Youth Health, Belgrade, Serbia | 20 January 2016 | www.kongres-zdravljemladih.org |
| 12-14 April, 2016 | Dubai Derma 2016 Dubai, UAE | 30 November 2016 | www.dubaiderma.com |
| 19-22 May, 2016 | 13th EADV Spring Symposium Athens, Greece | 10 January 2016 | www.eadvathens2016.org |
| 26-28 May, 2016 | 13th Congress of the European Society for Pediatric Dermatology Paris, France | 15 January 2016 | www.espd2016.com |

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net

 

# AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

### Categories of Manuscripts

**1. Editorials** *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

**2. Original studies** *(limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.*

**3. Review articles** *(limited to 10 pages) should provide systemic critical assessment of literature and other data sources.*

**4. Professional articles** *(limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.*

**5. Case reports** *(limited to 6 pages) should be new, interesting and rare cases with clinical significance.*

**6. History of medicine** *(limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.*

**7. Short Communications** *(limited to 3 pages) should disseminate most current results and developments in the shortest possible time. They will be reviewed by expert reviewers and evaluated by the Editor.*

*The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and "In Memoriam". All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.*

*All manuscripts should be submitted to the* **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@open.telekom.rs.*

*Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje.org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.*

### 1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

*For manuscript preparation, please follow these instructions:*

#### 1.1. Title page

*The title page should include the following information:*

*- The title of the article, which should be informative, without abbreviations and as short as possible;*

*- A running title (limited to 30 characters);*

*- Authors' names and institutional affiliations;*

*- The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.*

#### 1.2. Abstracts

**A structured abstract in English** *(limited to 150 words) should follow the title page. The abstract should*

*provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.*

*- An* **abstract in Serbian language***, (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

### 1.3. A list of abbreviations

*Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at* http://www.bipm.fr/en/si/.

### 1.4. Cover Letter

*Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.*

## 2. Tables and illustrations

**Tables** *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

*- Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.*

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## 3. References

References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The *Vancouver System* of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in *Index Medicus*, should be abbreviated according to the style in the *List of Abbreviated Titles of Yugoslav Serial Publications* available on http://vbsw.vbs.rs. For further information please visit www.ICMJE.org.

## 4. Additional information

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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani

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