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Keratosis Lichenoides Chronica – a Case Report and Literature Review

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Abstract

Keratosis lichenoides chronica represents a distinct entity, a rare disease of unknown etiology and pathogenesis, with clinical manifestations which, although typical, require extensive differential diagnosis. The course of the disease is chronic, progressive, and it is resistant to various treatment options, so despite variations in the clinical picture it is really easier to diagnose than to treat. This is a case report of a male patient in whom the diagnosis of keratosis lichenoides chronica was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy.

Key words

Keratosis; Lichenoid Eruptions; Signs and Symptoms; Disease Progression; Diagnosis; Diagnosis, Differential; Treatment Outcome; Review

The idea for this paper on keratosis lichenoides chronica (KLC) was born after the first visit of a patient with an unusual clinical picture resembling both psoriasis and lichen planus, but also distinct from them, posing a diagnostic and therapeutic dilemma. After a consultation with Prof. Danilo Stevanović, whom we hereby wish to thank, and repeated histopathological examinations, the diagnosis of keratosis lichenoides chronica was confirmed. Papers of Böer (1), Massi et al. (2) and Ackerman et al. (3) have encouraged us to continue our analysis of published papers.

Case report

Case history

We report a 40-year old man who developed skin lesions on the trunk and extremities more than 10 years earlier: asymptomatic, symmetrically distributed linear and reticular red to purple papules with white scaly surface. Before the appearance of skin lesions, the patient's history was unremarkable and he denied taking any medications. He was treated under the diagnosis of psoriasis vulgaris, and lichen verrucosus. In 2014, he underwent phimosis surgery. There was no family history of skin conditions.

Examination

On admission, the patient presented with symmetrical generalized eruptions of erythemolivid to dark livid papules and nodules with a keratotic surface, in a solitary, linear or reticular pattern on the lower lateral parts of the trunk and along the extremities (Figures 1-3); the infiltrated lesions were prominent, verrucous and hyperkeratotic. Mild erythematosquamous lesions were present on the face. Solitary erythematous papules on erythematous base

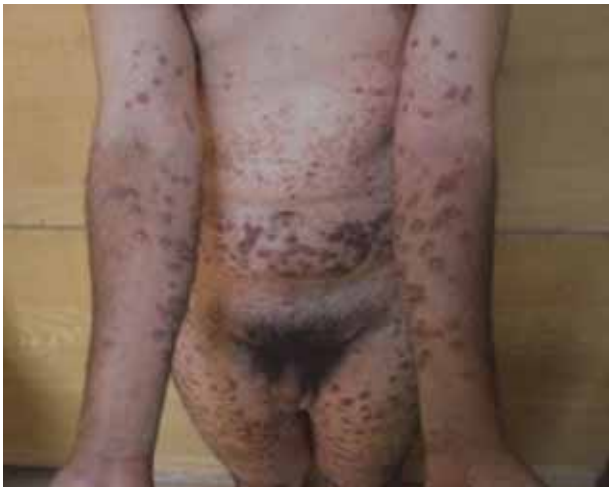

Figure 1. Skin lesions on the trunk and arms

were seen on the dorsal aspects of the feet (Figure 4), as well as palmoplantar focal hyperkeratosis. Hyperkeratotic papules were found on the preputium and scrotum preventing normal retraction over the glans (Figures 5-7).

Laboratory and histopathological tests

Relevant laboratory tests, including serologic tests for human immunodeficiency virus type 1 (HIV-1), hepatitis viruses and syphilis were within normal limits.

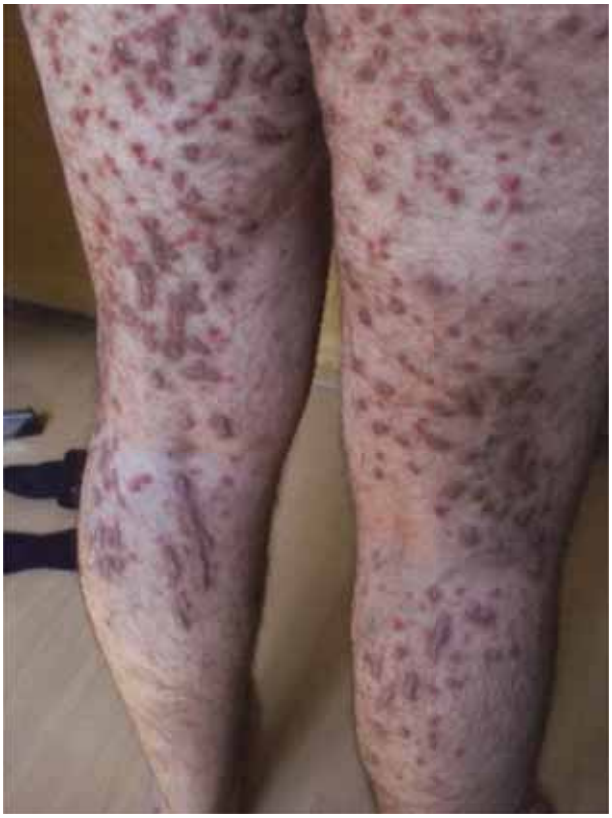

Figure 3. Lesions on the posterior aspects of lower extremities

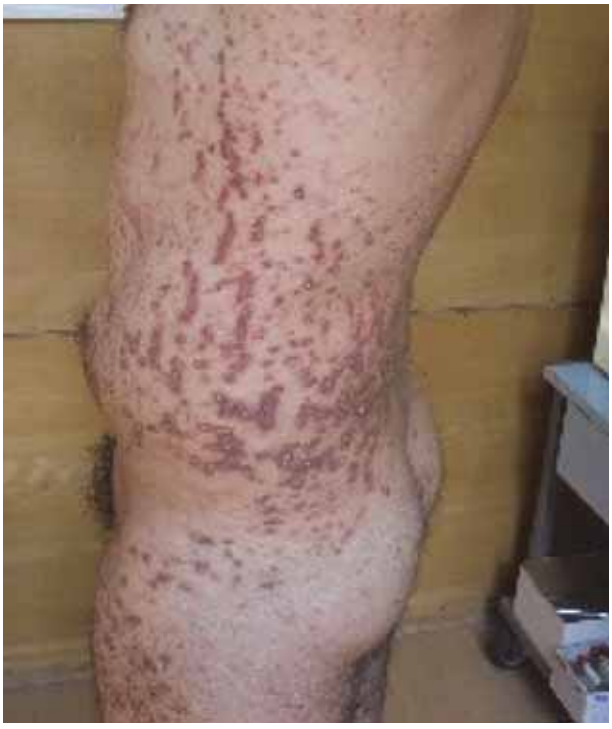

Figure 2. Lesions on the lateral aspects of the trunk

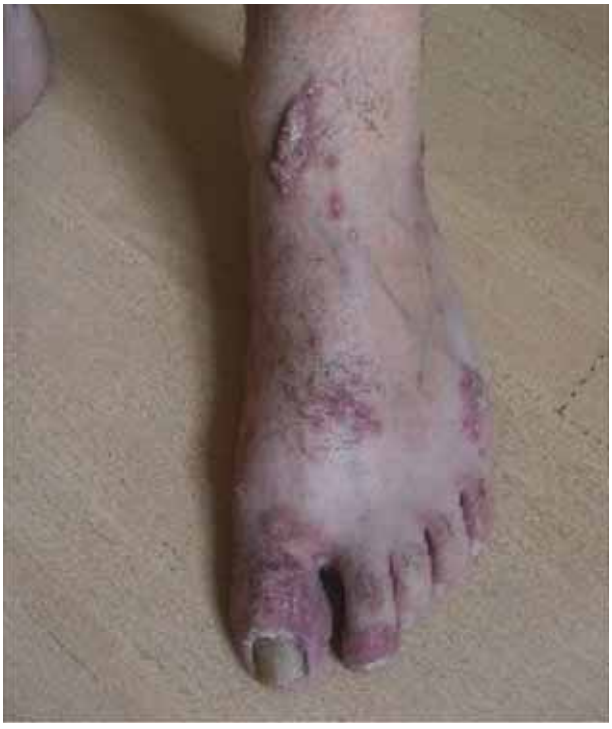

Figure 4. Lesions on the dorsal surface of the feet

Histopathological analysis of skin specimens was repeated several times: in 2004, findings pointed to psoriasiform dermatitis and later to lichenoid dermatitis; in 2009, they pointed to hypertrophic lichen planus, and in 2010 to pityriasis lichenoides. Histopathological analysis of the lower limb skin specimens performed in 2009 showed: irregular epidermal acanthosis, variable atrophy, moderate ortho-parakeratosis; telangiectasias and both superficial and deep inflammatory infiltrates in the dermis (Figure 8). Higher microscopy magnification showed vacuolar degeneration of the basal layer and distinct hyaline bodies ("civatte bodies") (Figure 9). Histopathological analysis of the preputium tissue was performed in 2014: epidermis showed irregular acanthosis, hyperkeratosis and focal parakeratosis; telangiectasia and abundant inflammatory infiltrates in the dermis (Figure 10). Higher magnification revealed irregular acanthosis, hyperkeratosis and focal follicular parakeratosis, vacuolar alteration of the basal layer of the epidermis with telangiectasia and abundant inflammatory infiltrates including lymphocytes and plasma cells in the upper dermis (Figures 11, 12).

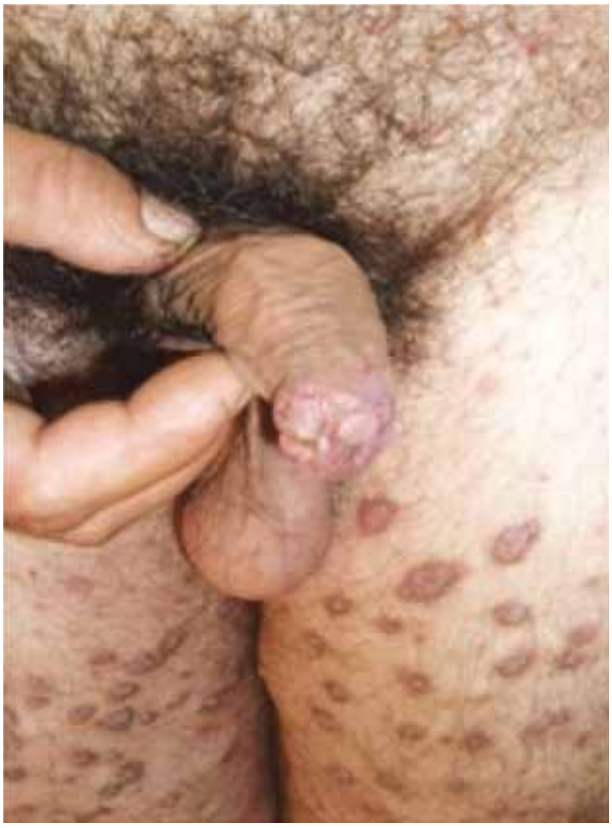

Figure 5. Penile lesions prior surgery

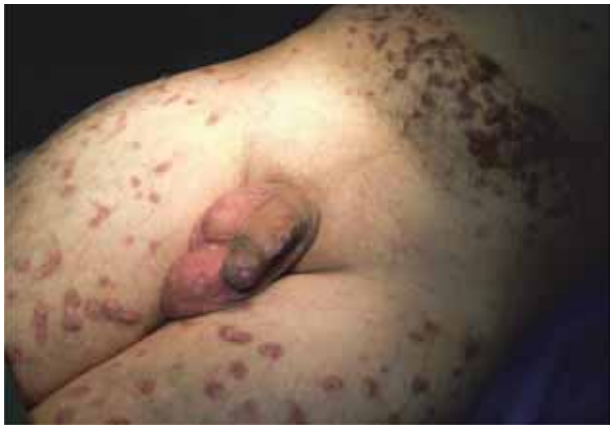

Figure 6. Penile and scrotal lesions prior surgery

Diagnosis and therapy

The diagnosis of keratosis lichenoides chronica was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy. Systemic corticosteroid therapy, UVB irradiation, topical corticosteroids and salicylic acid did not provide satisfactory results. The use of acitretin, at an initial dose of 0.3 mg/kg/bw which was increased to 1 mg/kg/bw, showed minimal therapeutic effects (Figures 13, 14).

Literature review

Keratosis lichenoides chronica is a rare, chronic, and progressive dermatosis of unknown origin (4, 5), characterized mostly by asymptomatic, papular or nodular lesions, in a linear or reticular pattern, symmetrically distributed on the trunk and extremities; facial lesions resemble seborrheic dermatitis or rosacea, but they may involve palms, soles, nails as well as oral, pharyngeal, laryngeal, ocular and genital mucous membranes (6 - 13).

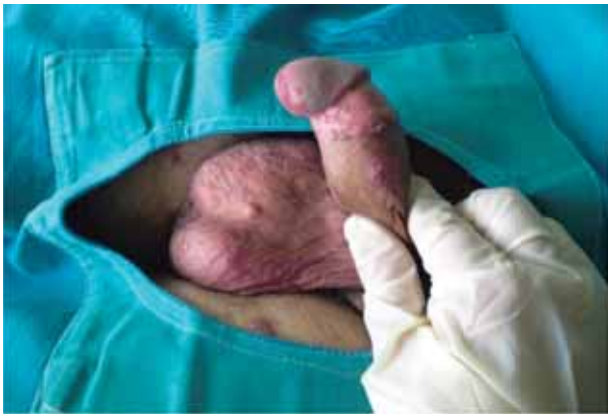

Figure 7. Penile and scrotal lesions after surgery

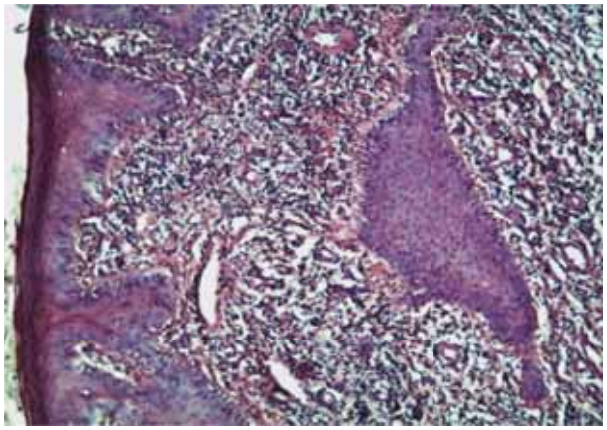

Figure 8. Histopathological finding from 2009; H&E, x 50

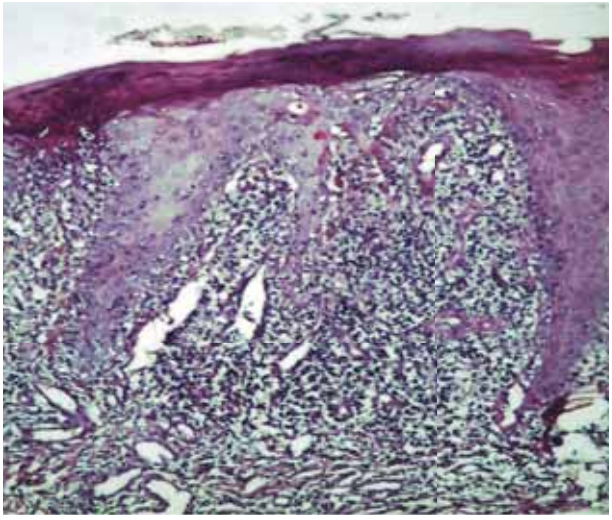

Figure 9. Histopathological finding from 2009; H&E, x 200

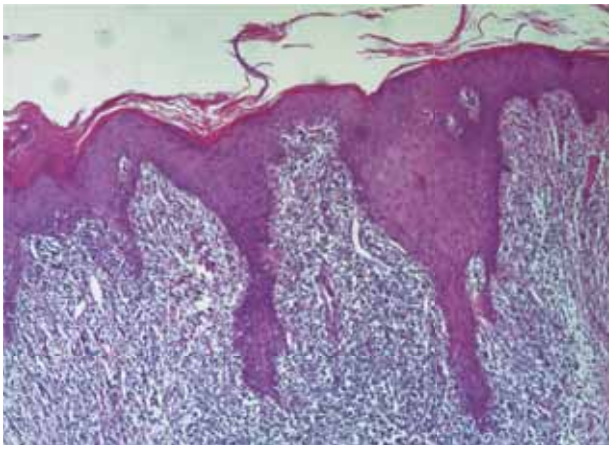

Figure 10. Histopathological finding from 2014; H&E, x 50

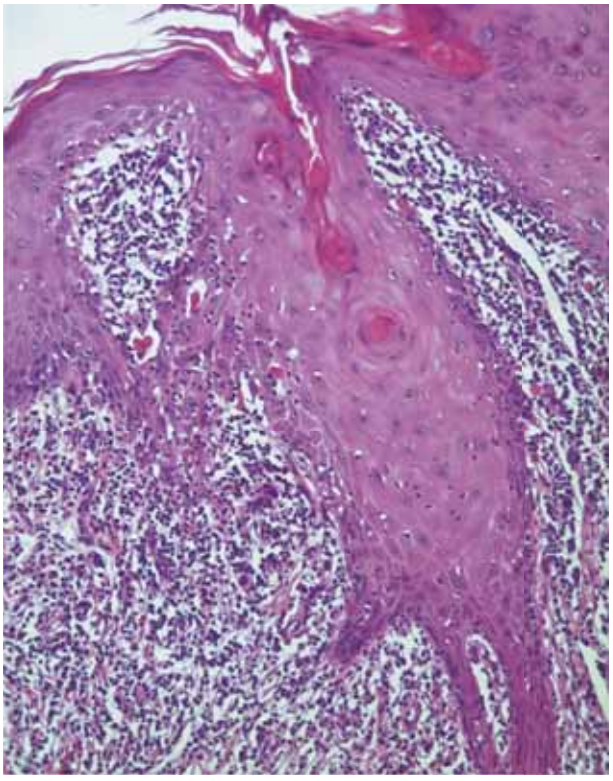

Figure 11. Histopathological finding from 2014; H&E, x 100

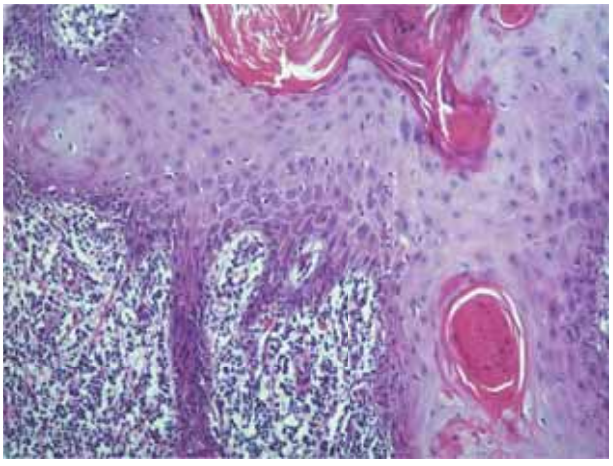

Figure 12. Histopathological finding from 2014; H&E, x 200

The first description of a patient with the clinical picture of KLC was given by Kaposi in 1886 (14) under the diagnosis of "lichen ruber moniliformis". However, in 1895, two patients with similar lesions were diagnosed with "lichen ruber acuminatus (verrucosus et reticularis)" (15). Further confusion

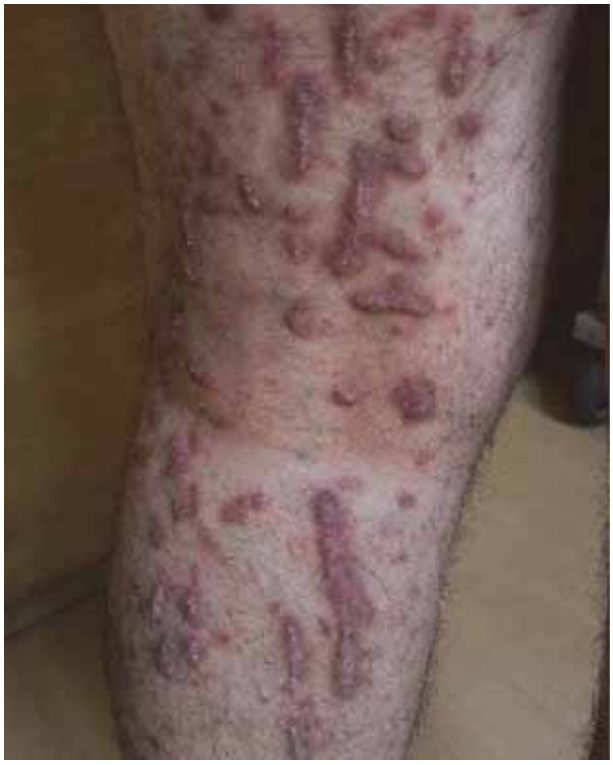

Figure 13. Skin lesions before acitretin therapy

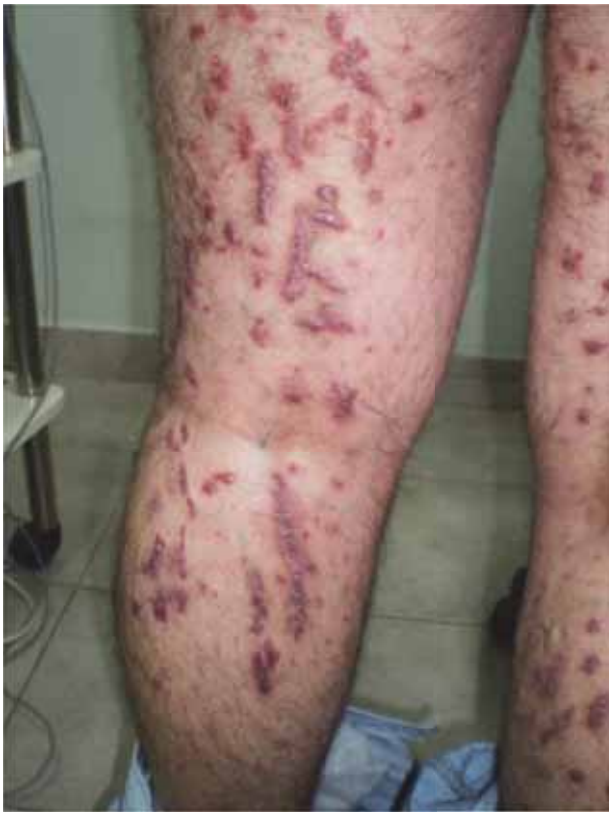

Figure 14. Skin lesions after acitretin therapy

over the name of the disease occurred in 1938 (16) when Nekam reported Kaposi's case from 1895 as "porokeratosis striata lichenoides." Since 1972, the term "keratosis lichenoides chronica", suggested by Margolis (17) for patients with a typical clinical picture, has been generally accepted for this condition, but in the meantime there were new terms as well. There are papers with terms "lichenoid trikeratosis" (18) "keratosis lichenoides striee" (19), and "dermatose papulohyperkeratosic en striée" (20).

Papers published on keratosis lichenoides chronica or synonyms from 1886 to 2014

To the best of our knowledge, in the last 128 years (1986 - 2014), 120 papers were published with keratosis lichenoides chronica or its synonyms as a topic (Table 1) (14 - 123).

In seven papers (26, 27, 29, 30, 60, 75, 93) KLC is referred to as Nekam's disease.

The etiology of the disease has not yet been identified. Mode of inheritance, influence of any other genetic alteration, relationship with any drugs or infection, has not been defined (1). The most common factors causing KLC as a variant of lichenoid drug eruption are antimalarials, antituberculosis agents (11, 20, 123), and tetanus antiserum (18); KLC may also be induced by mechanical skin damage, for example after trauma or skin transplantation (50, 84), or it is a cutaneous manifestation of toxoplasmosis (27).

The pathophysiology of KLC is not known (110). Some conditions associated with KLC, mentioned in the literature thus far, include appearance after drug-induced erythroderma (82), prolonged exposure to a source of heat (infrared radiation) (95); association with multiple eruptive keratoacanthoma-like lesions in patients with multiple myeloma (100), in patients with atypical sarcoidal granulomatous inflammation (107), or hypothyroidism (89), tuberculosis (10), kidney diseases, diabetes, lymphoma (81), toxoplasmosis (27), mycosis fungoides (78), multiple sclerosis (68) hepatitis (57, 70), lesions mimicking verrucous secondary syphilis (91), primary cutaneous anaplastic large cell lymphoma (122), atopic dermatitis (5, 10), allergic rhinitis, (3), and neurological diseases (11). However, significant association between KLC and internal diseases has not been established (87).

It has been a subject of controversy whether KLC is a distinctive inflammatory disease of the

Table 1. Papers published on keratosis lichenoides chronica or synonyms from 1886 to 2014

Diagnosis	No. of papers	Time period	References
Lichen ruber moniliformis	4	1886-1955	14, 21-23
Lichen ruber acuminatus (verrucosus et reticularis)	1	1895	15
Lichen verrucosus et reticularis	5	1944-1984	24-28
Porokeratosis striata	3	1938-1983	16, 29, 30
Lichenoid trikeratosis	1	1974	18
Keratosis lichenoides striata	9	1974-1989	19, 31-38
Dermatose papulohyperkeratosic en striées	1	1970	20
Keratosis lichenoides chronica	89	1972-2014	1-4,6, 9-13, 17, 39-123
Total	120	1886-2014	14-123

skin or whether it represents a manifestation of another well-known disease, such as lichen planus, lupus erythematosus, or lichen simplex chronicus. These dilemmas have existed for years: whether KCL represents an inherited type of epidermolysis bullosa (54), a disseminated variant of inflammatory linear verrucous epidermal nevus (ILVEN) (71), a variant of lichen planus (10, 41, 50, 53, 74, 77, 97, 86, 99, 107), or a transition of lichen planus to KLC, due to an increase in the number of focuses (109). Strong similarity between KLC and lupus erythematosus has been established (120). Basically, the condition may have an authentic disease underlying, such as lichen planus, lupus erythematosus, psoriasis vulgaris, or pityriasis rubra pilaris, if pre-existing disease is associated with signs of rubbing and scratching (2). Signs of artificiality of lesions of keratosis lichenoides chronica are striking linear lesions and a tendency for places that are easy to reach for scratching and rubbing (3). Thus, some cases of KLC may be the consequence of persistent rubbing and scratching, while others may be caused by rubbing and scratching due to a pre-existing disease (lichen planus, discoid lupus erythematosus, pityriasis rubra pilaris, psoriasis), which explains variations of histopathological findings (3).

However, it is an authentic pathological process (71), a distinct entity (1, 11), which is characterized by linear lesions, absence of Wickham's striae, long-term evolution, lack of response to corticosteroids (9), and differs from lichen planus, lupus erythematosus, pityriasis lichenoides, pityriasis rubra pilaris, psoriasis vulgaris, porokeratosis, mycosis fungoides, and porokeratosis variegata. KLC is generally considered a distinct dermatologic disease due to typical clinical and histopathological features (13).

Differential diagnosis includes lichen planus and lichen planopilaris, lupus erythematosus, pityriasis lichenoides, pityriasis rubra pilaris, psoriasis vulgaris, mycosis fungoides (78), lichenoid drug reactions (18), lichen hypertrophicus, parapsoriasis variegata, keratosis follicularis, epidermolysis bullosa pruriginosa, Reiter's and Kyrle's disease (5, 11, 53, 58, 98, 105, 117).

A full description of histopathological features of KLC was given by Böer (1): vaculoar alteration of keratinocytes along the dermo-epidermal junction;

numerous necrotic keratinocytes, sometimes in clusters, in surface epidermis and infundibular epidermis, especially in the lower parts; atrophy and sometimes erosion of epithelium in foci where there are many necrotic keratinocytes; irregular focal acanthosis; wedge-shaped hypergranulosis sometimes in zones of acanthosis; infundibular keratotic plugs of hair follicles and around acrosyringia; parakeratosis in staggered fashion; remnants of neutrophils in zones of parakeratosis; hypogranulosis beneath zones of parakeratosis; plasma cells in the infiltrate zones adjacent to erosions. Lichenoid infiltrate is found under the epidermis, often centered around an infundibulum or an acrosyringium; foreign body reaction is consequent to rupture of dilated infundibula and spewing of their contents into the dermis. Basically, it is a lichenoid dermatosis with irregular acanthosis, focal parakeratosis, variable atrophy, vacuolar degeneration of the basal layer and keratinocyte necrosis, chronic inflammatory infiltrate in the papillary dermis consisting lymphocytes, histiocytes, plasma cells and eosinophils and colloid bodies ("Civatte bodies") (67, 82, 86, 101, 107, 108, 110, 111, 113, 115, 120, 122).

KLC should be differentially distinguished from hypertrophic lichen planus: KLC is characterized by mild papillomatosis, focal parakeratosis, variable atrophy and epidermal acanthosis, vacuolar basal cell degeneration, superficial dermal telangiectasias; hyperkeratotic lichen (lichen verrucosus) is found in the epidermis and it is associated with compact orthokeratosis, papillomatosis, prominent irregular acanthosis and vacuolar basal cell degeneration.

In our patient, histopathological findings were consistent with KLC.

Due to a large number of conditions considered in the differential diagnosis and a possibility of comorbidity of two or more dermatoses (3), it sometimes happens that the patient actually suffers from a dermatosis other than KLC (1).

Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 - 2005

After analyzing the available literature, Böer (1) wrote a critical review of studies published in the period from 1886 to 2005. He found that a certain number of patients included in these studies should have been diagnosed with keratosis lichenoides chronica, no matter if they had characteristics of other similar diseases or if there was a lack of evidence for a reliable diagnosis (Table 2). According to Böer, out of the total number of patients reported from 1886 - 2005 under the controversial diagnosis of KLC or its synonym, there were 23 (34.33%) who suffered from other diseases, 20 (29.85%) with a lack of evidence for the diagnosis, while 24 (35.82%) patients suffered from keratosis lichenoides chronica, more or less certainly (Table 2) (1).

In his analysis, Böer argued that the diagnosis of KLC should be made only for patients presenting with at least two clinical and one histological feature: 1. chronic facial lesions reminiscent of seborrhoeic dermatitis; 2. tiny papules on the trunk and extremities, which assumed linear and reticulate shapes by way of confluence of lesions, with infundibulocentric papules and papules around acrosyringia; 3. histological feature: lichenoid dermatitis with numerous necrotic keratinocytes and parakeratosis. Among other characteristics, there may be mucosal involvement, including conjunctival hyperemia, but they are not indicative (1).

According to the findings of Böer (1), KLC affects men and women equally, mostly adults. Anamnestic data show that lesions often persist for years before diagnosis. The lesions are found on the face, extremities, especially on the acral regions, less often on the trunk, while mucous membranes are affected in 25% of patients. The lesions may be discrete, individual, linear or circular, atrophic, with erosions or crusts, forming keratotic papules or plaques. Pruritus is present in less than 20% of patients. Deviations from laboratory findings are nonspecific and are of no diagnostic value. The course of the disease is protracted, while complete resolution has never been reported.

Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 - 2014

Although a review of the available literature revealed about 120 papers on KLC, certainly with a larger number of patients, Böer's analysis (1) shows that the actual number of patients suffering from KLC in the period from 1886 to 2014 cannot be determined with certainty.

In order to get information about the patients and characteristics of KLC, we have reviewed 98

Table 2. Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 – 2005*

	Diagnosis*	References	Time period	No. of patients
Adults	Dermatitis atopica	70	1996	1
	Lichen planus	57, 80, 84, 95 97	1989-2005	5
	Porokeratosis	18	1974	1
	Lupus erythematosus	27,28	1976, 1984	2
	Lichen simplex	27, 43, 89	1976-2002	3
	Subepidermal bullous dermatosis	54	1986	1
	Unclarified diagnosis	11,13, 25, 27, 29, 49, 58, 62, 71, 72, 74, 76, 86, 94,	1954-2004	16
	Keratosis lichenoides chronica (KLC)	24, 31,45, 48, 73, 77, 79, 96	1981- 1999	8
	Possible KLC	20, 38, 97	1970- 2005	3
	Probable KLC	16, 17, 18, 26, 27, 41, 47, 71, 91	1938- 2003	9
Total				49
Children	Dermatitis atopica	15	1895	1
	Lichen planus	12, 81, 85	1982/2001	3
	Lupus erythematodes	46, 59	1981, 1993	2
	Subepidermal bullous dermatosis	40	1976	1
	Lichen simplex	33	1997	1
	Verrucae vulgaris	41	1995	1
	ILVEN	71	1997	1
	Unclear	44,60,71	1973-1993	4
	KLC	59, 71	1993, 1997	2
	Probable KLC 50	69	1996	1
	Possible KLC	34	1983	1
Total				18
Adults + children				67

*, Böer A. 2006 (1); KCL, keratosis lichenoides chronica; ILVEN, inflammatory linear verrucous epidermal nevus

papers published in the available literature in the period from 1886 to 2014, including a total of 115 patients (Table 3). Adult patients in whom the disease began in childhood were grouped as children. The disease is more common in males. The male to female ratio was around 1.97: 1 with male predominance (in children and adults, the ratio was 1.62:1 and 2.17:1, respectively). According to our analysis, the average age of KLC onset was 37 years (in children and adults it was 15 and 47 years, respectively). According to data from 1995 (10), KLC was also more common in males (the male to female ratio was 1.35:1), usually affecting people aged between 20 and 40 years of age, with an average age of onset of 28,5 years (10). According to data from 2010, the age of disease onset was between the ages of 20 to 50 years (110). Clinical signs of the disease are most typical among adolescents and young adults (107). The fact that KLC is uncommon in pediatric population (63, 66, 90) is not fully in agreement with our findings. It would be more precise to claim that it is less common in children, considering the fact that in 31.48% of patients the onset of the disease was in childhood. The rarity of pediatric cases may be due to late diagnosis, rather than actual low incidence among children (90). KLC rarely affects several persons from the same family (59, 106); only 10 (8.70%) cases have been reported so far, all being affected in childhood, while congenital cases were described only in 4 (3.48%) patients (Table 3).

Table 3 shows that KLC lesions are most commonly found on the extremities, both in children and adults, whereas 40% of patients present with palmoplantar hyperkeratosis; facial lesions are more common in adults than in children; nail lesions are more common in adults, affecting over 30% of patients, presenting as yellow discoloration, thickening and longitudinal ridging of the nail plate and nail bed hyperkeratosis; oral lesions are more common in adults than in children; ocular lesions include blepharitis, conjunctivitis, anterior uveitis and iridicyclitis which affect both children and adults; genital lesions, including keratotic papules on the scrotum and penis, chronic balanitis and phimosis, have been reported in 9.88% of adults, but in children they have not been described; pruritus occurs in less than 20% of patients, both in children and adults (Table 3).

Facial reticular lichenoid eruptions (121), vascular variant of the disease with telangiectasia (57, 89), purpura (111), as well as unilateral distribution of lesions (64) have been reported in the literature, although less commonly (124).

Based on the analysis of reported cases of KLC in adults and children, Ruiz-Maldonado et al. (9) pointed out clearly defined several characteristics of the disease that only occur in patients in whom the disease started in childhood: occurrence of the disease in members of the same family (autosomal recessive inheritance); in children, lesions including erythematous purpuric macules always appear first on the face with subsequent hyperpigmentation; alopecia has only been described in children.

The disease proved to be resistant to various therapeutic regimes, both topical and systemic (107). The following therapeutic modalities proved to be inefficient: systemic and topical corticosteroids, systemic antimalarials, diaminodiphenylsulfone, tetracyclines, cyclosporine, methotrexate (90, 91). Various results were obtained with systemic administration of acitretin, isotretinoin, etretinate, psoralen ultraviolet A radiation (PUVA), retinoids combined with PUVA or with narrow-band ultraviolet B radiation (NB-UVB) (4), as well as topical calcipotriol (89, 98) and NB-UVB monotherapy (106). NB-UVB has proven more effective in the treatment of children than adults (117). Significant improvement has been achieved with photodynamic therapy (104) and treatment with efalizumab (107). According to Ghislain (87), PUVA therapy is the first line therapy for this rare disease. There are also reports on spontaneous improvement or complete spontaneous remission (62, 63). Table 4 shows results of treatment using various medications and physical therapeutic procedures in the period from 1886 - 2014.

In 1938, Nekam (16) described a patient who had been reported by Kaposi in 1895 (15), even suggesting another term for the condition. We report a patient treated at our clinic since 2004 (119). He presented with genital lesions in 2014, and they were surgically resolved.

Conclusion

In our patient the diagnosis was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy. Keratosis lichenoides chronica represents a distinct entity, a rare disease of unknown etiology

Table 3. Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 - 2014

Keratosis lichenoides chronica	**Children**	**Adults**	**Total**
Number of papers	25 (25.51%)	73 (74.49%)	98 (100%)
Number of patients	34 (29.57%)	81 (70.43%)	115 (100%)
Males	21 (61.76%)	50 (68.49%)	71 (66.36%)
Females	1 (38.24%)	23 (31.51%)	36 (33.64%)
Unrecorded sex		8 (6.96%)	8 (6.96%)
Male/Female	1,62	2,17	1,97
Median age (y)	15	47	37
Median age at onset (y)	1	35	24
Range of age at onset (y)	Birth - 16	18 - 80	Birth- 80
Median duration of disease (y)	11	5	7
Range of disease duration (y)	0,3-49*	0.01- 48	0.3-49
Congenital cases	4 (11.76%)	0 (0.00%)	4 (3.48%)
Familial cases	10 (29.41%)	0 (0.00%)	10 (8.70%)
Initial site	Face	Extremities	
Facial lesions	Erythematous/purpuric	Seborrheic-like/rosacea like	
Face	30 (88.24%)	31 (38.27%)	61 (53.04%)
Extremities	19 (55.88%)	66 (81.48%)	85 (77.27%)
Trunk	9 (26.47%)	32 (39.51%)	41 (35.65%)
Dissemination	5 (14.71%)	8 (9.88%)	13 (11.30%)
Ocular lesions	4 (11.76%)	7 (8.64%	11 (9.57%)
Oral lesions	4 (11.76%(	22 (27.16%)	26 (22.61%)
Genital lesions	0 (0.00%)	8 (9.88%)	8 (6.96%)
Nail lesions	1 (2.94%)	29 (35.86%)	30 (26.09%)
Alopecia	5 (14.71%)	0 (0.00%)	5 (4.31%)
Pruritus	7 (20.59%)	10 (12.35%)	17 (14.78%)

Y, year; *, Adults with childhood onset were included in the group of children

Table 4. Treatment effects in patients with KLC treated in the period 1886 - 2014

Treatment effects	Therapy	Reference
No response	X rays, Vitamin A	24
	Topical steroids/retinoids/tar	6,45, 62,99,102, 108, 111, 117
	Miscellaneous	11, 107,120
	Dapsone, Calcipotriol	93, 106
	Acitretin, Griseofulvin, Corticosteroids	98
	Topical and systemic steroids and PUVA	55
	Systemic steroids, Sulphones, Methotrexate, Antimalarials, Irradiation, Cyclosporine	1, 4, 98, 107
Partial improvement	PUVA	6, 99
	Calcipotriol	97
	Acitretin	100, 111, 119
	Bath PUVA	101
	PUVA + oral retinoids	107, 118
	Etretinate	
	Sun exposure	106
Clinical improvement	Oral corticosteroids	44,68
	Levamosol	21
	PUVA	30, 65 , 67, 87, 114
	Oral retinoids	6, 9,22,23, 27,35, 49, 57, 63
	Retinoids + PUVA	53, 67, 98
	Calcipotriol	59
	NB-UVB	11, 122
	Neotigason + bath Puva	43
	Prednisolone	82
	Cyclosporine	102, 92
	Photodynamic therapy	104
	PUVA, Acitretin, Calcipotriol	108
	Methotrexate	45
	Sulphadiazine	40
	Cotrimoxazol	40
	Bath PUVA	66
	Sun exposure	90
	Topical tacrolimus	116
Complete resolution	Tigason	31
	Erythromycin	26
	Etoposide	102
	Efalizumab	107
Spontaneous resolution		62

PUVA, psoralen ultraviolet A irradiation; NB-UVB, narrow-band ultraviolet B irradiation

and pathogenesis, with clinical manifestations which, although typical, require extensive differential diagnosis. The course of the disease is chronic, progressive, and it is resistant to various treatment options, so despite variations in the clinical picture it is really easier to diagnose than to treat.

Abbreviations

KLC - keratosis lichenoides chronica
HIV-1 - human immunodeficiency virus type 1
ILVEN - inflammatory linear verrucous epidermal nevus
PUVA - psoralen ultraviolet A radiation
NB-UVB - narrow-band ultraviolet B radiation

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Hronična liheoidna keratoza – prikaz bolesnika iz sopstvene prakse i pregled literature

Sažetak

Uvod. Ideja za ovakav pristup liheoidnoj hroničnoj keratozi (*keratosis lichenoides chronica*), rodila se kao rezultat prvog susreta sa bolesnikom koji je imao neobičnu kliničku sliku koja je asocirala na lihen ili psorijazu, ali se ipak razlikovala od njih, što je dovelo do dileme oko dijagnoze i lečenja. Konsultacija sa profesorom Danilom Stevanovićem, kome ovom prilikom zahvaljujemo, i više puta urađen patohistološki pregled konačno su potvrdili dijagnozu: *keratosis lichenoides chronic* (KLC).

Prikaz obolelog. Prikazujemo muškarca starog 40 godina kod koga su se promene na koži trupa i ekstremitetima pojavile pre više od 10 godina u vidu asimptomatskih simetrično raspoređenih pojedinačnih i slivenih crtastih i mrežastih izbočenja crvenoljubičaste boje sa beličastim ljuspama na površini. Pre pojave promena na koži nije uzimao nikakve lekove niti je bolovao od drugih bolesti. Lečen je pod dijagnozom *psoriasis vulgaris*, *lichen verrucosus*. Operisao je fimozu 2014. godine. U porodici nije bilo obolelih srodnika.

Pri pregledu, na donjoj polovini i bočnim stranama trupa i duž ekstremiteta, registruje se simetrična generalizovana erupcija od eritemolividnih do tamnolividnih papula i nodusa sa keratotičnom površinom, pojedinačnih ili u linearnom i retikularnom rasporedu (slike 1–3); lezije su infiltrirane, prominentne, često verukoznog izgleda i hiperkeratotične ; na licu prisutni blago izraženi eritemoskvamozni plakovi, blagog intenziteta ; na dorzalnim stranama stopala vidljive pojedinačne eritematozne papule na eritematoznoj osnovi (Slika 4); palmoplantarno prisutna fokalna hiperkeratoza ; na prepucijumu i skrotumu pojedinačne hiperkeratotične papule sa otežanim prevlačenjem preko glansa (slike 5–7).

Relevantne laboratorijske analize, uključujući i serološke reakcije na HIV-1 (eng. *human immunodeficiency virus type 1*), viruse hepatitisa i sifilis, bile su u granicama fizioloških vrednosti. Patohistološka analiza isečka kože rađena je u više navrata, od 2004. godine kada je nalaz ukazivao na psorijaziformni dermatitis, potom lihenoidni dermatitis, 2009. godine na hipertrofični lihen planus, a 2010. godine *pityriasis lichenoides*. Patohistološka analiza isečka kože sa ekstremiteta rađena 2009. godine: epidermis pokazuje iregularnu akantozu, varijabilnu atrofiju, umerenu ortoparakeratozu; teleangiektazije i superficijalni i dublje lokalizovan inflamatorni ćelijski infiltrat u dermisu (Slika 8); na većem mikroskopskom povećanju prisutni su vakuolarna degeneracija bazalnog sloja i upadljiva hijalina tela (*civatte body*) (Slika 9). Patohistološka analiza isečka kože prepucijuma rađena je 2014. godine: iregularna akantoza, hiperkeratoza i fokalna parakeratoza u epidermisu; teleangiektazije uz inflamatorni infiltrat u dermisu (Slika 10); na većem uveličanju vidi se iregularna akantoza, fokalna folikularna hiperkeratoza i parakeratoza, vakuolna degeneracija ćelija bazalnog sloja epidermisa uz teleangiektazije i inflamatorni infiltrat sastavljen od limfocita i plazma ćelija (slike 11 i 12). Dijagnoza KLC je postavljena na osnovu tipične kliničke slike u prvom redu, na osnovu više puta ponovljene biopsije i patohistološkog nalaza, toka bolesti i slabog odgovora na bilo koji vid terapije:

sistemska primena kortikosteroida, UVB zračenje, topijski kortikosteroidi i salicilna kiselina nisu pružili zadovoljavajuće rezultate, primena acitretina u početnoj dozi od 0,3 mg/kgTT sa porasom do 1 mg/kgTT dala je neznatne terapijske efekte (slike 13 i 14).

Pregled literature. *Keratosis lichenoides chronica* (KLC) veoma je retka hronična i progresivna dermatoza nerazjašnjene etiologije koju najčešće karakterišu asimptomatske papulozne ili nodularne lezije, paralelne linearne ili retikularne, simetično raspoređene na trupu, ekstremitetima i na licu koje podsećaju na seborični dermatitis ili rozaceu; moguće su i lezije na dlanovima, tabanima, noktima i mukoznim membranama – oralnim, faringealnim, laringealnim, okularnim i genitalnim. Prvi opis bolesnika sa ovakvom kliničkom slikom dao je Kaposi 1886. godine pod dijagnozom *lichen ruber moniliformis; 1895. godine, kod* dva bolesnika sa sličnim promenama postavio je dijagnozu *lichen ruber acuminatus* (*verrucosus et reticularis*). Dalja konfuzija oko naziva bolesti nastaje kada je Nekam 1938. godine, opisujući Kaposijevog bolesnika iz 1895. godine, postavio dijagnozu *porokeratosis striata lichenoides*. Za bolesnika sa tipičnom kliničkom slikom Margolis 1972. godine predlaže naziv *keratosis lichenoides chronica*, koji je definitivno prihvaćen, mada je u međuvremenu bilo i novih termina. Tako se javljaju publikacije u kojima se navode termini *lichenoid tri-keratosis*, *keratosis lichenoides striee*, *dermatose papulohyperkeratosic en striée*.

Objavljeni radovi o slučajevima sa dijagnozom *keratosis lichenoides chronica* ili sinonimima u periodu 1886–2014. godine. U periodu od 1886. do 2014. godine, dakle poslednjih 128 godina, objavljeno je prema našem saznanju 120 radova pod naslovom *keratosis lichenoides chronica* (KLC) ili sinonimima (Tabela 1). Etiologija bolesti nije razjašnjena. Način nasleđivanja, ili uticaj drugih genetskih alteracija, ili povezanost sa nekim lekovima ili infekcijom nisu definisani. Faktori „okrivljeni" da izazivaju KLC kao varijantu lihenoidne erupcije na lekove su antimalarici, antituberkulotici, tetanusni antiserum; KLC se može javiti i posle mehaničkog oštećenje kože, npr. traume i transplantacije kože ili može predstavljati kutanu manifestaciju toksoplazmoze.

Patofiziologija takođe nije dovoljno razjašnjena. Opisana je pojava KLC posle lekovima izazvane eritrodermije, prolongirane ekspozicije izvoru toplote (infracrvena radijacija). Udruženost KLC sa lezijama sličnim/nalik keratomu opisana je kod bolesnika sa multiplim mijelomom i kod bolesnika sa atipičnom sarkoidalnom granulomatoznom inflamacijom; opisana je udruženost KLC sa hipotiroidizmom, sa tuberkulozom, bolestima bubrega, dijabetesom, limfomom, toksoplazmozom, *mycosis fungoides*, multiplom sklerozom, hepatitisom, lezijama sličnim verukoznom sekundarnom sifilisu, sa primarnim kutanim anaplastičnim krupnoćelijskim limfomom, sa atopijskim dermatitisom, alergijskim rinitisom, neurološkim bolestima. Međutim, nije moguće ustanoviti signifikantnu povezanost između KLC i oboljenja unutrašnjih organa. Još veće nejasnoće se javljaju kada se postavi pitanje da li KLC predstavlja klasičnu zapaljensku bolest, poseban entitet, ili predstavlja manifestaciju drugih poznatih dermatoza, ka što su *lichen planus*, *lupus erythematosus* ili *lichen chronicus*. Ove dileme traju godinama – da li KCL predstavlja nasledni oblik *epidermolysis bullosa*, ili diseminovanu varijantu inflamiranog linearnog verukoznog epidermalnog nevusa, ili tranziciju lihen planusa u KLC, usled porasta broja fokusa. Utvrđena je izuzetna sličnost KLC sa lupusom ertematozusom.

U osnovi, oboljenje se može pogrešno dijagnostikovati u okviru dermatoza kao što su *lichen planus*, *lupus erythematosus*, psori*asis vulgaris*, *pityriasis rubra pilaris*, ukoliko se na znake ovih dermatoza nadovezuju znaci češanja i trljanja. Znaci arteficijalnosti lezija su: upečatljiva linearnost lezija, sklonost za češanje i trljanje mesta koja su lako dostupna). Tako se neki slučajevi KLC mogu smatrati posledicom upornog trljanja i češanja, drugi mogu biti od već postojeće bolesti (*lichen planus*, diskoidni eritemski lupus *pityriasis rubra pilaris*, psorijaza), što objašnjava varijacije patohistološkog nalaza.

Međutim, radi se o autentičnom patološkom procesu, posebnom entitetu, koji karakterišu lezije u linearnom rasporedu, odsustvo Vikamovih strija, dugotrajna evolucija, slab odgovor na kortikosteroide, koji se razlikuje od manifestacija karakterističnih za: *lichen planus*, *lupus erythematosus*, *pityriasis lichenoides*, *pityriasis rubra pilaris*, *psoriasis vulgaris porokeratosis*, *mycosis fungoides* i *porokeratosis variegata*. KLC se generalno smatra posebnim dermatološkim oboljenjem na osnovu tipične kliničke i patohistološke slike.

Diferencijalno-dijagnostički dolaze u obzir: *lichen planus* i *lichen planopilaris*, *lupus erythematosus*, *pityriasis lichenoides*, *pityriasis rubra pilaris*, *psoriasis vulgaris*, *mycosis fungoides,* lihenoidna reakcija na lekove, *lichen hypertrophicus*, *parapsoriasis variegata*, *keratosis follicularis*, *epidermolysis bullosa pruriginosa*, Rajterova bolest, *morbus Kyrle*. Opsežan opis patohistoloških krakteristika dao je Ber (*Böer*): prisustvo vakuolarne degeneracije keratinocita na dermoepidermalnoj granici; brojni nekrotični keratinociti ponekad u jatima, u površnom epidermisu i infundibularnom epidermisu, naročito u nižim delovima; atrofija i ponekad erozija epitela u žarištima gde ima mnogo nekrotičnih keratinocita; neravnomerna akantoza u žarištima; može biti prisutna hipergranuloza klinastog oblika u zonama akantoze; keratinski čepovi u infunibulumu folikula dlake i oko akrosiringija; neravnomerna parakeratoza; ostaci neutrofila u zonama parakeratoze; hipogranuloza ispod zone parakeratoze; plazma ćelije u infiltratu u zonama pored erozije. Ispod površine epidermisa nalazi se limfoidni infiltrat koji je često centriran oko infundibula i akrosiringa; reakcija stranog tela kao posledica rupture dilatiranih infundibula i izbacivanja njihovog sadržaja u dermis.

U osnovi, radi se o lihednoidnoj dermatozi sa iregularnom akantozom, fokalnom parakeratozom, varijabilnom atrofijom, vakuolarnom degeneracijom bazalnog sloja i nekrozom keratinocita, hroničnim inflamatornim infiltratom u papilarnom dermisu sastavljenim od limfocita, histiocita, plazma ćelija i eozinofila i koloidnim telima (*Civatte body*). Diferencijlno- dijagnostički treba razlikovati KLC od oboljenja *lichen hypertrophicus*. Kod KLC nalazi se blaga papilomatoza fokalna parakeratoza, varijabilna atrofija i akantoza epidermisa, vakuolarna degeneracija bazalnih ćelija, teleangiektazije u superficijalnom dermu; kod oboljenja *lichen hyperkeratoticus* (*lichen verrucosus*) prisutna je u epidermisu kompaktna ortokeratoza papilomatoza, prominentna iregularna akantoza i prominentna vakuolarna degeneracija bazalnih ćelija.

Patohistološki nalaz kod našeg bolesnika bio je karakterističan za KLC. Upravo zbog velikog broja dermatoza koje diferencijalno-dijagnostički dolaze u obzir i zbog mogućnosti istovremenonog obolevanja od dve ili više dermatoza, dešavalo se da je prikazani bolesnik u stvari oboleo od druge dermatoze a ne od KLC. Slučajevi obolevanja pacijenata, objavljeni pod kontroverznom dijagnozom *keratosis lichenoides chronica* (KCL)/ili sinonimima, u periodu 1886–2005. godine. Analizom dostupne literature Ber je napravio kritički osvrt na objavljene podatke u periodu 1886–2005. godine i našao da bi za izvestan broj bolesnika obuhvaćenih ovom analizom trebalo da bude postavljena dijagnoza *keratosis lichenoides chronica*, bilo da ima karakteristike drugog sličnog oboljenja ili da nema dovoljno podataka kliničkih ili patohistoloških za postavjanje sigurne dijagnoze (Tabela 2). Radeći ovu analizu Ber je zastupao stav da se KLC može dijagnostikovati samo ako su prisutna najmanje dva klinička i jedan histološki kriterijum: 1. hronične rasprostranjene erupcije koje zahvataju lice, slične seboroičnom dermatitisu; 2. papularna erupcija sa karakterističnim linearnim i retikularnim rasporedom na trupu i ekstremitetima, pri čemu se centar papula nalazi u infundibulumu ili u akrosiringu; 3. histološki: lihenoidni dermatitis sa mnogobrojnim nekrotičnim keratinocitima i parakeratozom. Od ostalih znakova, može se javiti mukozno zahvatanje, uključujući konjunktivalnu hiperemiju, ali ono nije karakteristično. Prema nalazima Bera odstupanja u laboratorijskim nalazima su nespecifična i nemaju dijagnostički značaj. Tok je protrahiran, kompletna rezolucija promena nije nikada opisana.

Slučajevi obolevanja pacijenata objavljeni pod kontroverznom dijagnozom KCL/ili sinonimima u periodu 1886–2014. godine. Iako je prema nama dostupnoj literaturi registrovano oko 120 radova sa KLC i svakako sa većim brojem obolelih, s obzirom na analizu Bera, ne može se sa sigurnošću odrediti koliko je u periodu 1886–2014. godine bilo stvarno obolelih od KLC. Da bismo prikazali podatke o bolesnicima i karakteristike KLC, obradili smo 98 radova objavljenih u nama dostupnoj literaturi u periodu 1886–2014. godine, u kojima je prikazano ukupno 115 bolesnika (Tabela 3). Bolest se pokazala rezistentnom na mnoge terapijske modalitete, bilo lokalne bilo sistemski primenjene). U Tabeli 4 prikazani su rezultati lečenja raznim medikamentima i fizikalnim metodama u periodu 1886–2014. godine.

Nekam je 1938. godine opisao bolesnika koga je Kaposi prikazao 1895. godine i čak predlozio drugi naziv za oboljenje. Mi prikazujemo bolesnika koga pratimo na našoj klinici od 2004. godine. Povod je bio želja da prikažemo i promene na genitalijama,

koje su se pojavile 2014. godine a koje su morale biti hirurškim putem rešene.
Zaključak. Dijagnoza je kod pacijenta koga smo prikazali postavljena na osnovu tipične kliničke slike, na osnovu više puta ponovljene biopsije i patohistološkog nalaza, toka bolesti i slabog odgovora na bilo koji vid terapije. Tok bolesti je inače hroničan, progresivan sa rezistencijom na razne vrste terapije, tako da je i pored varijacija u kliničkoj slici zaista lakše postaviti dijagnozu bolesti nego je lečiti.

Ključne reči

Keratoza; Lihenoidne erupcije; Znaci i simptomi; Tok bolesti; Dijagnoza; Diferencijalna dijagnoza; Ishod terapije; Pregled literature

