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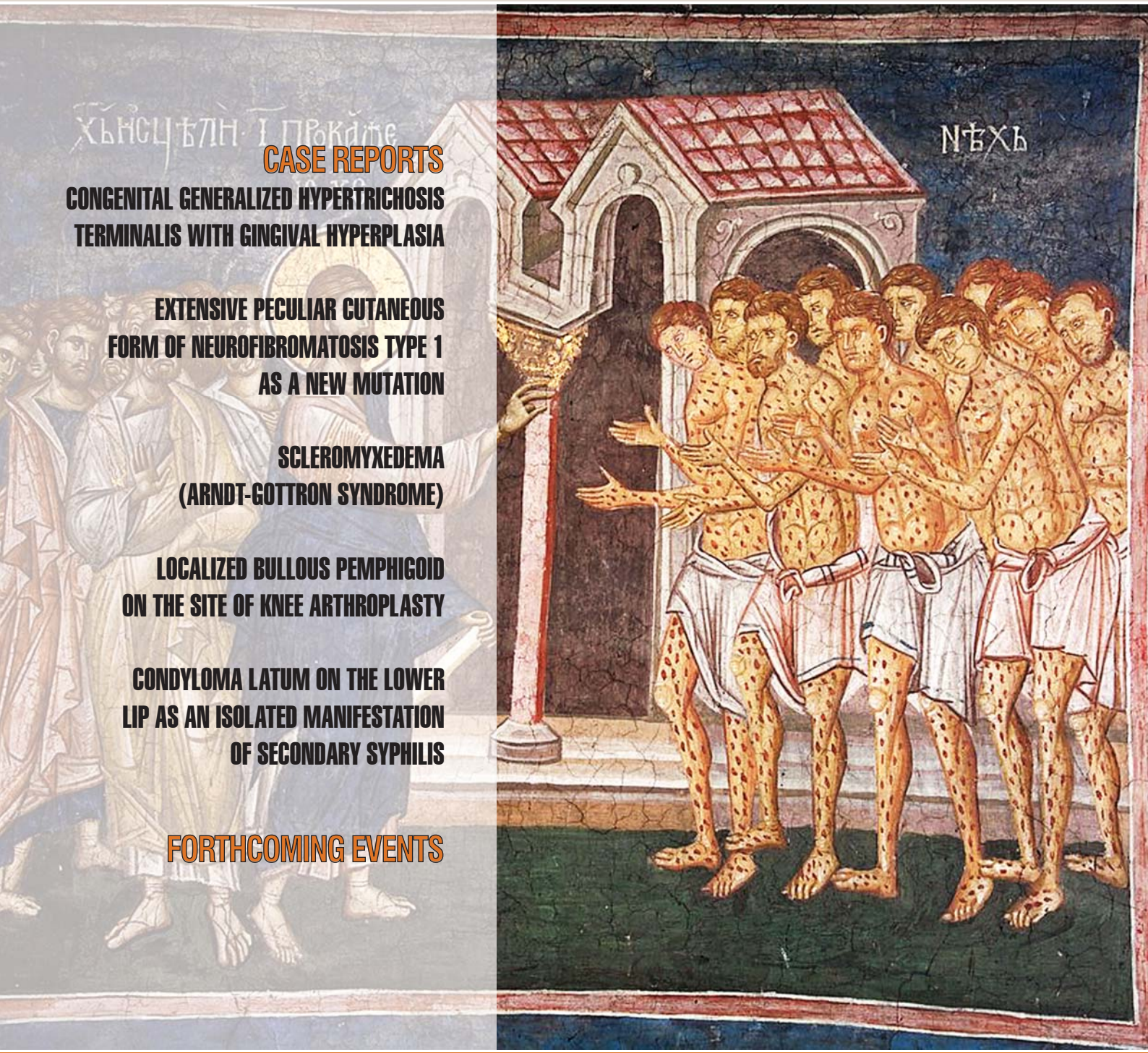

CASE REPORTS

CONGENITAL GENERALIZED HYPERTRICHOSIS TERMINALIS WITH GINGIVAL HYPERPLASIA

EXTENSIVE PECULIAR CUTANEOUS FORM OF NEUROFIBROMATOSIS TYPE 1 AS A NEW MUTATION

SCLEROMYXEDEMA (ARNDT-GOTTRON SYNDROME)

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CONDYLOMA LATUM ON THE LOWER LIP AS AN ISOLATED MANIFESTATION OF SECONDARY SYPHILIS

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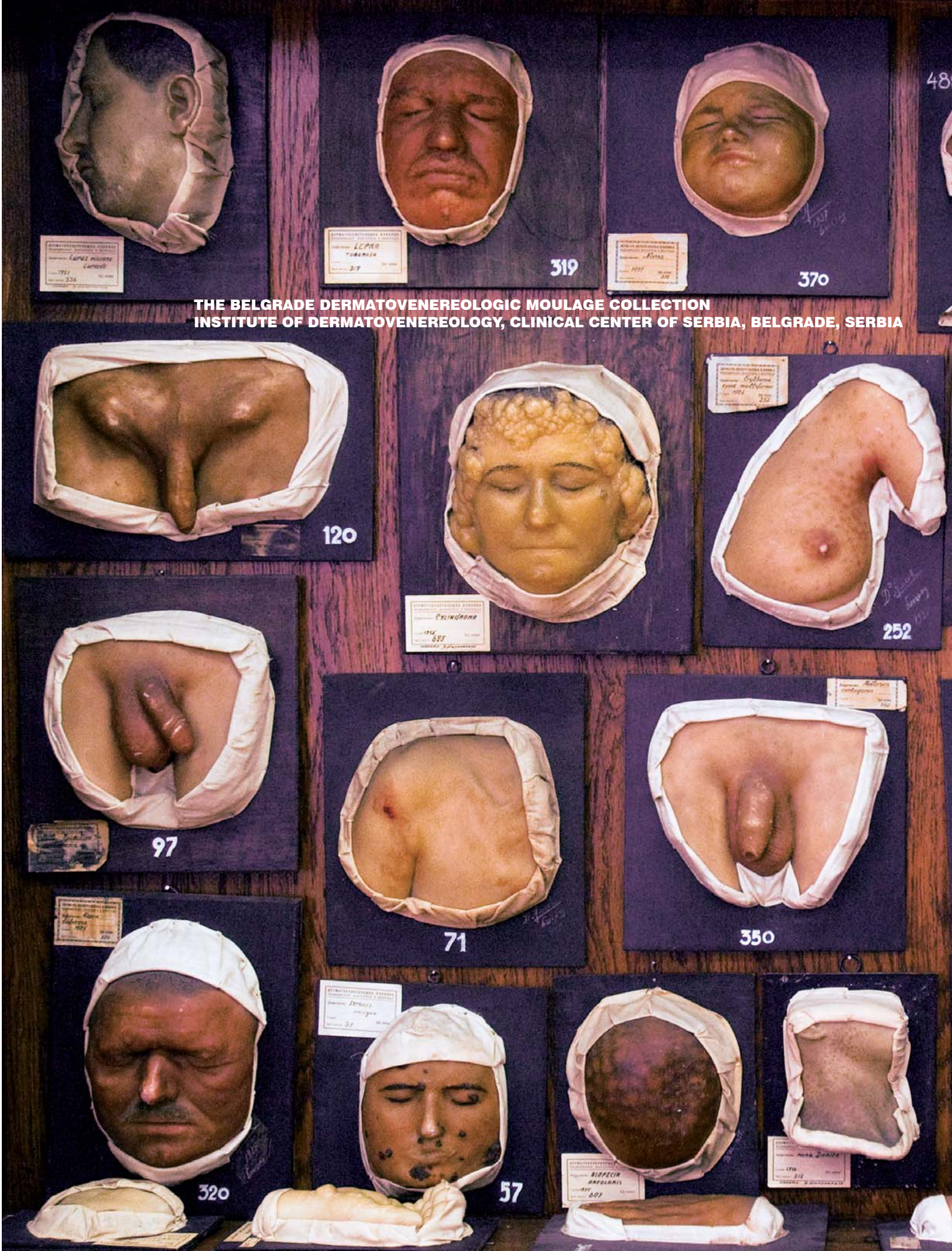

THE BELGRADE DERMATOVENEREOLOGIC MOULAGE COLLECTION
INSTITUTE OF DERMATOVENEREOLOGY, CLINICAL CENTER OF SERBIA, BELGRADE, SERBIA

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Congenital Generalized Hypertrichosis Terminalis with Gingival Hyperplasia and a Coarse Face: a Case Report

Jana KAZANDJIEVA[1,*], Elisaveta STEFANOVA[2], Zdravka TODOROVA[1,2], Malena NIKOLOVA GERGOVSKA[3], Kristina SEMKOVA[4]

[1]Department of Dermatology and Venereology, Medical Faculty, Medical University, Sofia, Bulgaria
[2]Pediatric Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria
[3]Dermatology Clinic Euroderma, Sofia, Bulgaria
[4]St. John's Institute of Dermatology, Guy's and St. Thomas' Hospital Trust, London, UK

*Correspondence: Jana Kazandjieva, E mail: janaderm@abv.bg

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Abstract

Congenital generalized hypertrichosis, in its most common form, is idiopathic. In the absence of underlying endocrine or metabolic disorders, congenital generalized hypertrichosis is rare in humans, affecting as few as one in a billion individuals and may be an isolated condition of the skin, or a component feature of other disorders or syndromes. Congenital generalized hypertrichosis terminalis is an extremely rare condition, a distinct subset of disorders with congenital hypertrichosis, presenting with excessive hair as the primary clinical feature. Congenital generalized hypertrichosis terminalis is characterized by universal excessive growth of pigmented terminal hair and often accompanied with gingival hyperplasia and/or a coarse face. Gingival hyperplasia may be delayed even until puberty. Its pathogenesis may be caused by one of the following mechanisms: conversion of vellus to terminal hairs and/or prolonged anagenetic stage, and/or increase in the number of hair follicles. Since the Middle Ages, less than 60 individuals with congenital hypertrichosis terminalis have been described, and, according to the most recent estimates, less than 40 cases were documented adequately and definitively in the literature. Recent articles identified congenital generalized hypertrichosis terminalis as a genomic disorder.

This report is a follow up of a six-year-old boy born from the first normal pregnancy of non- consanguineous parents, starting from delivery. Our investigation revealed a history of: excessive hair growth and a coarse face from birth; increased body weight with high blood pressure and gingival hyperplasia at the age of four months. The parents denied any medication or chemical intake during pregnancy, as well as a history of hypertrichosis in their families. The child had a congenital hydronephrosis of the right kidney. Ultrasound and magnetic resonance imaging revealed severe congenital hydronephrosis of the right kidney and suspicion of hypertrophy of the left adrenal gland suggestive of an adenoma. The follow up showed normal values of hormones which excluded adrenal tumor. At the age of 8 months the patient underwent right-sided nephrectomy after several urinary infections. The child was admitted again to our Clinic at the age of four years, with generalized hypertrichosis, gingival hyperplasia and a coarse face without any other pathological signs. He has had a normal intellectual development, but was extremely shy, unconfident and dependent on his mother. The relevant laboratory investigations showed normal full blood count, biochemical, hormonal test results and normal function of the single kidney. Molecular chromosome analysis revealed heterozygous deletion on chromosome 17q12 region. Prolonged follow-up with routine checkups every 6–12 months was advised, including regular outpatient appointments particularly with an endocrinologist, because of the risk of diabetes mellitus, and with a nephrologist, for control of renal function.

Laser hair removal was suggested and the patient underwent one procedure with long pulsed neodynium:yttrium-albumin-garnet laser with a wavelength of 1064 nm. The procedure was effective and well-tolerated and the treatment course is currently ongoing.

Although it is now believed that most people with congenital generalized hypertrichosis have an unknown genetic defect, up to date, a clear specific molecular abnormality has not been proved. It has been suggested that the distal portion of human chromosome 17q may contain dosage-sensitive genes that contribute to excessive hair growth.

We present a sporadic case of an extremely rare congenital generalized hypertrichosis terminalis in a six-year-old boy born to non-consanguineous parents, with gingival hyperplasia, a coarse face and congenital hydronephrosis, with heterozygous deletion on chromosomal region 17q12 consistent with his renal phenotype.

Key words

Hypertrichosis + congenital; Gingival Hyperplasia; Chromosomes, Human, Pair 17 + genetics; Child; Hydronephrosis; Case Reports

Hypertrichosis (H) refers to increased androgen-independent lanugo, vellus or terminal hair, associated with numerous pathological conditions and heterogeneous etiological disorders. H may be generalized or circumscribed, congenital or acquired where congenital is loosely interpreted as that seen in early infancy (1, 2, 3). The clinical pattern of hypertrichosis varies, ranging from lanugo, to vellous and terminal hairs (4).

Congenital generalized hypertrichosis (CGH) is a rare group of phenotypically and genetically heterogeneous conditions, most frequently present at birth, characterized by excessive hair growth all over the body as compared to the normal of the same age, sex, and race (5). CGH in its most common form is idiopathic in the absence of underlying endocrine or metabolic disorders. In the past, many cases of excessive hairiness caused by congenital, metabolic or endocrine disorders, including androgen-dependent, were considered to be congenital generalized hyper-trichosis. There are more than 29 different terms in the literature: "bear man", "dog man", "ape man"; "wild man", human Skye terriers, werewolves, and *Homo sylvestris*. Idiopathic CGH is assumed to be related to an excess of stimulation of the hair follicles with normal levels of androgen-like hormones and it may be a classical example of an atavistic reversion of a suppressed ancestral gene (4). Although it is now believed that most people with CGH have an unknown genetic defect, up to date, a clear specific molecular abnormity has not been established (4). However, specific molecular defects have been reported in well-known syndromes presenting with hypertrichosis (4).

CGH is rare in humans and it affects as few as one in a billion individuals and may be an isolated condition of the skin or a component feature of other disorders. The incidence is higher if CGH is one of several signs involved in a syndrome. In this case, the incidence of CGH is related to the single condition associated with it (4). In idiopathic CGH, an autosomal dominant (AD) trait inheritance, autosomal recessive (AR) pattern of inheritance, as well as an involvement of chromosome X at the locus Xq24-q27.1 have been described. Although many additional anomalies are associated with hypertrichosis, only a distinct subset of disorders presents with an excessive hair as the primary clinical feature, this includes the following: congenital hypertrichosis lanuginose, which is thought to occur as an autosomal dominant trait with variable expressivity; if it is possible to make distinction between lanugo and vellus hair, those with vellus hair may be classified as a form of universal hypertrichosis known as autosomal dominant Ambras syndrome, or congenital hypertrichosis universalis which is a subtype of a unique congenital hypertrichosis universalis, that is associated with a balanced pericentric inversion on chromosome 8 (p11.2; q22); X-linked generalized hypertrichosis and congenital generalized hypertrichosis terminalis (CGHT) with or without gingival hyperplasia (1, 6, 7).

Congenital generalized hypertrichosis terminalis (CGHT) is an extremely rare condition characterized by universal excessive growth of pigmented terminal hairs and often accompanied with gingival hyperplasia and/or a course face (5, 8). Gingival hyperplasia may be delayed even until puberty. Its pathogenesis may be caused by one of the following mechanisms: conversion of vellus to terminal hairs and/or prolonged anagenetic stage, and/or increase in the number of hair follicles. Since the Middle Ages, less than 60 individuals with congenital hypertrichosis terminalis have been described, and, according to the most recent estimates, less than 40 cases were documented adequately and definitively in the literature (9, 8, 10-14). Recent articles identified CGHT as a genomic disorder (8). It has been suggested that the distal portion of human chromosome 17q may contain dosage-sensitive genes that contribute to excessive hair growth (7).

Case report

This report is a follow up of a six-year-old boy comming from the first normal pregnancy of non-consanguineous parents, starting from delivery. The study revealed a history of excessive hair growth and a coarse face from birth; increased body weight with high blood pressure and gingival hyperplasia at the age of four months. The parents denied any medication or chemical intake during pregnancy, as well as a history of hypertrichosis in the family. The child had congenital hydronephrosis of the right kidney. Imagining studies, including ultrasound and magnetic resonance imaging (MRI) revealed severe congenital hydronephrosis of the right kidney and suspicion of hypertrophy of the left adrenal gland suggestive of an adenoma. The

follow up showed normal values of hormones which excluded adrenal tumor. At the age of 8 months the patient underwent right-sided nephrectomy after several urinary infections. The child was admitted again to our Clinic at the age of four years, with generalized hypertrichosis, gingival hyperplasia and a coarse face without any other pathological signs. He has had a normal intellectual development, but was extremely shy, unconfident and dependent on his mother.

Physical examination at the age of four months

On examination there were distinct facial features – prominent and broad forehead, very broad nose with a round tip, full lips, abundant facial hair with thick eyebrows and eyelashes, profuse hair on the upper and lower limbs and on the back (Figure 1). Pulmonary and cardiovascular functions were normal, except for several readings of high blood pressure. The differential diagnosis included: androgen producing adrenal gland or ectopic tumor, Cushing syndrome, or syndromes with CGHT.

Laboratory and other test results soon after delivery

Laboratory tests revealed the following abnormal results: serum testosterone level 2.32 nmol/l (normally less than 1,0 nmol/l), serum dehydroepiandrosterone sulphate level (DHEAS) 0.18 μg/ml (normally 0.25 - 1.0 μg/ml) and cortisol at 8 h A. M. 166.3 nmol/l (normally 244 - 727). Chromosomal analysis revealed 46, XY, with abnormal rearrangement in the 13 and 14 chromosome pair [der (13; 14) (q10; q10)].

The ultrasound and magnetic resonance imaging (MRI) revealed severe congenital hydronephrosis of the right kidney and suspicion of hypertrophy of the left adrenal gland suggestive of an adenoma. The follow up showed normal values of hormones and excluded adrenal tumor. At the age of 8 months the patient underwent right-sided nephrectomy, after several urinary infections.

Physical examination at the age of four years

On examination, there were aformentioned distinct facial features with generalized hypertrichosis and gingival hyperplasia without any other pathological signs (Figures 2 and 3). The gingival hyperplasia was more prominent but did not progress to the extent that could interfere with tooth eruption and feeding.

Laboratory tests at the age of four years

The relevant laboratory tests showed normal full blood count, biochemical, hormonal laboratory analyses and normal function of the single kidney.

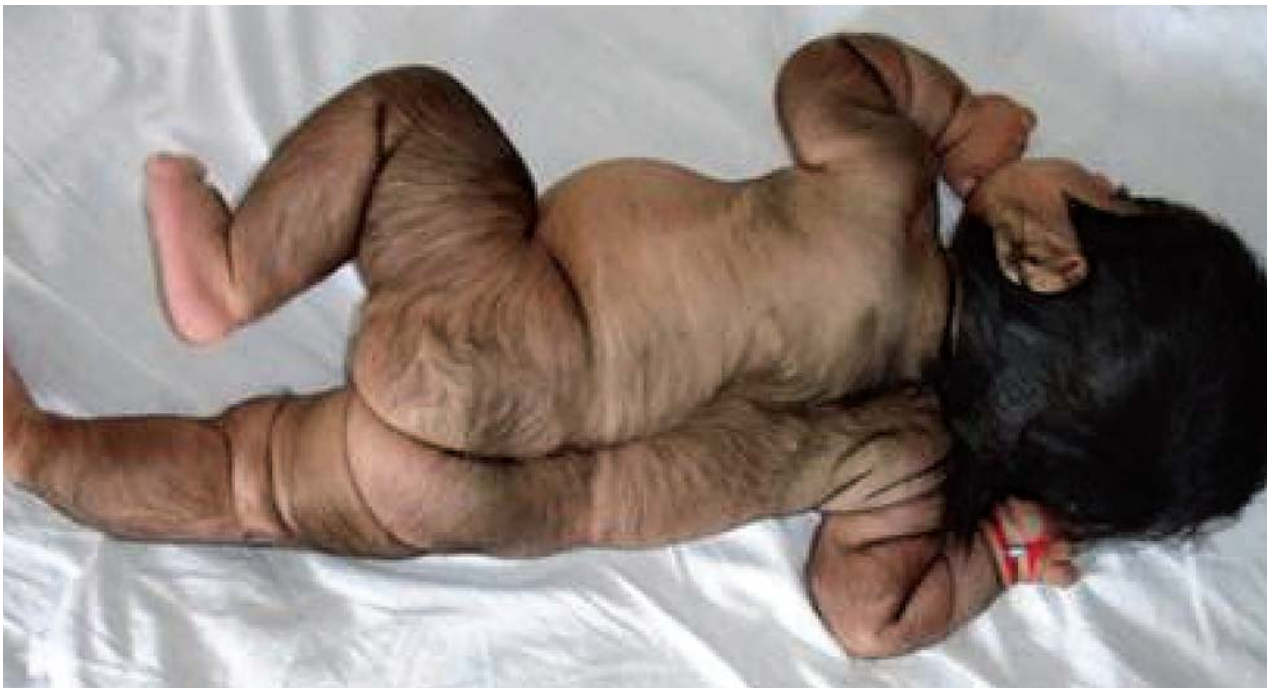

Figure 1. Physical examination at the age of four months showing profuse hair on the upper and lower limbs and on the back

Molecular chromosome analysis revealed heterozygous deletion on chromosome 17q12 region.

Prolonged follow-up with routine checkups every 6–12 months was advised, including regular outpatient appointments particularly with an endocrinologist due to the risk of diabetes mellitus, and a nephrologist for control of renal function.

Therapy

Laser hair removal was suggested and the patient underwent one procedure with long pulsed neodynium: yttrium-albumin-garnet (Nd:YAG) laser with a wave length of 1064 nm.

The procedure was effective and well-tolerated and the treatment course is currently ongoing.

Discussion

Hypertrichosis has been described in many genetic disorders, but CGHT with or without gingival hyperplasia is considered an extremely rare form. A literature review done by Afifi et al. revealed only five reports of seven families with generalized hypertrichosis with or without gingival hyperplasia and/or a coarse face (7, 8, 9, 11 13).

Recently, a series of deletions and duplications greater than 1,000 nucleotides, called copy number variants (CNVs) were reported in CGHT. In 2009, Sun et al. identified three Han Chinese families and 22 affected members with CGHT, a coarse face but no gingival hyperplasia, non-recurrent microdeletions on chromosome 17q24.2–q24.3 and one, *de novo* microduplication within this same region on chromosome 17, in one sporadic case of CGHT with a course face and gingival hyperplasia (8). The minimal 555 kb region common to each of these cases encompassing four genes: ABCA6, ABCA10, ABCA5, and MAP2K6, suggested that disruption of one of these genes may operate in the CGHT phenotype. The region was identified 2.5 Mb upstream of SOX9, a gene previously shown to be required for the specification and maintenance of hair follicle stem cells in mice (8).

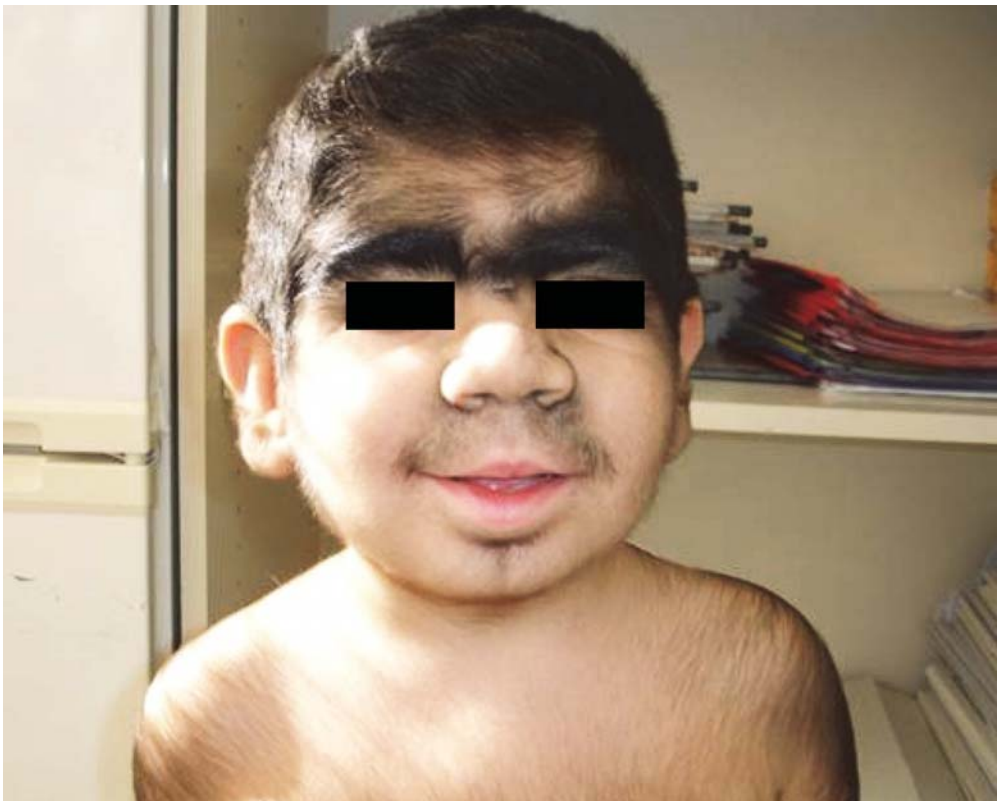

Figure 2. Physical examination at the age of four years revealed a distinctive coarse face with: bilateral epicanthic folds, prominent and broad forehead, very broad nose with a round tip, full cheeks and lips, abundant facial hair with thick eyebrows and eyelashes

Figure 3. Physical examination at the age of four years revealed profuse hair on the upper and lower limbs and on the back

In 2012, Fantauzzo et al. also identified a series of four microduplications on chromosome 17q24.2–q24.3 in a father and son who both presented with CGHT and a coarse face and mild gingival hyperplasia, and reported a position effect on the SOX9 gene, situated 1 Mb downstream of these variants (7). These results and the previously reported pedigrees supported the AD inheritance of CGHT (7, 8). An Irish family with CGHT presented with a coarse face and normal gingivae, AD has also been observed (14), but genetic linkage to 17q24.2-q24.3 was excluded after haplotype analysis. Moreover, further genome-wide linkage scan in this family yielded a maximum but not statistically significant probability score of genetic linkage with single nucleotide polymorphism (SNP) markers on a chromosome 6 region, pointing to the presence of genetic heterogeneity in AD-CGHT with a coarse face (8). Although a wide family genome-linkage scan is lacking in our case, our results also substantiate this observation, since chromosomal analysis in our patient revealed the two following abnormalitie: 46, XY, with abnormal rearrangement in the 13 and 14 chromosome pair [der (13;14) (q10;q10)] and heterozygous deletion on chromosome 17q12 region. The first abnormality was not consistent with the phenotype, but with the presence of so-called Robertsonian translocation. The latter represents a rare significant form of chromosomal rearrangement; in humans it occurs in the five acrocentric chromosome pairs, namely 13, 14, 15, 21 and 22; it is produced by fusion of the whole long arms of two acrocentric chromosomes with the centromere near the very end. The second abnormality is consistent with the kidney phenotype of our patient. Several new microdeletion and microduplication syndromes, including 17q12 deletion/duplication, have been proven to cause multiple congenital anomalies (MCA). Apart from diaphragmatic hernia, genital disorders in females and pulmonary cysts, deletion producing MCA also include renal cysts which can cause obstruction/hydronephrosis (15).

Another rare form of CGHT with gingival hyperplasia was previously described showing AR mode of inheritance (11, 12, 16). DeStefano et al. identified two girls with CGHT. The first with gingival hyperplasia and normal face was from a consanguineous family for whom whole-exome sequencing revealed a novel, rare homozygous variant of ABCA5 gen, demonstrating AR mode of inheritance. The second girl represented an unrelated case with gingival hyperplasia and a coarse face, showed a [t(3;17)] translocation and cryptic 1.3 megabase (Mb) deletion involving ABCA5 gen, demonstrating AD mode of inheritance, indicating that ABCA5 defects might be the primary cause of many features of the CGHT phenotype (11). Furthermore, significantly reduced levels of ABCA5 transcripts and transcribed proteins in the patient's hair follicles suggested an important role of ABCA5 in hair growth regulation (11). Therefore, ABCA5 has attracted the most attention as a causative gene for either AR- or AD-CGHT (11). An overlap between AD and AR inheritance pattern is apparent at the phenotypic

and pathological level, suggesting a common genetic background. Nevertheless, the presence or absence of gingival hyperplasia among patients with CNVs also present in our case is still not yet completely understood, because of the limited number of patients. Interestingly, all reported microdeletion patients did not manifest gingival hyperplasia (8, 11, 14). In comparison, patients with microduplication showed gingival hyperplasia of variable severity. Although an Egyptian female patient, reported by Afifi et al, as well as our patient with CGHT also had a microdeletion, they both apparently presented with gingival hyperplasia (10). Such a correlation between genomic alterations and phenotype is not well understood. Afifi et al. suggested that these might be partially explained by the observation that reciprocal deletion and duplication syndromes usually present with abnormalities of the same organs or functions exhibit different clinical severity and penetrance (10, 17). Despite the identification of CNVs and/or position effects in this region on chromosome 17q24.2-q24.3, no point mutations in these or any other single genes have been described to underlie the CGHT phenotype (11).

In regard to the association between CGHT and a characteristic coarse face, Laurence [1857] was the first to describe a Mexican lady with a congenital generalized hypertrichosis terminalis (CGHT) with gingival hyperplasia and a distinctive coarse face showing bilateral epicanthic folds, thick and abundant eyelashes, broad nose, full cheeks, and lips (18). These coarse facial features were similarly observed in all patients with CNVs on 17q24.2–q24.3 with (7, 8, 9, 11, 13) or without gingival hyperplasia (8, 11, 14). In contrast, DeStefano et al. (11), as well as Anavi et al., (12) and Douzgou et al. (16), did not describe these coarse features in an AR patient with CGHT. Based on his own observations, Afifi stated that patients with AR type disease lacked the characteristic coarse facial features seen in the AD type (10). He stated that the distinctive facial and oro-dental features might be used as a specific morphological characteristic to describe AD-CGHT and gingival hyperplasia. However, further studies are needed to clarify the role of the genes located within 17q24.2– q24.3 in the pathogenesis of CGHT. Moreover, several new microdeletion and microduplication syndromes, including 17q12 deletion/duplication, have been proven to cause multiple congenital anomalies (MCA), autistic spectrum disorders (ASD) and other phenotypic findings, associated with intellectual disability (ID). Deletion presents congenital disorders such as diaphragmatic herniae, pulmonary cyst and renal disorders as in our patient (15).

The diagnosis of CGH should be based on a detailed history, with special attention given to the presence of other anomalies, particularly of the face, teeth, and kidneys (4). The differential diagnosis should distinguish CGH from the acquired forms such as drug induced, particularly due to phenytoin, corticosteroids, cyclosporine and interferon alpha; consequences of malnutrition and anorexia nervosa, endocrine disorders, metabolic diseases such as congenital porphyrias, and adrenal enzymatic deficiency, ovarian and adrenal neoplasms as in our case. The prognosis depends on the associated pathological events.

CGH may cause significant emotional distress, not only in the affected patient, but his family as well. There are different approaches to the treatment of excess hair, including: cosmetic procedures such as electrosurgical epilation, pulsed light source, treatment with ruby, alexandrite, diode and especially neodynium:yttrium-albumin-garnet (Nd:YAG) laser, as in our case, and pharmacological treatment. It should be underlined that not all treatments are effective in the long run, and the choice of therapy should be made accordingly. Pharmacological treatment consists of topical eflornithine, a specific and irreversible inhibitor of the enzyme ornithine decarboxylase, which is located within the hair follicle stimulating hair growth. In general, good results can be obtained, but in approximatelly one third of cases hair regrowth occurs, thus necessitating further procedures (4).

Conclusion

We present a sporadic case of extremely rare congenital generalized hypertrichosis terminalis in a six-year-old boy born to non-consanguineous parents with a coarse face, gingival hyperplasia, and congenital hydronephrosis, with heterozygous deletion on 17q12 chromosome region consistent with his kidney phenotype.

Abbreviations

H - hypertrichosis
CGH - congenital generalized hypertrichosis
AD - autosomal dominant

AR - autosomal recessive
CGHT - congenital generalized hypertrichosis terminalis
MRI - magnetic resonance imaging
DHEAS - dehydroepiandrosterone sulphate level
A.M. - ante meridiem, meaning *before midday*
CNVs - copy number variants
Kb - kilobase
Mb - megabase
SNP - single nucleotide polymorphism
MCA – multiple congenital anomalies
ASD - autistic spectrum disorders
ID - intellectual disability
Nd:YAG - neodynium:yttrium-albumin-garnet

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Kongenitalna generaliziovana terminalna hipertrihoza udružena sa gingivalnom hiperplazijom i grubim crtama lica – prikaz slučaja

Sažetak

Uvod. Kongenitalna generalizovana hipertrihoza najčešće je idiopatska. U odsustvu relevantnih metaboličkih i endokrinih poremećaja, ona je izuzetno retka, procenjuje se da pogađa jednu među bilion osoba. Istovremeno može predstavljati izolovani poremećaj u koži ili biti deo različitih sindroma. Kongenitalna generalizovana terminalna hipertrihoza se ekstremno retko javlja, a pripada grupi onih oboljenja u kojima prekomerni porast dlake predstavlja primarni poremećaj. Karakteriše je prekomerni rast pigmentovane terminalne dlake i često je udružena sa gingivalnom hiperplazijom koja se može javiti kasnije, ponekad čak u pubertetu. U

patogenetskom smislu može biti posledica jednog od sledećih mehanizama: prelaz velus dlake u terminalnu i/ili produženje anagenskog stadijuma, i/ili povećanje broja folikula dlake. Počevši od srednjeg veka pa do današnjih dana, opisano je manje od 60 obolelih, od kojih je samo 40 adekvatno dokumentovano. Rezultati novijih istraživanja ukazuju na genetsku etiologiju.

Prikaz slučaja. U ovom radu, autori prikazuju slučaj šestogodišnjeg dečaka čiju bolest prate od prvih dana posle rođenja. Dečak je rođen u nekonsangvinom braku u prvoj trudnoći, koja je protekla bez poremećaja. Na rođenju, kod deteta je bio prisutan univerzalan prekomeran rast pigmentovane terminalne dlake, karakteristične grube crte lica, povišen krvni pritisak, a nakon četiri meseca, pored povišene telesne težine, došlo je do pojave hiperplazije gingiva. Roditelji su negirali upotrebu bilo kog leka ili hemikalija za vreme trudnoće majke i prisustvo hipertrihoze u porodici. Laboratorijska ipitivanja koja su odstupala od fizioloških vrednosti odnosila su se na povišen nivo testosterona u serumu koji je iznosio 2,32 nmol/l (normalno manje od 1 nmol/l), serumskog nivoa dehidroepiandrosteron sulfata u iznosu od 0,18 μg/ml (normalno 0,25–1 μg/ml) i smanjenog nivoa kortizola u 8 h ujutro koji je iznosio 166,3 nmol/l (normalno 244–727). Analizom hromozoma pored kariotipa 46, XY, utvrđeno je postojanje rearanžmana između hromozoma 13 i 14 [der (13;14) (q10;q10)] čime se mogla objasniti pojava kongenitalne hidronefroze.

Zbog kongenitalne hidronefroze desnog bubrega i nekoliko epizoda pijelonefritisa, dečaku je u osmom mesecu života odstranjem desni bubreg.

Ultrazvučna i radiološka ispitivanja, kao i magnetna rezonancija ukazala su na postojanje teškog oblika kongenitalne hidronefroze, kao i sumnju na postojanje hipertrofije/adenoma leve nadbubrežne žlezde. Rezultati redovnih laboratorijskih kontrolnih hormonalnih analiza, koje su potom usledile, bili su u granicama fizioloških vrednosti, a sumnja o postojanju adenoma je isključena.

U četvrtoj godini života, dete je ponovo hospitalizovano u našoj ustanovi. Pored generalizovane hipertrihoze, grubih crta lica i hiperplazije desni, nije bilo drugih poremećaja. Iako je intelektualni razvoj bio neometan, dete je bilo ekstremno stidljivo, nesigurno i zavisno od svoje majke.

Relevantne laboratorijske analize uključujući i hormonske, bile su uz očuvanu funkciju preostalog levog bubrega i dalje u granicama normale. Molekularna genetska analiza hromozoma ukazala je na postojanje heterozigotne delecije na hromozomskoj 17q12 regiji.

Planiran je nastavak sprovođenja redovnih kontrolnih pregleda svakih 6–12 meseci uključujući pored dermatologa, pedijatra-nefrologa sa ciljem kontrole renalne funkcije i dijabetologa zbog postojanja povišenog rizika za dobijanje dijabetesa melitus.

Kod dečaka je započeto lečenje uklanjanjem dlaka pomoću neodinijum:itrijum-albumin-garnet lasera talasne dužine 1064. Lečenje se pokazalo efikasnim i njegovo sprovođenje je i dalje u toku.

Diskusija. Iako se danas smatra da se u osnovi većine slučajeva kongenitalne generalizovane hipertrihoze nalazi genetski poremećaj, njegova specifičanost na molekularnom nivou još uvek nije potvrđena. Pretpostavlja se da se geni koji pospešuju prekomerni porast dlake kod ljudi, nalaze na distalnom delu hromozoma 17q.

Zaključak. U radu je prikazan ekstremno redak slučaj kongenitalne generalizovane terminalne hipertrihoze kod šestogodišnjeg dečaka sa kongenitalnom gingivalnom hiperplazijom i karakterističnim grubim crtama lica, rođenog u nekonsangvinom braku, kod koga je utvrđeno prisustvo heterozigotne delecije na hromozomskoj regiji 17q12 koja je rezultirala pojavom kongenitalne hidronefroze.

Ključne reči: Hipertrihoza + kongenitalna; Gingivalna hiperplazija; Humani hromozomi, par 17 + genetika; Dete; Hidronefroza; Prikazi slučajeva

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Extensive Peculiar Cutaneous Form of Neurofibromatosis Type I as a New Mutation - a Case Report

Jagoda BALABAN[1,*], Dragana POPOVIĆ[1], Svetlana PAVLOVIĆ[2]

[1]Clinic of Skin and Venereal Diseases, University Clinical Centre of the Republic of Srpska, B&H
[2]Department of Pathology, University Clinical Centre of the Republic of Srpska, B&H

*Correspondence: Jagoda Balaban, E-mail: jagoda.balaban@yahoo.com

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Abstract

Neurofibromatosis-1 (NF1) is one of the most common hereditary multisystemic disorders. The disease manifests a variety of characteristic features that include: hyperpigmentary abnormalities of the skin (café-au-lait macules, freckles in the axillae, and iris Lisch nodules) and growth of benign peripheral nerve sheath tumors (neurofibromas) in the skin. Associated extracutaneous clinical features include: skeletal abnormalities, neurological, cardiovascular, endocrine and other malformations. NF1 is caused by mutation in the neurofibromatosis-1 gene, which codes for the protein neurofibromin. The inheritance of NF1 follows an autosomal dominant trait, although about 50% of patients present with new („de novo“) mutations, and represent the first member of their family. No difference in the severity of the disease can be found in patients with familial mutations versus those with new mutations. We present a 78-year-old female patient with an extreme cutaneous form of neurofibromatosis who reported no affected family member. Apart from skin problems, she had no major health issues in childhood and adolescence, but in recent decades she had frequent headaches, occasional abdominal pain, and vision and hearing impairment. About 10 to 14 days before admission, she developed a severe cough, shortness of breath, and chest and abdominal pain. On examination, the patient of short stature (hight: 152 cm, weight: 49 kg) presented with thousands of soft nodules dispersed over the whole body, except on extensor sides of thighs and lower legs; the nodules varied in color from skin-colored, livid erythematous, to brown-grey; the nodules on the abdomen were moist, partly bleeding from the base, and accompanied by an unpleasant odor. Her feet were also densely covered by dark purple lumps, with dystrophic changes of the toe nails that were thickened, frayed, and yellowish. The skeletal abnormalities included: short stature, severe osteoporosis and osteosclerosis of the head bone structure; degenerative arthropathc-spondylotic changes of the thoracolumbar spine segment with signs of diffuse skeletal hyperostosis; pronounced degenerative changes of the lumbar spine. CT scans of the head, chest and abdomen showed the following abnormalities: flattening of the paraventricular gyri and reduction of brain parenchyma with hypodensity of the white matter in terms of cortical atrophy; periventricular bilateral small post-ischemic microvascular brain lesions of varying chronicity; in the parenchyma of the upper left lung lobe the apical presence of small areas of pleural effusion with consequent subatelectic region; distended stomach and a small inner wall herniation; hypotrophic right kidney; atherosclerotic lesions of the abdominal aorta; low grade infrarenal kinking of the abdominal aorta. Pathohistological analysis of biopsy specimen taken from the nodule corresponded with cutaneous neurofibroma. Consultative examinations of various specialists pointed to the existence of the following comorbidities: obstructive respiratory syndrome and right lobe pneumonia that were treated by antibiotics, aminophylline and dexamethasone infusions; psycho-organic syndrome without focal neurological deficit; Lisch nodules in each eye, and senile cataract. Considering the age and medical presentation of the patient, no other treatment was considered.
In conclusion, this is a sporadic case of cutaneous neurofibromatosis 1 in a 78-year-old female patient who presented with extremely severe cutaneous neurofibromas, making this case at least rather peculiar.

Key words

Neurofibromatosis 1; Neurofibromin 1; Café-au-Lait Spots; Iris Diseases; Melanosis; Neurofibroma; Skin Neoplasms; Case Reports; Comorbidity

Neufibromatoses (NFs) comprise several distinct genetic disorders that lead to the formation of tumors involving nerve tissue. The two main forms are NF1 and NF2, the first also known as von Recklinghausen disease with characteristic skin lesions, opposite to the second which does not present with cutaneous manifestations (1).

Neurofibromatosis 1 (NF1), or von Recklinghausen disease, is a multisystemic disorder that affects approximately 1 in 3.500 people (2). Althouh the earliest historical descriptions originate from the 13th century, in 1882, Friederich von Recklinghausen published a landmark paper *On the Multiple Fibromas of the Skin and Their Relationship to the Multiple Neuromas*, describing this disease and pointing out that the skin tumors were derived from peripheral nerves (3). More recently, in 1956, Crowe, Schull and Neel published a milestone manuscript detailing the numerous manifestations of this disorder (4, 5). NF1 is caused by a heterozygous mutation in the NF1 gene located on chromosome 17 which encodes a protein named neurofibromin. The NF1 gene has one of the highest mutation rates among all other genes within the human genome. More than 500 different mutations in the NF1 gene have been identified. The mode of inheritance is autosomal dominant, with almost 100% penetrance by the age of 5 years (1). Familial occurrence is reported in about half of affected individuals, the rest are sporadic cases resulting from a high gene mutation rate which accounts for 50% of all cases (6). Since each affected individual and family has specific mutations, genetic screening is highly challenging (1). No difference in the severity of the disease can be found in patients with familial mutations versus those with new mutations. Major diagnostic criteria for NF1, established by the National Institutes of Health (NIH) are based on clinical findings and require 2 or more of the following criteria: 6 or more "cafe au lait macules" (CALMs) with diameter > 5 mm and >15 mm in prepubertal and postpubertal patients, respectively; ≥2 of any type of neurofibromas, or at least 1 plexiform neurofibroma; axillary or inguinal freckling; ≥ 2 Lisch nodules on the iris; distinctive osseous lesion; an optic nerve glioma; first-degree relative with NF1. The hallmark features of the disorder are CALMs and neurofibromas. The disease is not only a neurocutaneous but also a multisystemic disorder, with multifaceted implications throughout nearly every organ system in the human body. The most common extracutaneous complications are related to skeletal abnormalities, ophthalmic, neurological, endocrine, vascular and cardiac disorders including tumors (7). The treatment of NF1 focuses on symptom management, as well as radio- and chemotherapy in case of malignant alterations. Other treatment options include lovastatin, rapamycin (or sirolimus), imatinib mesylate and even topical vitamin D3 analogues (8).

Case report

We present a 78-year-old female patient, resident of the *Gerontology Centre* in Banja Luka, who was referred to the Clinic of Skin and Venereal Diseases of the University Clinical Center of the Republic of Srpska, due to itching in the area of anterior abdominal wall, coughing, shortness of breath, chest and abdominal pain. On admission, the patient reported having skin tumors since childhood, whose number gradually increased, especially after 30 years of age, and they covered the skin of her entire body; due to learning difficulties, she could not read or write, and no other family member, including seven brothers and two sisters, who are all alive except one brother, had similar skin tumors. This information was confirmed by the head nurse and director of the Gerontology Center who are in contact with her family. Apart from skin lesions, she had no major health problems in childhood and youth, but in recent decades she had frequent headaches, occasional abdominal pain, and vision and hearing impairment. The patient also reported an elbow surgery on her left arm a few decades ago; she had no other health problems, and apart from analgesics, she was not taking other medications. Since no proper medical documentation was available, and she had a scar on her elbow, we assumed that she underwent surgical excision of one of the largest tumors. About 10 to 14 days before admission, she developed a severe cough, shortness of breath, and chest and abdominal pain.

Physical examination

On examination, the patient of short stature (height: 152 cm, weight: 49 kg) presented with thousands of soft nodules dispersed over the whole body, except

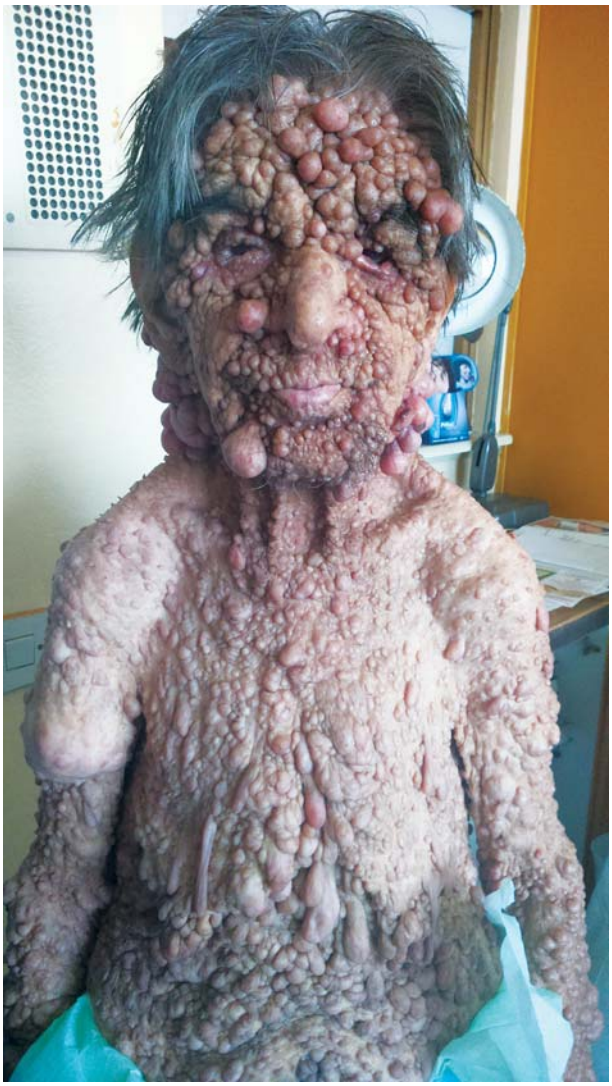

Figure 1. Numerous, densely distributed cutaneous neurofibromas on the face and on the chest, different in size, many connected to the skin by a stalk

on extensor sides of thighs and lower legs (Figures 1 – 3); the nodules varied in color from skin-colored, livid erythematous, to brown-grey; the nodules on the abdomen were moist, partly bleeding from the base, and accompanied by an unpleasant odor (Figure 4). The size of nodules ranged from 0.5 cm to 15 cm in diameter, many of which had elongated patellar base; some nodules were covered by comedones (Figure 5); nodules were most densely grouped in the occipital and abdominal region, and along the central part of the back forming clusters (Figure 6). The two largest, giant, baggy nodules were localized on the extensor

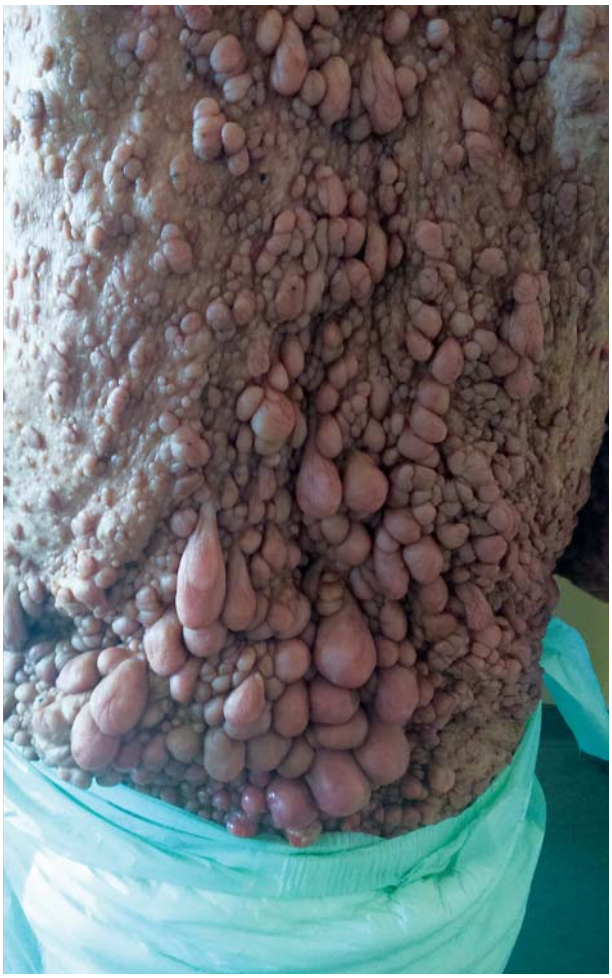

Figure 2. Densely distributed neurofibromas forming clusters in the lumbosacral region

aspects of the right upper arm and left leg (Figure 7). Four typical "café au lait" spots of different sizes were found on the trunk and lower extremities, as well as 4 - 5 smaller pale brown maculae (Figure 8). A large number of brownish spots were found in the inguinal region and on the inner sides of thighs (Figure 9). Her feet were also densely covered by dark purple lumps, with dystrophic changes of the toe nails that were thickened, frayed, and yellowish.

Laboratory and other test results

Erythrocyte sedimentation rate 65 mm/h, C-reactive protein 147.5 mg/L (reference level <5.0 mg/L), white blood cell count $9.2x10^9$/L (reference range 3.4 - 9.3) with neutrophils 80.8% (reference range 40 – 77%), lymphocytes 11.7% (reference range 16 - 44); red

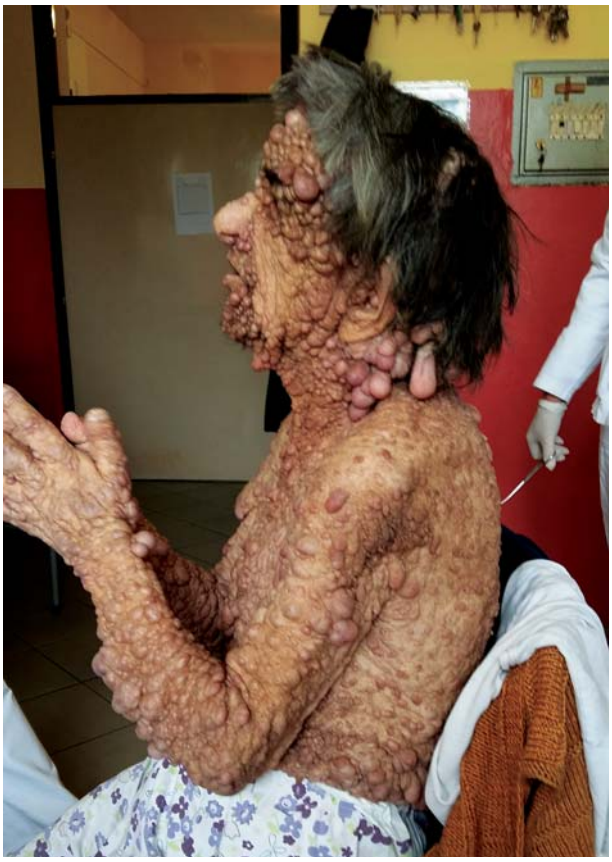

Figure 3. Neurofibromas on the upper body and arms

blood cell count 4.8 x10^{12}/L (reference range 3.8 - 5.1 x$10^{12/}$L), hemoglobin 114 g/L (reference range 119 - 157), platelets 452x10^{9}/L (reference range 158 - 424 10^{9}/L), urea 9.2 mmol/L (reference range 2.8 - 7.2 mmol/L), creatinine 125 μmol/L (reference range 44 - 80 μmol/L), alanine aminotransferase 53 U/L (reference value < 40 J/L), aspartate aminotransferase 110U/L (reference value < 37 J/L). The following serum levels of tumor markers were estimated (ECLIA, Cobas E601): CA 125 carbohydrate antigen 16.3 KU/L (reference value < 5 U/L). CA 19-9 carbohydrate antigen 30.2 KU/L (reference value <27.0), CA 72-4 (s) serum cancer antigen 2.2 KU/L (reference value < 6.9 kU/L), carcinoembryonic antigens CEA 6.4 μg/L (reference value <5.0 μg/L), serum neuron-specific enolase antigen NSE (s) 7.2 μg/L (reference value < 16.3 μg/L). Urinalysis showed 2+ protein.

Microbiology testing: Staphylococcus aureus and Viridans streptococci were isolated from the skin specimens collected from the surface of the inflammed nodules.

Microbiology testing of nasal swabs: Proteus mirabilis was isolated.

Microbiology testing of throat swabs: normal flora.

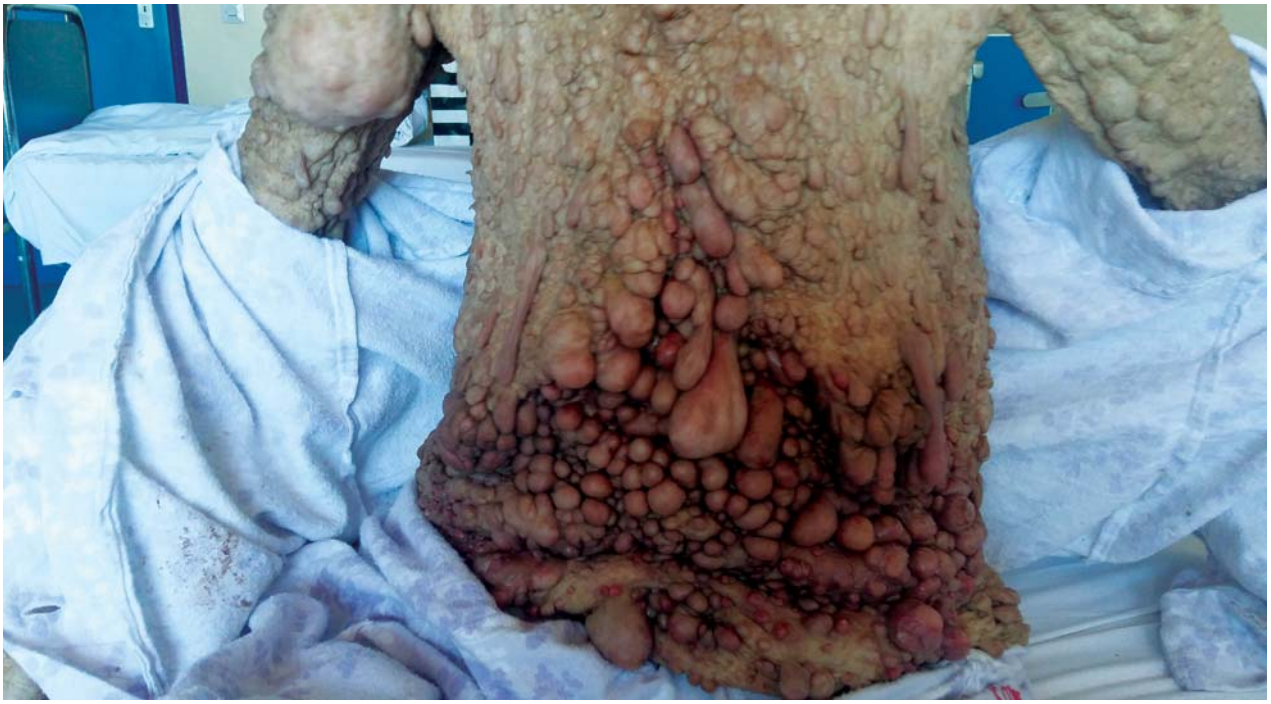

Figure 4. Inflamed neurofibromas in the abdominal area (erythematous, moist, some bleeding at the base)

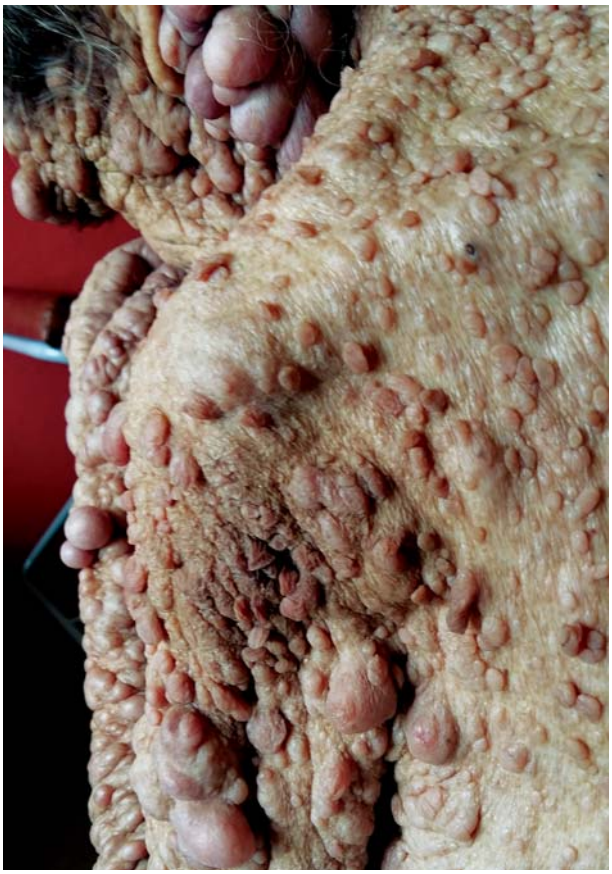

Figure 5. A small fibroma with comedone on the upper back

Native abdominal X-ray: normal findings.

X-ray of the lower extremities and pelvis (standard views): bone structures showed no evidence of trauma or other pathological changes; normal joint width.

CT of the head: bone structures showed marked osteoporosis, as well as osteosclerotic lesions; flattening of the paraventricular gyri and reduction of brain parenchyma with hypodensity of the white matter in terms of cortical atrophy; periventricular bilateral small post-ischemic microvascular brain lesions of varying chronicity.

Thoracic CT detected: in the lung parenchyma of the upper left lobe the apical presence of small area of pleural effusion with consequent subatelectatic zone; left hilum of involutile appearance with posterobasal, partly anterior, as well as laterobasal parts of atelectasis; no signs of axillary or mediastinal lymph nodes enlargement; coronary vessels without pathological changes, no pericardial effusions; bone structures showed no signs of infiltrative changes; arthropathic-spondylotic degenerative changes of the thoracic-lumbar spine segment with signs of diffuse skeletal hyperostosis.

CT of the abdomen revealed the following disorders: diffuse fatty liver infiltration; markedly distended stomach filled with heterogeneous contents; small inner stomach wall herniation, posterior and medially to the left; hypotrophic right kidney; atherosclerotic lesions of the abdominal aorta;

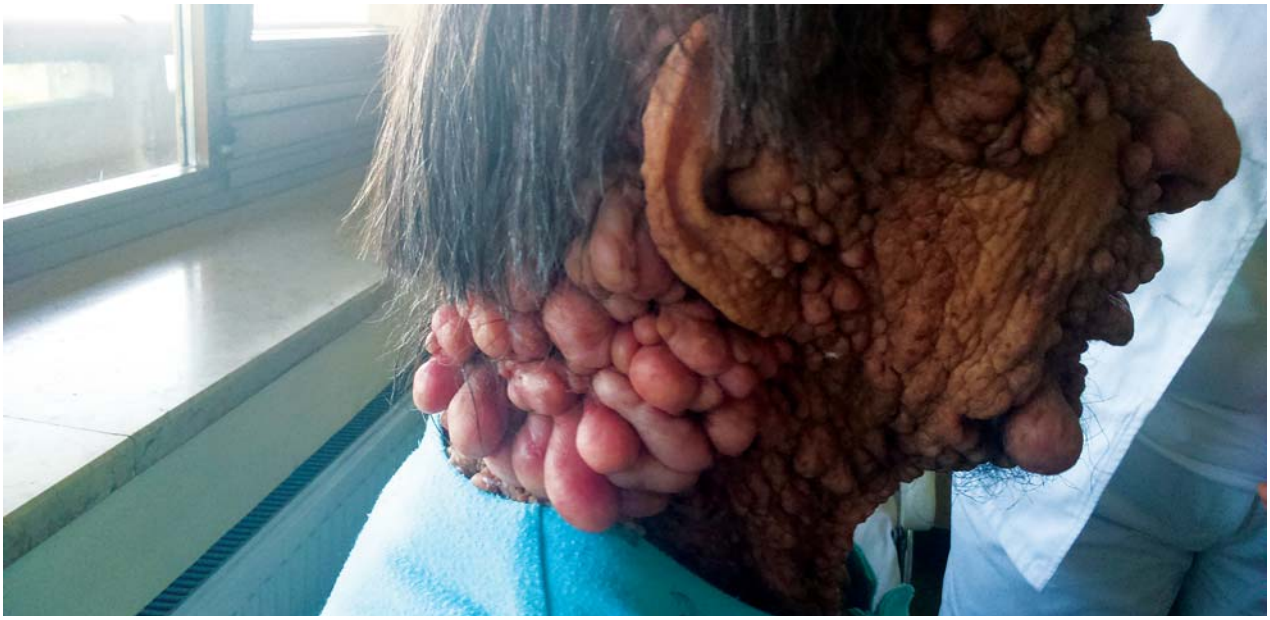

Figure 6. Clusters of neurofibromas on the occipital region and the neck

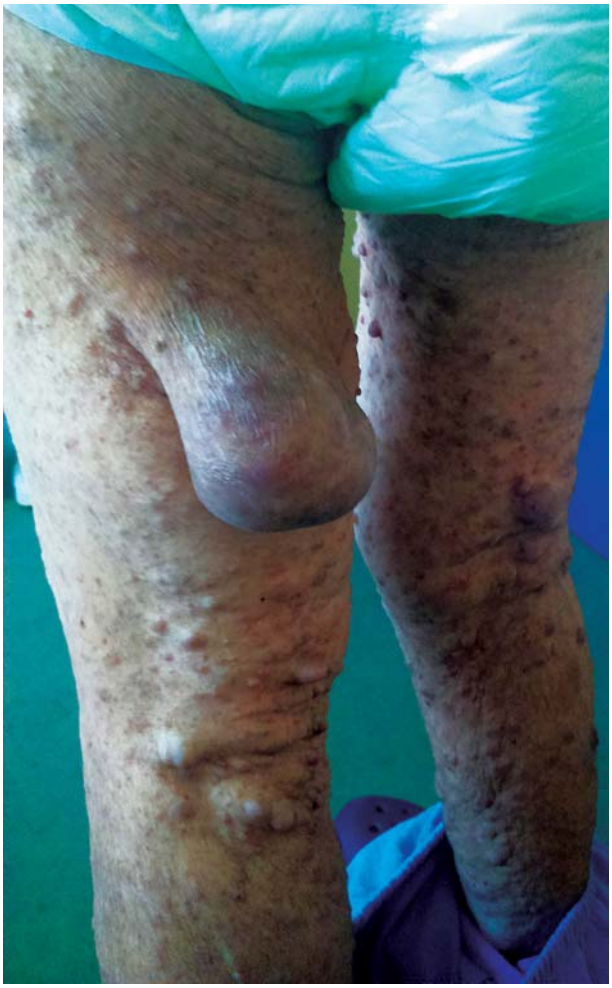

Figure 7. A giant, "bag-like" neurofibroma on the back of the left thigh

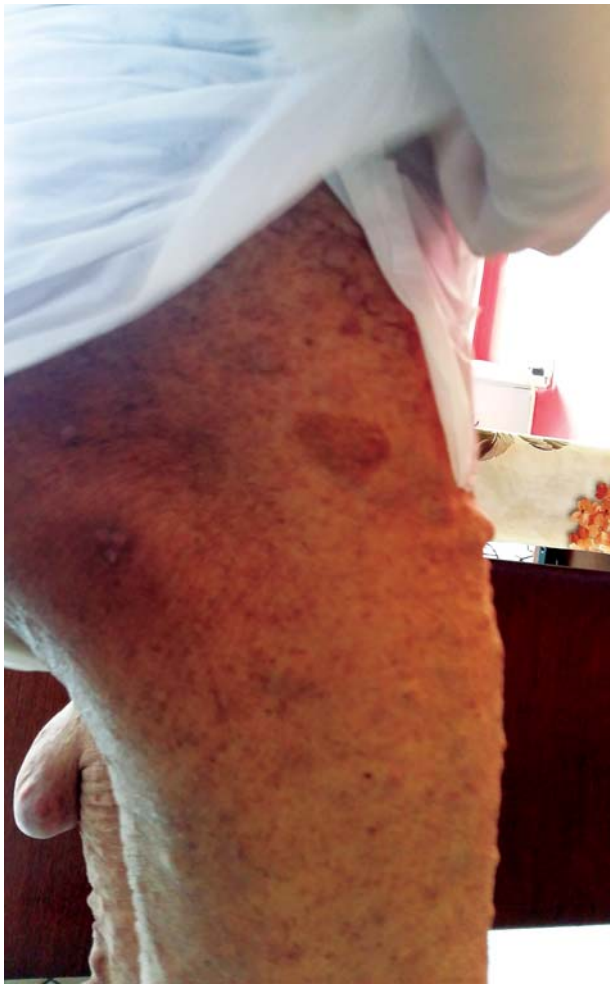

Figure 8. Café au lait macula on the right side of the body

low grade infrarenal kinking of the abdominal aorta; pronounced degenerative changes in the lumbar spine.

Pathohistological analysis of biopsy specimens taken from the nodules corresponded to cutaneous neurofibroma (Figures 11 and 12).

Consultative examinations of various specialists pointed to the existence of the following comorbidities: obstructive respiratory syndrome and right lobe pneumonia that were treated by antibiotics, aminophylline and dexamethasone infusions; psycho-organic syndrome without focal neurological deficit; Lisch nodules in each eye, and senile cataract.

Control laboratory tests

After the patient was dismissed from the hospital, control laboratory tests showed abnormal test results as follows: C-reactive protein 36.7 mg/L, hemoglobin 109 g/L, white blood cell count $10.22x10^9$/L, urea 8.1 mmol/L, creatinine 113 μmol/L; urinalysis 1+ protein.

Therapy

During the hospital stay, the patient received oral antibiotics (cephalexin capsules 2 x 1 g/day for ten days, followed by azithromycin 1 x 250 mg tablets/day for five days), and dexamethasone and aminophylline infusions in 0.9% NaCl solution, plus oral ranitidine. Inflamed neurofibromas were topically treated by aqueous solution of eosin 2%. She was discharged in good general condition, the inflammation of neurofibromas was managed and she showed no distinct respiratory symptoms.

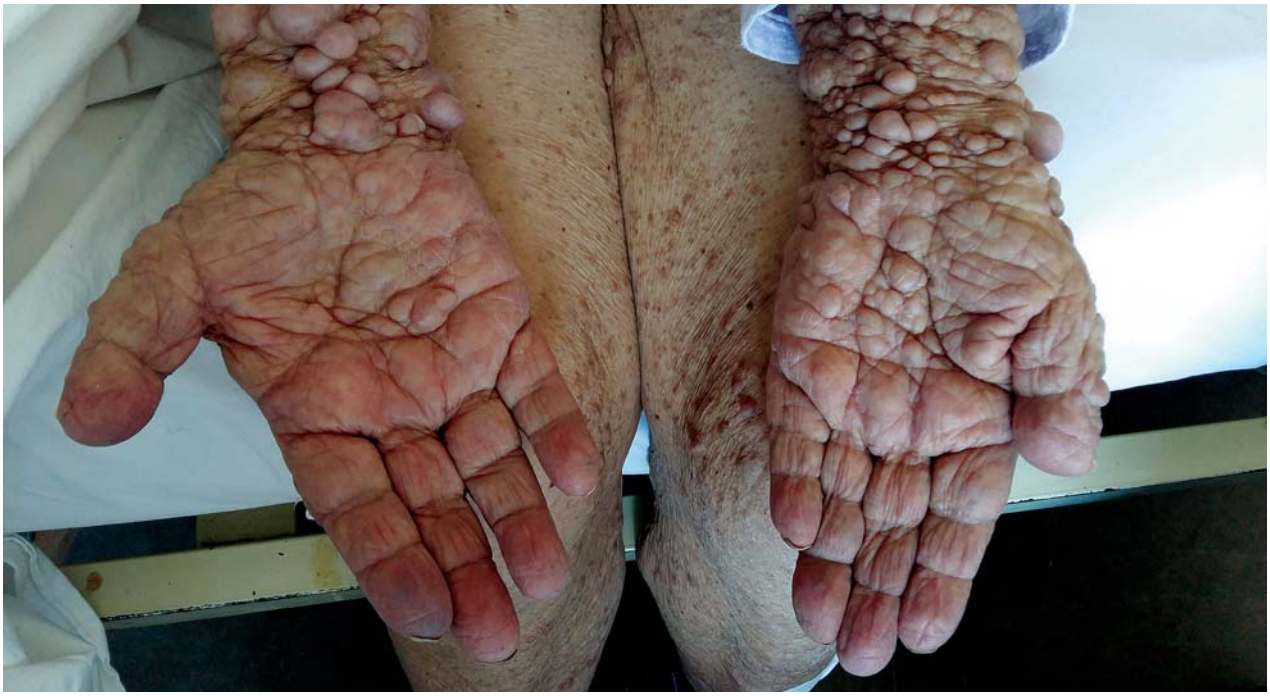

Figure 9. Neurofibromas on the distal parts of forearms and hands with small brownish hyperpigmented spots, involving the groin region and the proximal part of thighs

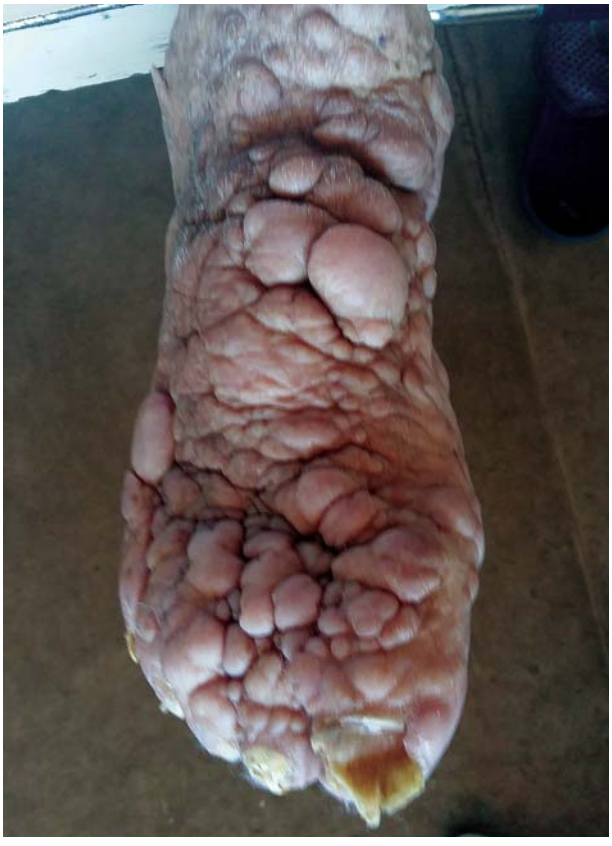

Figure 10. Neurofibromas on the dorsal aspect of feet

Discussion

The large NF1 gene is located on chromosome 17q11.2. This gene comprises 60 exons and spans 350 kb of genomic DNA. The protein product of this gene, neurofibromin, consists of 2,818 amino acids and is present in various tissues, mostly in nervous tissue (6, 9). Mast cells increase in neurofibromas and may enhance growth of these tumors by producing several growth factors, such as histamine and tumor necrosis factor (TNF) (1). The neurofibromin protein shows significant regions of similarity to the guanosine triphosphatese (GTPase)-activating protein and is capable of down-regulation of Ras activity. NF1 germline mutations cause haploinsufficiency of neurofibromin, which is only 50% of the normal protein production by cells. Further investigations support the view that the NF1 gene acts as a suppressor of tumor activity, with a variety of somatic inactivating mutations identified in neurofibromas. The random acquisition of somatic mutation partly explains the delayed age of onset of the tumors associated with NF1 and variability of expression (1).

Neurofibromin deficiency affects cell types throughout the entire body, especially the neural crest cells that include Schwann cells, melanocytes,

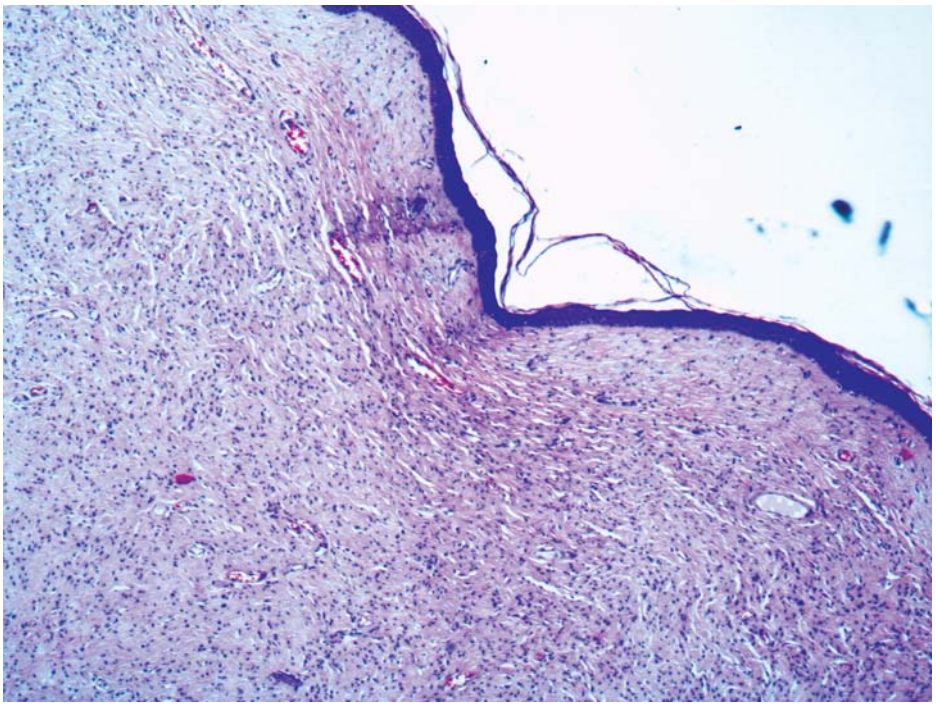

Figure 11. Pathohistological analysis of biopsy specimens taken from the nodule: the epidermis is thin, atrophic; cutaneous neurofibroma, vaguely defined from the surrounding dermis, infiltrated into the dermal connective tissue (HE stain, x 50)

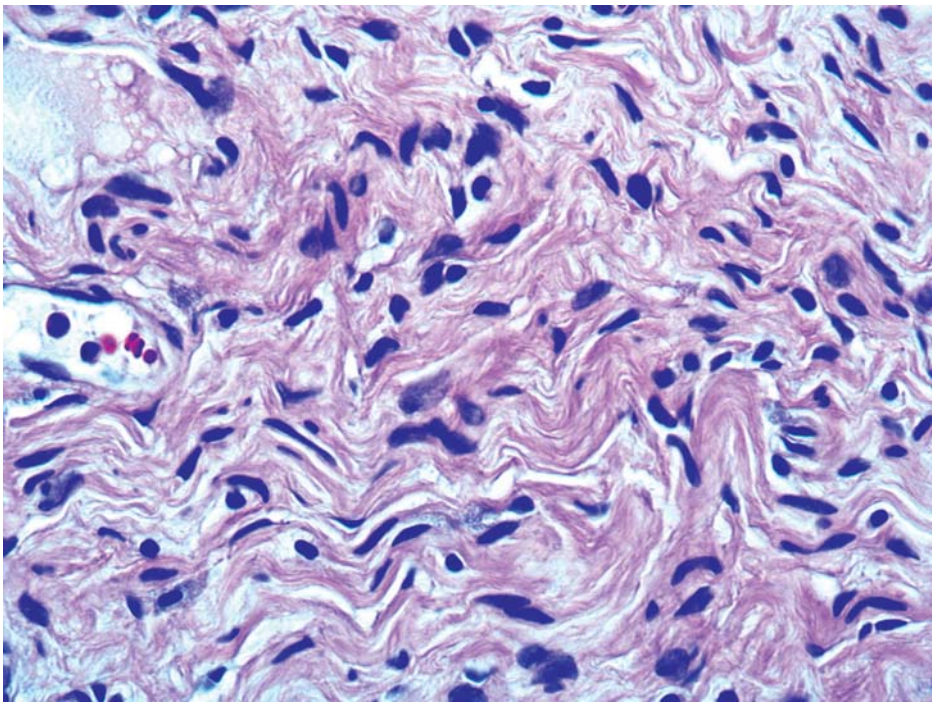

Figure 12. Higher manignification reveals: the tumor tissue comprises thin wavy fibers forming rare bundles; between uniform wavy fibers there are individual oval to spindle shaped nuclei, similar in size, located mainly in parallel rows; small amount of mature eosinophilic collagen is found between the aforementioned structures (HE stain, x 200)

and endoneurial fibroblasts (6, 9). Consequently, the clinical manifestations of NF1 are extremely variable and unpredictable not only among individuals with this disease but with the same genotype.

The National Institutes of Health (NIH) Consensus Conference developed diagnostic criteria for NF1 that require at least two of the following clinical features, as outlined in Table 1 (10, 11).

The diagnosis is established based of clinical criteria. Molecular genetic testing is feasible. Identification of the NF1 gene means that prenatal/presymptomatic diagnosis for this disease is now possible, with greater than 95% accuracy in families with affected members (1). The clinical manifestations of NF1 usually appear in a certain order as age increases: *café au lait* macules (CALMs), axillary freckling, Lisch nodules, and neurofibromas (9).

Table 1. Diagnosticic criteria for NF1

Criterion
6 *Café au lait* macules, diameter: >5 mm in prepubertal; >15 mm in postpubertal patients
≥ 2 Cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
Freckling of armpits or groin
Optic pathway glioma
≥ 2 Lisch nodules (benign iris hamartomas)
Bone dysplasia (sphenoid wing dysplasia, long bone abnormalities - pseudoarthritis)
First-degree relative with NF 1

CALMs are frequently the first sign of NF1, occurring in 99% of NF1 patients within the first year of life (1, 3). Their color can range from skin color to dark brown. The prevalence of CALMs in the general population has varied from 3% to 36% depending on the study groups selected, but the presence of multiple macules in the general population typically is less than 1% (12). Patients continue to develop lesions throughout childhood, but they often fade in adulthood (13).

Skinfold freckling (Crowe's sign) is the most specific of the cardinal criteria for NF1. It is considered nearly pathognomonic (2). Generally, it occurs between the ages of 3 and 5 years, in either the axillae and/or groins. A majority of adults (about 90%) have skinfold freckling. Other sites include neck folds, skin under the breasts, around the lips, and even the trunk in adults. Our patient presented with a great number of brown spots in the groin area and inner thighs. The size of freckles may vary from 1mm to 3 mm (14).

Our patient presented with thousands of cutaneous neurofibromas which is the third hallmark signs of NF1. Neurofibromas usually do not become apparent until puberty and may continue to increase in size and number throughout adulthood. Neurofibromas can occur anywhere on the body and there is a wide variation in their shape and size. Generally, the "cutaneous" tumors are dome-shaped, soft, fleshy as in our patient, their color varies from unchanged to slightly hyperpigmented. They may have the pathognomonic buttonhole-like invagination when pressed with a finger. „Subcutaneous" tumors are firm and nodular. Pregnancy induces tumor growth (9, 14). The tumors are composed of Schwann cells, fibroblasts, mast cells, and perineural cells. There is also an admixture of collagen and extracellular matrix. There are several unusual, but well recognized variants of cutaneous neurofibromas that were not seen in our patient. The first are plexiform neurofibromas,

uncommon variant of NF1 in which neurofibromas arise from multiple nerves as bulging and deforming masses involving also connective tissue and skin folds. Plexiform neurofibromas occur in up to 30% of cases with NF1, most frequently in the craniomaxillofacial region. These tumors are diffuse, growing along the length of a nerve and feel like a "bag of worms"; malignant progression is generally considered the main cause of mortality, occurring in 2 - 16% of cases (15). The second are blue-red and pseudoatrophic macules, unusual variants of cutaneous neurofibromas (2, 6). The increased serum levels of tumor markers were detected in our patient. Because of the extremely high number of tumors with different sizes, malignant alteration could not be excluded in the patient, although we did not detect plexiform neurofibromas.

Another common manifestation/symptom in NF1 is pruritus. Generally, it is a widespread cutaneous phenomenon, but anecdotally, some patients are able to distinguish certain tumors as more itchy than the others. The pathogenesis of this finding is uncertain, but may be related to the increased number of mast cells that are found in neurofibromas. However, if localized, pruritus can be a clue for the presence of an underlying spinal cord or central nervous tumor (16).

Our patient had all three cardinal skin manifestations: CALMs, groin freckling, and cutaneous neurofibromas. What makes this case rather peculiar is extremely high number of cutaneous neurofibromas of various sizes that covered almost the entire skin. Before being inflammed, neurofibromas in the abdominal region were very itchy causing severe scratching. On the rest of the skin, there were 4 typical and few faded CALMs. Due to the presence of fade CALMs, considering the patient's age, as well as the density and number of brownish neurofibromas, the pre-existence of CALMs in early age was indicative. Although early onset and rapid progression before puberty usually indicates a poor prognosis, minimal cutaneous involvement in the young child does not necessarily imply a favourable course. Extensive involvement of the urinary or gastrointestinal tract or the central nervous system carries a poor prognosis (1).

NF1 may affect almost every organ system, but the complaints vary between individuals, even within a single family. Extracutaneus findings of NF1 are numerous, and usually include skeletal, ophthalmologic, neurologic/psychologic, cardiovascular, endocrine, gastrointestinal, as well as malignant (2, 9) (Table 2). In fact, the diagnosis of NF1 is often made in the middle age or later in life, as in our patient. The enormous variability of presentations appears to be at least partially genetically determined and is unrelated to the unaffected NF1 allele (1).

Bone abnormalities in NF1 are variable and include scoliosis, sphenoid wing or long bone dysplasia, but recently osteopenia/osteoporosis has been noted. The underlying pathogenic mechanisms are not fully understood, but experimental evidences suggest that NF1-deficient osteoblasts affect osteoclast differentiation leading to increased degradation of bone tissue. Scoliosis is the most common orthopedic finding in NF1, occurring in up to 10% of patients, being more apparent with aging and increases in puberty, suggesting a possible hormonal influence (1). The pathogenesis of this finding in NF1 is unknown, but it may be related to osteopenia and subsequent dysplastic bony elements. Dysplasia of long bones is another common manifestation of NF1, occurring in nearly 14% of patients, and it is usually evident within the first year of life. This finding is particularly relevant in dermatology, as young patients come to the Clinic for evaluation of "birthmarks" during the first year of life and can be easily screened for this manifestation. The tibia is the most commonly affected bone, bowing in an anterolateral direction. Coupled with the appropriate number and size of CALMs, this orthopedic manifestation is sufficient to make the diagnosis of NF1 at this age. Other findings may include overgrowth of a limb or congenital pseudoarthrosis (usually of the tibia), in which a fracture heals abnormally. Other skeletal abnormalities include short stature, relative macrocephaly, and a prominent forehead and brow. Nevertheless, 29 - 45% of patients with NF1 have a head circumference greater than or equal to two standard deviations above the mean for sex and age (17, 18). Skeletal abnormalies detected in our patients were: short stature, head bone structures showed marked osteoporosis, as well as osteosclerotic lesions; degenerative spinal arthropathic spondylotic changes with signs of diffuse skeletal hyperostosis; pronounced degenerative changes in the lumbar spine.

Table 2. Extracutaneus findings of neurofibrmatosis 1

Finding	Symptom/Sign
Skeletal	Scoliosis
	Dysplasia of the long or sphenoid bones Macrocephally
	Pectus excavatum
	Prominent brow
	Pseudoarthrosis (especially of the tibia)
	Short stature
Ophthalmologic	Lisch nodules
	Optic glioma
Neurologic/psychologic	Learning disabilities
	Attention-deficit hyperactivity disorder
	Seizures
	Headaches
	Epilepsy
Gastrointestinal	Constipation
	Gastrointestinal stromal tumors
Endocrine	Pheochromocytoma
	Precocious puberty
	Hyposalivation
Cardiovascular	Hypertension
	Vascular dysplasia
Malignant	Juvenile myelomonocytic leukemia
	Malignant peripheral nerve sheath tumor

The presence of two or more Lisch nodules is another cardinal NF1 diagnostic criterion that was also present in our patient. These nodules are small, dome-shaped hyperpigmented macules of the iris that usually do not cause vision impairment. They are commonly seen: in about 15 - 20% of patients by the age of six years and in 95% of adults (2, 5). The optic nerve glioma, usually present in 15 - 20% of patients with NF1, but not in our case, is another diagnostic NF1 criterion. It is a slow-growing tumor and can present clinically as: proptosis, decreased visual acuity, or precocious puberty (the latter most commonly after the age of six) with accelerated linear growth as the evidence of early puberty, thus necessitating the use of growth charts in NF1 patients. Symptomatic optic gliomas are typically present prior to the age of six, with most children being diagnosed by the age of three (19). Ophtalmological abnormalities in our patient included lots of Lisch nodules and corticonuclear senile cataract of both eyes.

Cognitive dysfunctions, including significant learning difficulties, behavioral problems, and attention deficits, are the most common neurological problems associated with NF1. The prevalence of

these cognitive deficits, also present in our patient, approaches 70% (8, 20). Macrocephaly is another common feature of children with NF1. Macrocephalic subjects show significant increase in volume of the white matter, while increase of the grey matter of the brain has not achieved statistical significance (21). In contrast, our 78-year-old patient presented with flattening of the paraventricular gyri and reduction of brain parenchyma with hypodensity of the white matter in terms of cortical atrophy; periventricular bilateral small post-ischemic microvascular lesions of varying chronicity. Other, uncommon but wellknown neurological complications include headaches, sleep disorders, epilepsy, cerebral edema, mental retardation and tumors of the spinal cord and brain (22, 23). As our patient had learning difficulties in early childhood, due to which she did not finish elementary school similarly to her brothers and sisters, it can be concluded that she had cognitive disabilities as a neurological manifestation of NF1. In addition, the patient declared frequent headaches in the past two to three decades, the reason why she has been taking analgesics all the time.

Gastrointestinal manifestations of NF-1 are generally unrecognized by both clinicians and pathologists. The frequency of intra-abdominal (gastrointestinal or retroperitoneal) manifestations of NF-1 varies greatly in studies, ranging from 5 - 25%. Gastrointestinal manifestations usually arise during midlife or later; generally later than cutaneous manifestations. Compared to the cutaneous manifestations, neurogenic tumors are relatively uncommon in the gastrointestinal tract. They may occur at any site from the esophagus to anorectum and in the associated peritoneal and mesenteric soft tissues (24, 25). Our patient complained of occasional abdominal pain, whereas CT of the abdomen showed distended stomach and a small inner wall herniation.

The American Academy of Pediatrics has published diagnostic and health supervision guidelines for children with NF1, which include measurement of blood pressure, as well as assessing children for precocious puberty by annual evaluation of growth and sexual development (26). NF1 patients have a lifetime risk of 1 – 5% for the development of a pheochromocytoma with sustained hypertension in approximately 60% of all cases. These tumors are almost exclusively localized on a single or both adrenal glands. Rarely they are malignant and in most patients can be treated by surgery (27). Inherited pancreatic endocrine tumors, especially duodenal carcinoids (somatostatinomas) can occur as a part of NF-1, with a penetrance of approximately 1% (28). In a recent case–control study, hyposalivation was estimated in 59% of 49 individuals with neurofibromatosis 1. Authors suggested that hyposalivation may be a consequence of NF1, but more studies are needed to prove this hypothesis (29). No such abnormalities have been detected in our patient.

Patients with NF1 are at increased risk for a variety of cardiovascular disorders (30). Cardiovascular complications include hypertension, vasculopathy, cardiomyopathy, heart defects and superior vena cava obstruction. Mediastinal neurofibromas have been well documented as causes of superior vena cava compression. Congenital lesions have potential long-term hemodynamic consequences that justify an early diagnosis (9, 31). During hospitalization the patient´s blood pressure and electrocardiogram were normal. CT scans revealed a hypotrophic right kidney; atherosclerotic lesions of the abdominal aorta; low grade infrarenal kiking of the abdominal aorta.

A study on NF1 associated mortality included 1895 patients in France; the mortality rate was significantly increased, and malignant nerve sheath tumors were the main cause of death in about 60% of all cases (32). Cutaneous neurofibromas are invariably benign but subcutaneous and plexiform neurofibromas may undergo malignant transformation in about 8 - 13% of patients with NF1 (33). High grade lesions herald a poor prognosis. The clinical symptoms include pain, rapid growth, changes in texture and neurological deficit (34, 35). Long-term follow-up has shown reduced life expectancy related to the development of malignancy and other tumors that may occur such as gastrointestinal stromal tumors, gastric carcinoid, juvenile myelomonocytic leukemia, glomus tumors, astrocytomas and pheochromocytomas (1, 7).

Currently, there are no effective treatment modalities specific for NF1. The treatment is symptomatic. Some disfiguring lesions can be excised if not too diffuse. Painful and bleeding tumors and cosmetic enhancement warrant surgical intervention, including various surgical techniques and lasers. The

advent of new treatment options for NF1 such as topical vitamin D3 analogues, lovastatin, rapamycin (or sirolimus), and imatinib mesylate have added new dimensions that require further investigations to prove their therapeutic efficacy.

We used antibiotic therapy for pneumonia and secondary skin infection in our patient. Considering the age and medical presentation, we did not consider any other treatment.

Genetic counselling is important. It should be made clear to patients that 50% of their children are likely to be affected and that the disease may be severe. First-degree relatives (e.g. siblings and offsprings) who have no stigmata of the disease are unlikely to carry the gene and the risk for their offsprings is small but not absent, as gonadal mosaicism has been observed. Prenatal diagnosis is also not an option for approximately 50% of cases who will present with new mutations (1).

Conclusion

This is a sporadic case of cutaneous neurofibromatosis 1 in a 78-year-old female patient who exhibited extremely severe clinical aspects of cutaneous neurofibromas, making this case at least rather peculiar.

Abbreviations

NFs - neufibromatoses
NF1 - neurofibromatosis 1
NIH - National Institutes of Health
CALMs - “caffe au lait macules”
Kb – kilobase
GTPase - guanosine triphosphatase
TNF- tumor necrosis factor
RTG – X-ray
CT – computed tomography

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Ekstremno izražena kutana neurofibromatoza tip i posledica nove mutacije - prikaz slučaja

Sažetak

Uvod. Neurofibromatoza tip 1 predstavlja jedno među najčešćim naslednim multitistemskim oboljenjima. Manifestuje se nekolikim karakterističnim promenama koje imaju dijagnostički značaj: većim brojem makula boje bele kafe (fr. *café-au-lait macules*), hiperpigmentacijama u pazušnim jamama, Lišovim čvorićima na šarenici (dužica) oka i neurofibromima (benigni tumori poreklom iz ovojnice perifernih nerava). Udružene ekstrakutane kliničke manifestacije bolesti podrazumevaju najčešće prisustvo skeletnih abnormalnosti, neuroloških, kardiovaskularnih, endokrinih ili malformacija drugih organa i sistema.

Neurofibromatoza tip 1 nastaje kao posledica mutacije na NF-1 genu koji kodira sintezu neurofibromin proteina. Bolest se nasleđuje autozomno-dominanto, ali kod 50% obolelih oboljenje nastaje kao posledica novonastale (*de novo*) mutacije, tako da osoba predstavlja prvog obolelog u porodici. Nisu utvrđene razlike u kliničkoj slici ili težini oboljenja između onih koji su nasledili oboljenje i onih koji predstavljaju prve obolele u porodici.

Prikaz slučaja. U radu je prikazana 78-godišnja ženska osoba sa ekstremno izraženim kutanim manifestacijama oboljenja i koja je predstavljala prvi slučaj bolesti u porodici. U detinjstvu i mladosti, osim kožnih, nije imala značajnijih problema sa zdravljem, ali poslednjih decenija je imala češće glavobolje, povremene bolove u stomaku, slabiji vid i sluh. Desetak do četrnaest dana pre prijema u bolnicu počela je jače da kašlje, da otežano diše, i da oseća bolove u grudima i stomaku. Na pregledu, izuzev na koži ekstenzornih strana natkolenica i potkolenica, koža celog tela pacijentkinje niskog rasta (152 cm), telesne mase 49 kg bila je prekrivena hiljadama gusto raspoređenih mekih kutanih nodusa; boja nodusa varirala je od boje kože, lividnoerimatozne do sivkastosmeđe; nodusi u predelu abdomena su bili vlažni, mestimično su pri bazi krvarili i bili praćeni neprijatnim mirisom. Na

stopalima su takođe bile prisutne gusto raspoređene čvoraste, tumorozne promene uz distrofične promene na noktima koji su bili zadebljali, iskrzani, žućkastog kolorita. Skeletne malformacije prisutne kod naše pacijentkinje bile su: nizak rast, izražena osteoporoza i zona osteosklerotskog karaktera na koštanim strukturama glave; degenerativne artropatsko-spondilotske promene torakolumbalnog segmenta kičme sa znacima difuzne skeletne hiperostoze; izrazito degenerativne promene lumbalne kičme.

Pregledom glave (CT), grudnog koša i abdomena utvrđene su sledeće abnormalnosti: aplatacije girusa paraventrikularno i redukcija moždanog parenhima sa hipodenzitetom bele mase u smislu znakova kortikalne atrofije; periventrikularno obostrano, manje mikro-vaskularne cerebralne postishemijske lezije različitog hroniciteta; u plućnom parenhimu gornjeg levog plućnog režnja apikalno, kao i apikoposteriorno odnosno anteriorno, prisustvo manje zone pleuralne efuzije sa subatelektatičnom zonom kao posledicom; distendiran želudac i manja unutrašnja hernija zida želuca; hipotrofičan desni bubreg; aterosklerozne promene abdominalne aorte; niskostepeno uvrtanje (engl. *kinking*) infrarenalnog segmenta abdominalne aorte. Patohistološka analiza bioptiranog nodusa je po opisu odgovarala kutanom neurofibromu. Konsultativni pregledi lekara različitih specijalnosti ukazali su na postojanje sledećih komorbiditeta: opstruktivni respiratorni sindrom i levostrana upala pluća i zbog toga je ordinirana antibiotska terapija, aminofilin i deksametazon u infuziji; psihoorganski sindrom bez fokalnog neurološkog deficita; Lišovi noduli na irisu oba oka; senilna katarakta. Uzimajući u obzir starost i klinički status pacijentkinje, sprovedena je antibiotska i relevantna internistička simptomatska terapija.

Zaključak. U radu je prikazan sporadičan slučaj kutane neurofibromatoze 1 kod 78-godišnje ženske osobe sa preko hiljadu ekstremno izraženih neurofibroma.

Ključne reči: Neurofibromatoza 1; Neurofibrin 1; Café-au-Lait fleke; Bolesti dužice; Melanoza; Neurofibrom; Kožne neoplazme; Prikazi slučajeva; Komorbiditet

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Scleromyxedema (Arndt-Gottron Syndrome): a Case Report

Danijela POPOVIĆ*, Mirjana PARAVINA, Dragan JOVANOVIĆ, Vesna KARANIKOLIĆ, Dragana LJUBISAVLJEVIĆ

Clinic of Skin and Venereal Disease, Clinical Center Niš, Serbia
Medical Faculty, University of Niš, Serbia

*Correspondence: Danijela Popović, e-mail: danijelapopovicnis@gmail.com

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Abstract

Lichen myxedematosus, also known as papular mucinosis, is a primary diffuse cutaneous mucinosis. It is a rare cutaneous myxedematous condition characterized by formation of numerous lichenoid papules. Scleromyxedema, also known as Arndt–Gottron syndrome, is a rare, confluent, papular and sclerotic variant of lichen myxedematosus, characterized by diffuse thickening of the skin underlying the papules. The condition is associated with systemic, even lethal manifestations, fibroblast proliferation and accumulation of acid mucopolysaccharides of the hyaluronic acid. Serum IgG class paraproteinemia is always present and it can be detected in all patients if appropriate or even repeat testing is used.

Herein, we present a 67-year-old patient with a 2-year history of skin problems. He had no health problems other than hypertension and diabetes, wich were both diagnosed 15 years before. On examination, the patient exhibited sclerodermoid lesions with diffuse pseudo-sclerodermatous thickening of the exposed skin, microstomia and sclerodactyly-like changes; on the face, there were numerous solid, shiny 2 - 4 mm in diameter skin-coloured lichenoid papules, scattered across the forehead, glabellar area, nasolabial folds, perioral region, ear lobes and the neck. Histopathological examination revealed: highly distinctive collagenosis and fibrosis in the middle dermis, increased fibroblasts; collagen bundles with irregular arrangement and fragmentation; alcian blue-positive deposits with appearance consistent with acid mucins. Serum protein electrophoresis detected IgG lambda paraproteinemia. The patient was treated with systematic corticosteroids during 9 months with subsequent introduction of methotrexate and showed satisfactory results.

The etiology of scleromyxedema remains unknown, since the purified IgG paraprotein itself has no direct effects on fibroblast proliferation. In scleromyxedema, numerous therapeutic modalities are proposed, unfortunatelly with limited effects.

In colclusion, we report a case of an adult male with lichenoid papules; after a two-year progression, they evolved into scleromyxedema and exhibited well response to conventional therapy.

Key words

Scleromyxedema; Skin Diseases; Diagnosis; Therapeutics; Case Reports; Treatment Outcome

Lichen myxedematosus, also known as papular mucinosis, is a primary diffuse cutaneous mucinosis. It is a rare cutaneous myxedematous condition characterized by formation of numerous lichenoid papules. Scleromyxedema, or Arndt–Gottron syndrome, is a rare, confluent, papular and sclerotic variant of lichen myxedematosus, which is characterized by diffuse thickening of the skin that underlies the papules. The condition is associated with systemic, even lethal manifestations, fibroblast proliferation and accumulation of acid mucopolysaccharides of the hyaluronic acid. Serum IgG class paraproteinemia is always present and it can be detected in all patients after appropriate or repeat testing (1, 2, 3).

A case of an adult male with IgG paraproteinemia, in whom lichenoid papules evolved to scleromyxedema after two years, is reported.

Case Report

A 67-year-old patient was referred with a 2-year-long history of skin lesions that initially started on the forehead and earlobes, and then subsequently spread to the trunk and extremities. The patient was previously treated as an out-patient with the following diagnoses: steatocystoma multiplex< xanthelasma< erythroderma. He had no health problems other than hypertension and diabetes mellitus, wich were both diagnosed 15 years before.

On admission, the patient exhibited sclero-dermoid lesions, with diffuse pseudosclerodermatous thickening of the exposed skin, microstomia and

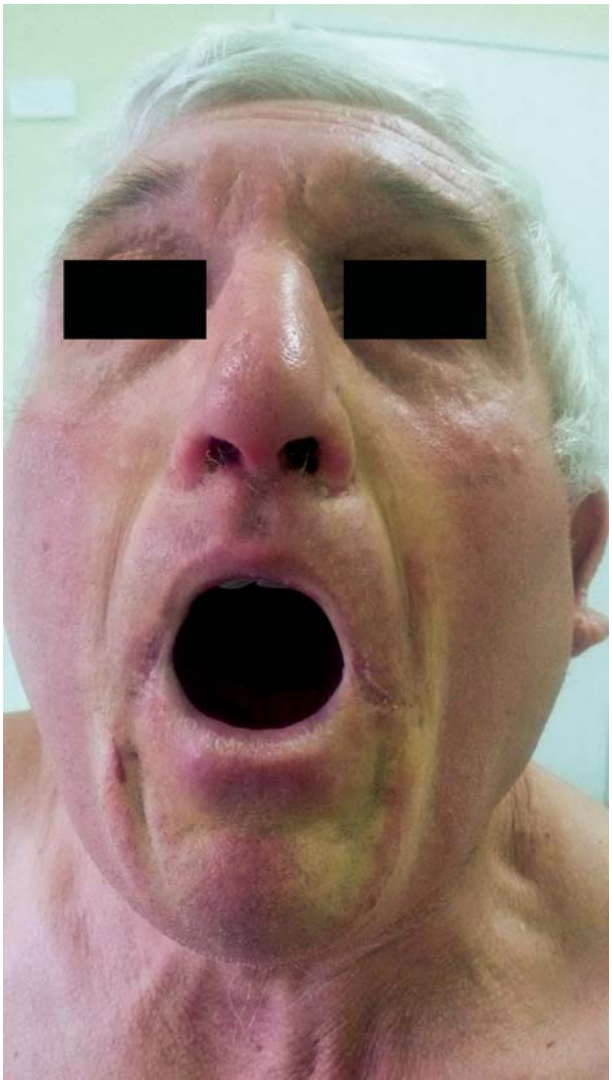

Figure 1. Persistent skin induration on the face, forehead, nasolabial area, and chin with microstomy

Figure 2. Diffuse thickening of the skin of the hands

sclerodactyly-like changes (Figures 1, 2, 3), as well as elephatiasis thickening on the trunk and extremities (Figures 4, 5, 6, 7) There were numerous lichenoid, solid, hemispherical, shiny, skin-coloured papules 2 - 4 mm in diameter, scattered across the forehead, glabellar area, nasolabial folds, perioral region, ear lobes, with linear distribution on the neck (Figures 8, 9, 10).

Laboratory test results

Laboratory tests revealed the following abnormal test results: elevaed erythrocyte sedimentation rate - 19, C-reactive protein - 15,5 mg/L (normal range 0 - 5 mg/L), fibrinogen - 6,1 g/L (normal range 1,86 - 3,86 g/l), glucose - 9,2 mmol/L, (normal range 3,9 - 6,1 mmol/l), glycated hemoglobin (HbA1c) level - 9,30% (normal range 4.8 - 5.9), b2 microglobulin - 3,27 (normal range 0,97 - 2,64 mg/l). Serum protein electrophoresis revealed "M spike" present in the lambda fraction, and immunofixation showed IgG lambda paraprotein; urinalysis for free light chains (Bence-Jones proteins) was negative. All other findings were within normal limits including the following: baseline laboratory tests such as complete blood count,

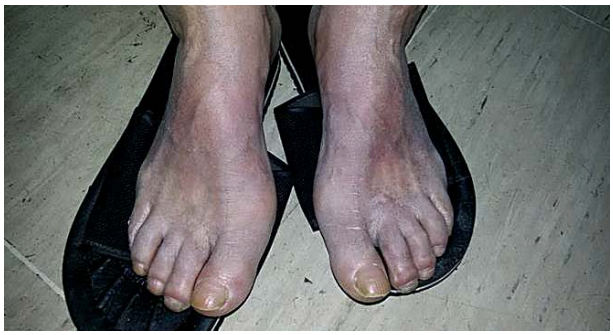

Figure 3. Diffuse hyperpigmentation and induration of the skin of the legs

Figure 4. Elephantiasis thickening of the skin of the trunk

Figure 5. Skin thickening on the trunk with coarse folds

serum electrolytes, blood urea nitrogen and creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, amylase, lipase, creatine phosphokinase, lactate dehydrogenase, alkaline phosphatase, rheumatoid factor, antistreptolysin titer, lipid status, ferritin, thyroid hormones - thyroxine, triiodothyronine and pituitary thyroid stimulating hormone, as well as antinuclear antibodies, antibodies to double-stranded DNA (dsDNA), antibodies to Sjogren's Syndrome related antigen A (anti-Ro/SS-A), antibodies to Sjogren's Syndrome related antigen B (anti-SS-B/La), antibodies to topoisomerase (anti-Scl-70), anticentromere and anticardiolipin antibodies.

Histopathological analysis

Histopathological analysis of skin biopsy specimens showed: profound epidermolytic hyperkeratosis in the epidermis; discrete lymphocytic perivascular infiltrate in the upper dermis, flattening of the epidermal dermal junction, atrophy of the adnexal structures; highly distinctive collagenosis and fibrosis; increased fibroblasts; collagen bundles exhibiting irregular arrangement and fragmentation; alcian blue-positive deposits in reticular dermis, with appearance consistent with acid mucins (Figure 11).

Histopathological analysis of bone marrow biopsy specimens was normal.

Figure 6. Numerous lichenoid papules on the arms

Nailfold capillaroscopy

Nailfold capillaroscopy showed a significant decrease in the number of capillaries, which were fragile and irregularly distributed but without markedly dilated capillary loops.

Radiography

Chest and esophageal passage x-ray (including barium swallow) were normal.

Bone redaiographs of the hands revealed osteodegenerative changes with narrowing of the distal interphalangeal spaces.

Ultrasonography

Ultrasound of the upper abdomen revealed a cyst, 10 mm in diameter, in the right kidney.

Figure 7. Diffuse hyperpigmentation and induration of the skin of the legs

Specialist consultations

Specialist consultations established the diagnosis of insulin-dependent diabetes, therefore insulin therapy was indicated.

Therapy

Apart from insulin, systemic methylpred-nisolone was initiated parenterally at a dose of 60 mg daily, with gradual dose reduction and conversion to oral therapy. Two months later, the clinical status showed considerable improvement: the number of lichenoid papules on the face (Figure 12) and on the neck was reduced; elephantiasic skin folds and hyperpigmentation dramatically decreased, especially on the trunk and extremities (Figures 13,

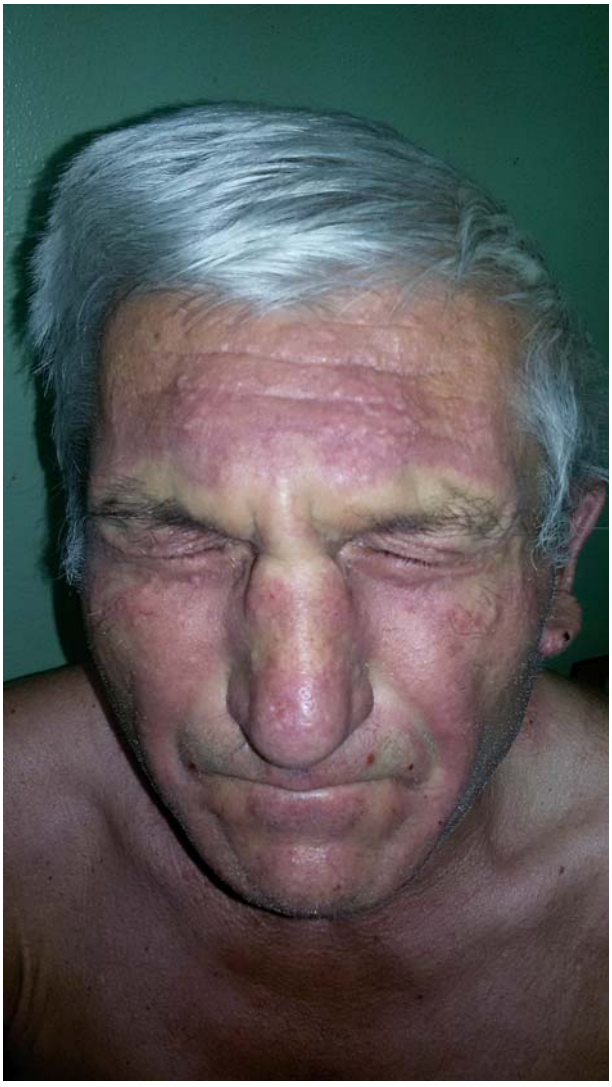

Figure 8. Numerous lichenoid papules - especially on the forehead and in the glabellar region

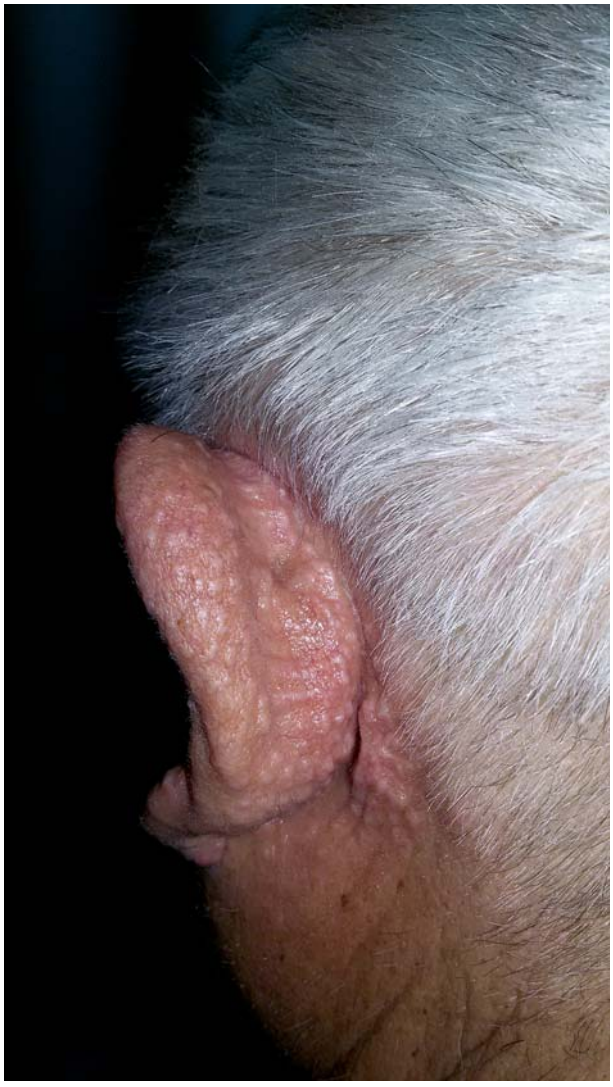

Figure 9. Solitary, hemispherical, solid papules on the earlobes

14). The most resistant to therapy were nasolabial folds, earlobes and hands, where induration, papules and sclerodermoid appearance were still present, but with a subjective feeling of better mobility of fingers. After being dismissed from the hospital, the patient was treated with prednisone tablets - 30 mg per day. Six months later, due to persistent skin induration of the face, cheeks, chin and microstomy, the dose was increased to 40 mg per day and methotrexate was introduced at a weekly dose of 12,5 mg as an adjunct therapy, which resulted in marked improvement once again.

Discussion

Scleromyxedema (papular mucinosis, lichen myxedematosus, lichen fibromucinodosis, lichen myxedematosus generalisatus et sclerodermoides, Arndt Gottron) is a variant of cutaneous mucinosis (1, 2). The original description of cutaneous mucinosis was given by Dubreuilh in 1906 and Reitmann in 1908 (4, 5).

All cutaneous mucinoses are divided into primary and secondary. Primary mucinoses can be subdivided into diffuse degenerative inflammatory mucinoses, focal hamartomatous neoplastic mucinoses and

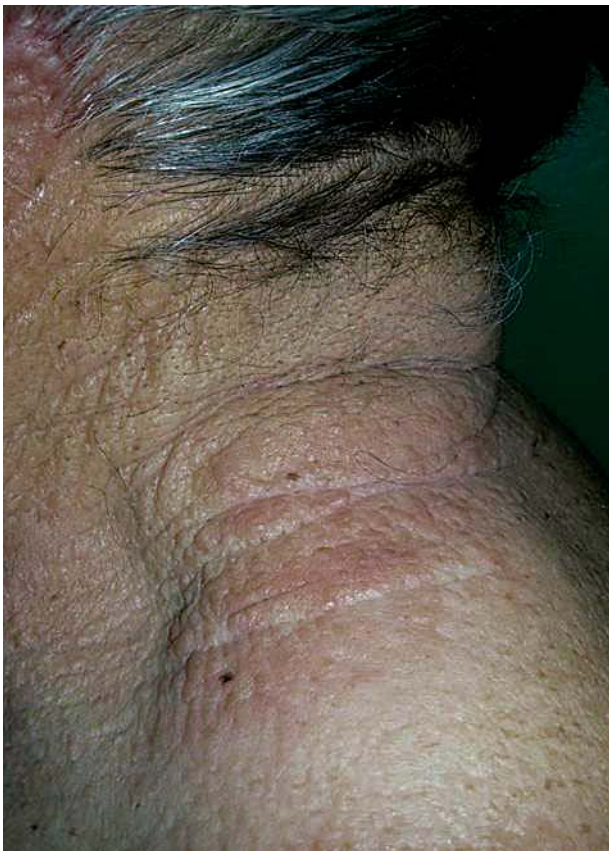

Figure 10. Linear papules on the neck

follicular mucinoses. The group of degenerative inflammatory mucinoses comprises several different conditions, such as generalized and several localized forms of lichen myxedematosus (LM) (1).

In 1953, Montgomery and Underwood distinguished 4 types of LM: 1) generalized lichenoid eruption, later called scleromyxedema; 2) discrete papular form; 3) generalized or localized lichenoid plaque form; and 4) urticarial plaque form (6). The term "scleromyxedema" was coined by Gottron in 1954 to signify the generalized lichenoid papular eruption with sclerodermoid appearance (7). In the literature, terms LM, papular mucinosis, and scleromyxedema have been often used indiscriminately as synonyms, but in 2001 based on personal experience and literature review, Rongioletti concluded that most reported cases of LM or papular mucinosis published without indication of the subtype, appeared in fact to be cases of scleromyxedema. He also recognized two clinico-pathological subsets of LM, a generalized papular and a sclerodermoid form (also called scleromyxedema) with systemic, even lethal, manifestations, and a localized papular, more benign form, without a demonstrable paraprotein, with 5 subtypes: 1) a discrete papular form involving any site; 2) acral persistent papular mucinosis involving only the extensor surface of the hands and wrists; 3) self-healing papular mucinosis, of a juvenile and adult type; 4) papular mucinosis of infancy, a pediatric variant of the discrete form or of acral persistent papular mucinosis; and 5) nodular form (8).

Scleromyxedema is a rare chronic cutaneous myxedematous condition of the connective tissue (1, 9, 10) which occurs in middle-aged individuals (11), most commonly between the ages of 30 and 80, in all ethnic groups and equally in both sexes (10, 11). The etiopathogenesis of scleromyxedema hasn't been fully clarified. There is hyperproliferation of dermal fibroblasts which produces mucin in quantities larger than normal fibroblasts, with increased collagen deposition (3). The serum shows the ability to stimulate fibroblast proliferation in vitro, thus indicating the role of monoclonal paraproteinemia. The presence of monoclonal component (M component) or paraprotein in sera of patients with lichen myxoedematosus and scleromyxedema has been noted in nearly all cases. However, this ability of the serum remains even after the removal of IgG, which indicates that in addition to paraproteinemia, another circulatory factor is responsible. Thus, the role of serum paraproteins in scleromyxedema pathogenesis remains unknown (1, 2, 3, 12). It has been suggested that innate altered regulation of dermal fibroblast growth might play a role in pathogenesis of sclermyxedema (3). Paraproteinemia, or monoclonal gammopathy, delineates an immunoproliferative disorder manifested by the presence of excessive amounts of one monoclonal gamma globulin in blood. There are three types of paraproteins: light chain, heavy chain, and whole immunoglobulin, each of them can be present alone, or combined. Light chains can be excreted through urine, and then they are called Bence-Jones proteins. Potential causes of paraproteinemia include the following: leukemia and lymphatic myeloma (in 8.7% of the cases it is combined with multiple myeloma), plasmacytoma, or it is manifested as in our patient idiopathically as monoclonal gammopathy of unspecified cause. As far

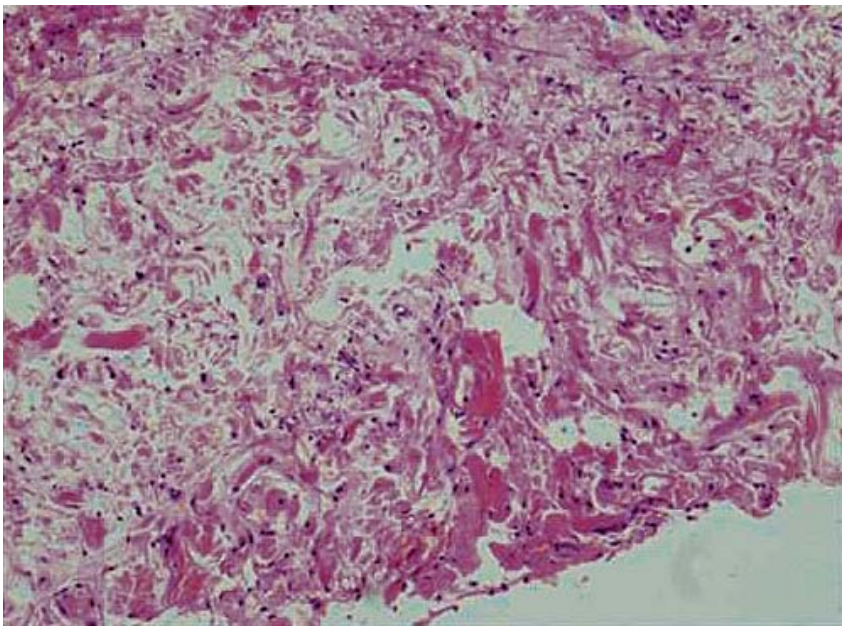

Figure 11. Histopathological analysis of the skin biopsy specimens showed: highly distinctive collagenosis and fibrosis, as well as an increased number of fibroblasts; irregular arrangement and fragmentation of collagen bundles (HE stain, x 100)

as scleromyxedema is concerned, the serum protein electrophoresis most frequently detects a monoclonal type IgG paraprotein of lambda light chain isotype, while IgA and IgM proteins are less common. Paraprotein IgG lambda, also present in our patient, has a molar eght of 110.000 daltons, whereas normal IgG weighs 160.000 daltons. These findings suggest that paraprotein IgG is an incomplete IgG molecule which lost a significant antigen part of Fc fragment. The IgG of lichen myxedematosus differes from the IgG of multiple myeloma not only by usually showing slower electrophoretic migration, but also by the fact that its IgG molecules nearly always possess light chains of the lambda type. The role of the monoclonal IgG in lichen myxedematosus is not clear. Although the serum from patients with lichen myxedematosus stimulates fibroblast proliferation *in vitro*, the purified IgG paraprotein itself has no direct effects on fibroblast proliferation (3).

Scleromyxedema, a generalized papular form of LM is characterized by the presence of the following criteria (13): 1) multiple cutaneous manifestations (papules, nodules, plaques) and sclerodermiform diffuse thickening of the skin of the elephantiasis type; 2) specific histologic findings, including mucin deposits, fibrosis and fibroblast proliferation; 3) monoclonal paraproteinemia; 4) absence of thyroid disease; 5) potential systematic spreading, sometimes with lethal outcome. In scleromyxedema, these characteristics represent crucial criteria in diagnosing the generalized disease (1). However, in order to diagnose localized LM, the presence of the first and second of the aformentioned characteristics is required, as well as the absence of the third, fourth, and the fifth one. Our patient met 4 of 5 aforementioned criteria: skin lesions, specific histologic findings, monoclonal paraproteinemia and absence of thyroid disease.

There is a triad of histopathologic characteristics of scleromyxedema (8, 3): 1) diffuse mucin deposition in the upper and mid reticular dermis; 2) increase collagen deposition, 3) significant proliferation of irregularly distributed fibroblasts. The epidermis may be normal or thickened due to mucin pressure and fibrosis, hair follicles may be atrophic, as in our patient; slight, perivascular, superficial lymphoplasmacytic infiltrate is often present, as it was in our patient; the elastic fibers are fragmented and decreased in number; in systematic spreading of the disease, mucin may fill the walls of myocardial blood vessels, as well as the interstitium of kidney, pancreas, adrenal glands and

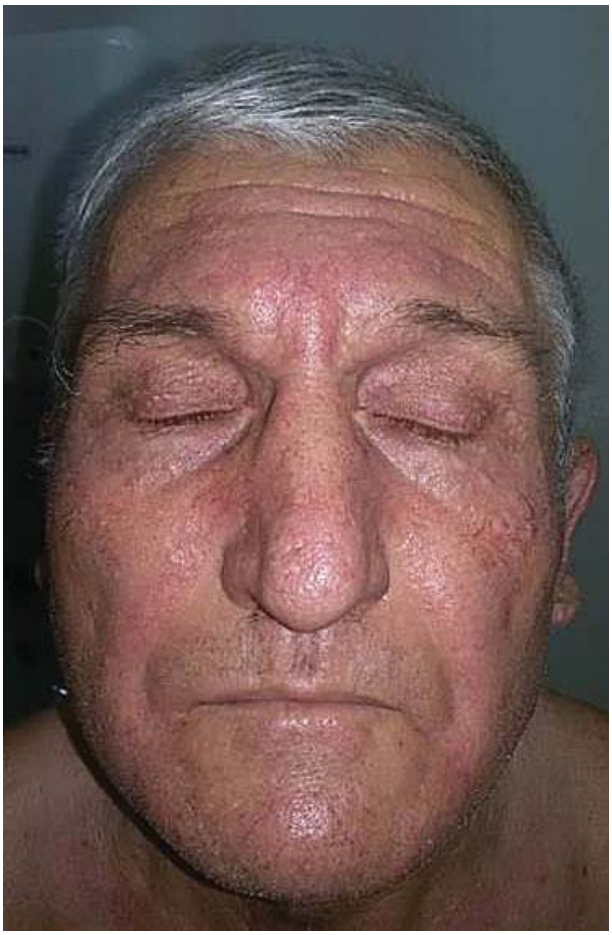

Figure 12. Reduced papular lesions on the skin of the face after 2 months of therapy

nerves (2). The mucin present in mucinous stains: light blue in sections stained with hematoxylin-eosin; alcian blue at 2.5 ph but negative at 0.5 pH and shows metachromasia with toluidine blue at 7.0 pH and 4.0 pH but no metachromasia below 2.0 pH< it is PAS negative, indicating absence of neutral mucopolysacharides, and aldehyde-fuchsin negative (indicating absence of sulfated mucopolysacharides). Regular demonstration of the presence of mucin in the dermis is possible only in pretibial myxedema, in self healing-juvenile cutaneous mucinosis and in lichen myxedematosus (3). There were alcian blue positive-deposits detected in the lesions of our patient.

Our patient presented without a thyroid disease, but he had diabetes mellitus and hypertension. Although no endocrine abnormalities have been found, there are numerous extracutaneous manifestations that can be present in patients with

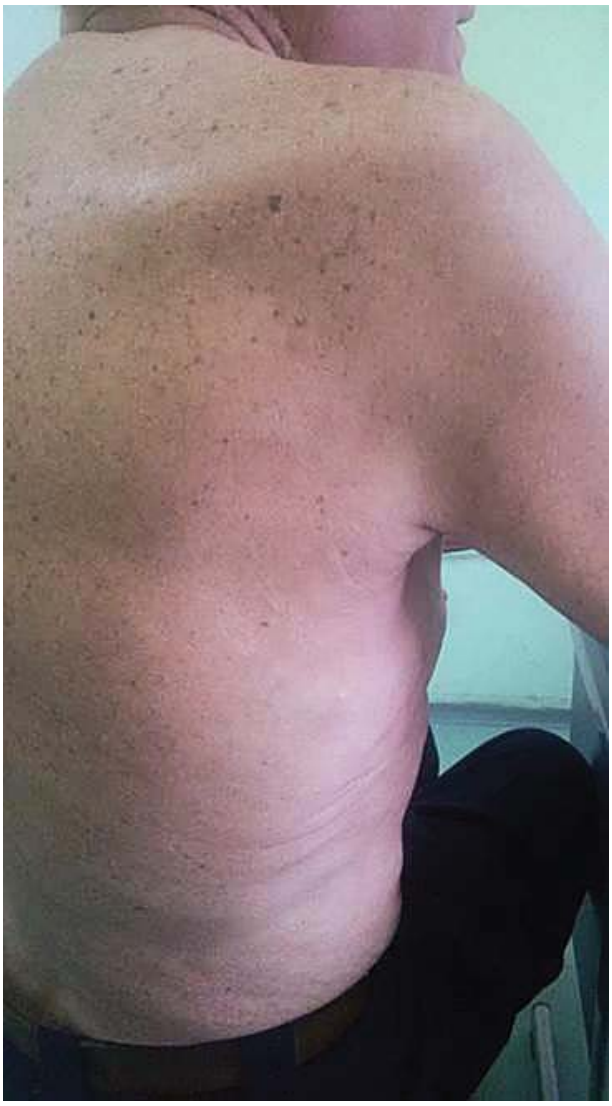

Figure 13. A dramatic improvement of skin lesions over the trunk after 2 months of treatment

scleromyxedema, eg. hematological alterations such as eosinophilia, neurological manifestations (confusion, dysarthria, ascending paralysis, convulsions and coma; combination of high temperature, convulsions and coma), proximal myopathy, inflammatory polyarthritis, laryngeal alterations, esophageal dysfunction, pulmonary restrictive disease, and in 10% cardial alterations (1). Occasionally, systemic involvement may occur in other internal organs. There are reports of hepatitis C virus infection (9), bilateral scleromyxedema of the eyelids (14), and dermato-neuro syndrome (10); malignant hematological neoplasia (multiple myeloma, acute leukemia and

T-cell lymphoma) as well as cancers, including thymic carcinoma (15).

Scleromyxedema can be clinically differentiated from scleroderma by the presence of papules and the absence of telangiectasias: scleromyxedema, presents with generalized eruption of papules as in lichen myxedematosus and diffuse erythematous tickening of the skin which is movable over the subcutis, not bound down as in scleroderma (1, 3).

No established standard therapy exists for systemic treatment of scleromyxedema. Various medications and methods are used with varying, mostly insufficient therapeutic effects (11). These include: topical application and intralesional injection of hyaluronidases, topical, intralesional and systemic administration of corticosteroids, radiotherapy, psoralen and ultraviolet A (PUVA) phototherapy, plasmapheresis combined with pulsed corticosteroid and/or immunosuppressive therapy, intravenous immunoglobulin combined with thalidomide, extracorporeal photochemotherapy (12, 16, 17, 18), retinoids (11), peripheral blood autologous stem cell transplantation (16). Aggressive surgical interventions may be indicated for palliative care, esthetic corrections, and functional training. Melphalan, as a cytoreduction chemotherapeutic agent, has been considered as the first line therapy for decades (16, 18). Our patient was treated with systemic corticosteroids continuously during 9 months, with subsequent introduction of methotrexate. Satsifactory results have been achieved, which was also reported by other authors (19).

The disease has a chronic progressive course. Spontaneous improvement is possible, but extremely rare. The possibility of other organs being affected must also be taken into consideration (11). The prognosis is rather poor. Lethal outcome is also possible as a result of non-specific complications, but also hematological malignancy (1). Clinical staging of scleromyxedema has been proposed as follows: 1) limited cutaneous papular mucinosis; 2) generalized cutaneous mucinosis and/or extracutaneous manifestations; 3) generalized cutaneous mucinosis and/or extracutaneous manifestations with a Karnofsky performance status less than 50% (20, 21). The Karnofsky Performance Status (KPS) is a widely used method to assess the functional status of patients.

Full staging investigations should always be undertaken before making any decisions concerning the treatment strategy. Our patient presented with the first limited cutaneous stage of the disease.

Conclusion

We reported a case of an adult male in whom lichenoid papules of lichen myxedematosus evolved into scleromyxedema after a two-year pregression with no extracutaneous manifestations, and good response to conventional therapy.

Abbreviations

LM - lichen myxedematosus
HbA1c - glycated hemoglobin A1c
ds DNA - double stranded deoxyribonucleic acid
Ro/SS-A - Sjogren's Syndrome-related antigen A
SS-B/La - Sjogren's Syndrome-related antigen B
Scl-70 - topoisomerase 1
KPS - Karnofsky performance status

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Skleromiksedem (Arndt–Gottron syndrome) – prikaz slučaja

Sažetak

Uvod. Miksedematozni lihen (lat. *lichen myxoedematosus*) takođe poznat pod nazivom papulozna mucinoza, klasifikovan je kao primarna kutana difuzna mucinoza. Predstavlja retko miksedematozno stanje u koži koje karakteriše formiranje brojnih lihenoidnih papula. Skeromiksedem, poznat i kao Arnt–Gotronov (*Arndt-Gottron)* sindrom, retka je papulozna sklerodermiformna varijanta miksedematoznog lihena, u kojoj aglomerirane papule rezultuju difuznim zadebljanjem kože. Stanje je povezano sa sistemskim, čak i letalnim, manifestacijama, tako da se razlikuju tri stadijuma skleromiksedema: 1) limitirana, kutana papulozna mucinoza; 2) generalizovana kutana mucinoza i/ili ekstrakutane manifestacije; 3) generalizovana kutana mucinoza i/ili ekstrakutane manifestacije uz *Karnofski status* manji od 50%.

U osnovi patogenetskog mehanizma skleromiksedema je proliferacija fibroblasta i akumulacija kiselih mukopolisaharida tipa hijaluronske kiseline. Paraproteinemija IgG klase je prisutna u serumu i može biti detektovana kod svih pacijenata ukoliko se sprovodi na adekvatan način, ponekad u više ponovljenih pokušaja.

Dijagnoza bolesti se postavlja na osnovu kliničke slike, histopatološkog nalaza depozita kiselih mucina u retikularnom dermisu, proliferisalih fibroblasta i fragmenacije umnoženih kolagena vlakna, uz prisustvo u serumu monoklonalne gamapatije. U diferencijalnoj dijagnozi potrebno je razlikovati sklerodermiju, u kojoj nema papula, a zadebljala koža nije čvrsto srasla za potkožno masno tkivo.

Prikaz slučaja. Prikazujemo pacijenta starosti 67 godina, sa dvogodišnjom evolucijom promena na koži. Pacijent nije imao drugih zdravstvenih tegoba osim hipertenzije i dijabetesa melitus, koji su dijagnostikovani 15 godina ranije.

Tokom ispitivanja, pacijentova koža je imala sklerodermoidni izgled sa difuznim pseudo-sklerodermatskim zadebljanjem, ”mikrostomijom” i promenama sličnim sklerodaktiliji; na licu, u predelu glabele na čelu, nazolabijalnim brazdama, perioralnoj regiji, ušnim školjkama i vratu, bio je prisutan veliki broj sjajnih, uniformnih, 2–4 mm u dijametru lihenoidnih papula, normalne boje kože.

U isečku ledirane kože, histopatološkom analizom otkrivene su sledeće promene: kolagenoza i fibroza u retikularnom dermisu; između kolagenih vlakana povećan broj fibroblasta; nepravilan raspored i fragmentacija kolagena usled alcijan plavo-pozitivnih depozita koji bi mogli odgovarati kiselom mucinu. Elektroforezom serumskih proteina detektovana je IgG lambda paraproteinemija.

Pacijent je lečen sistemskim kortikosteroidima tokom 9 meseci; uveden je i metotreksat, što je dovelo do

privremene ali ne i trajne remisije.
Diskusija. Etiologija skleromiksedema ostaje nepoznata pošto za razliku od seruma obolelih, prečišćen IgG paraprotein samostalno nema direktni efekat na proliferaciju fibroblasta.
I pored brojnih terapijskih modaliteta, prognoza oboljenja je loša, a prisustvo paraproteina uvek može značiti uvod u malignu hemopatiju.
Zaključak. U radu je prikazan slučaj odrasle muške osobe, kod koje su lihenoidne papule nakon dvogodišnje progresije evoluirale u generalizovane, difuzne sklerodermoidne lezije skleromiksedema, bez zahvatanja drugih organa, sa dobrim odgovorom na primenjenu kovencijalnu terapiju.

Ključne reči

Skleromiksedem; Kožne bolesti; Dijanoza; Terapija; Prikazi slučajeva; Ishod terapije

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Localized Bullous Pemphigoid on the Site of Knee Arthroplasty: A Case Report

Lucija KOSI[1], Jelena PERIĆ[1], Milica PANTOVIĆ[1], Gorana BIJELIĆ[1], Jelica VUKIĆEVIĆ SRETENOVIĆ[1,2], Dušan ŠKILJEVIĆ[1,2*]

1Clinic of Dermatovenereology, Clinical Center of Serbia; Belgrade, Republic of Serbia
[2]Clinic of Dermatovenereology, Clinical Center of Serbia; Department of Dermatovenereology, School of Medicine, University of Belgrade; Republic of Serbia

*Correspondence: Dušan Škiljević, e-mail: dusanskiljevic@yahoo.com

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Abstract

Localized bullous pemphigoid is a rare variant of bullous pemphigoid, and its exact etiopathogenesis is yet to be elucidated. We present a case of a 74-year-old Caucasian male with a 3-month history of skin lesions that appeared 9 months after he underwent a knee arthroplasty. Dermatological examination showed several pruritic tense bullae on the right knee, localized around the surgical scar, as well as erosions covered with crusts. The diagnosis of localized bullous pemphigoid was confirmed by direct immunofluorescence test (conventional and split-skin). The patient was treated with potent topical steroids, which led to complete resolution of cutaneous lesions.

We suppose that the occurrence of localized bullous pemphigoid in our patient may be explained by the concept of "immunocompromised district" in which one disease (surgery) caused an immunological alteration which is a predisposing factor for the development of secondary disease such as localized bullous pemphigoid.

Key words

Pemphigoid, Bullous; Skin Diseases; Cicatrix; Immunocompromised Host; Clobetasol; Arthroplasty, Replacement, Knee

Bullous pemphigoid (BP) arising on the site of skin injuries, has intrigued the researchers ever since the first description by Sneddon and Church in 1955 (1). Types of injury that can lead to BP vary greatly, among them, surgical procedures such as arthroplasty, are infrequently reported (2, 3). Some authors attribute this rare form of disease to a novel concept in dermatology, so called "immunocompromised district" (ICD) (4).

Case report

We present a case of a 74-year-old Caucasian male who was referred to our Clinic for itching and bullous eruptions that developed on his right knee three months earlier. He was otherwise healthy, except for hypertension, which was treated for several years with the same medications (fosinopril, acetylsalicylic acid and propafenone). His history was also significant for orthroprosthesis of the right knee; due to degenerative changes, a total prosthesis was implanted nine months prior to skin lesions. The patient received systemic and topical antibiotic therapy (gentamicin injections, and topical bacitracin and neomycin), but without favorable results.

Skin examination revealed several tense bullae on erythematous skin, as well as erosions covered with crusts and scars, whereas the patient´s main complaint was itching. No milia were seen. The lesions were localized on the incision scar from the above-mentioned orthopedic intervention, as well as on the surrounding skin (Figure 1).

Laboratory tests were not significant, except

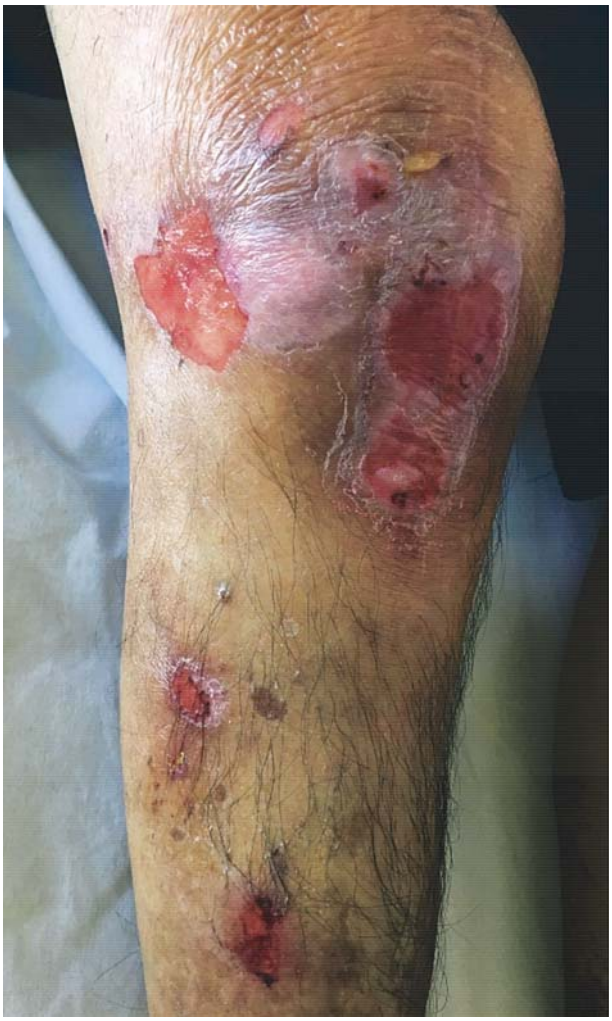

Figure 1. Tense bullae, erosions and crusts on the incision scar site after total knee prosthesis

for: elevated erythrocyte sedimentation rate of 48 mm/h and C-reactive peptide of 31.5 mg/l (normally < 6 mg/l). Other test results, for neoplastic processes, such as tumor markers, chest X-ray and abdominal ultrasound, were all unremarkable.

Histological analysis of perilesional skin biopsy specimens was performed by direct immunofluorescence (DIF), which revealed linear deposits of IgG and C3c at the basement membrane zone (BMZ) (Figure 2a). Also, direct immunofluorescence using the salt-split skin (DIF-SS) technique with 1 mol/L sodium chloride, revealed linear deposits of the same immunoreactants on the epidermal side („roof") of the split (Figure 2b), which was consistent with the diagnosis of bullous pemphigoid.

Therapy was initiated by using only potent topical corticosteroids, 0.05% clobetasol propionate ointment twice a day, because of the localized nature of patient´s condition, which lead to complete resolution of skin lesions over the course of eight weeks (Figure 3). No recurrence was observed during a 3-month follow-up.

Discussion

Bullous pemphigoid is an acquired, autoimmune disease confined to the skin, characterized by formation of autoantibodies which are directed towards components of hemidesmosomes in the basement membrane (5). It is the most common autoimmune bullous disease in Western Europe and North America (6), and probably in most countries of the world (5), which affects mostly the elderly (7). The reported incidence varies greatly among different countries: from 0.25/100.000 inhabitants per year in Romania (6), through 2.2/100 000 inhabitants in France or 2.4/100.000 persons per year in the United States (8), to 4.3/100 000 persons per year in the United Kingdom (9). The incidence appears to be increasing in the last two decades (8,9), which may be attributed to greater proportion of older persons in the population (9), or to increasing incidence of neurological diseases, and use of certain medications which are implicated as risk factors for development of BP (10).

Generally, it is thought that BP occurs as a result of delicate interaction between genetic predisposition and various inducing factors (11). As for genetic factors of BP, the strongest association has been documented for human leukocyte antigen DQβ1*0301 which was observed in 90% of patients with BP in one of the first studies that tackled this matter (12). Among triggering factors which can be identified in only 15% of cases (2), several different factors have been implied, such as drug intake (i.e. furosemide) (7), viral infections (6), systemic diseases - malignancy (7), diabetes mellitus (11), and physical trauma (4).

Bullous pemphigoid arising on the site of skin injury firstly appears as a localized form, regardless of the type of physical trauma causing the skin injury. Later on, it remains confined to the particular body area (as it was the case in our patient), or it becomes generalized (3), which appears to be more common (6).

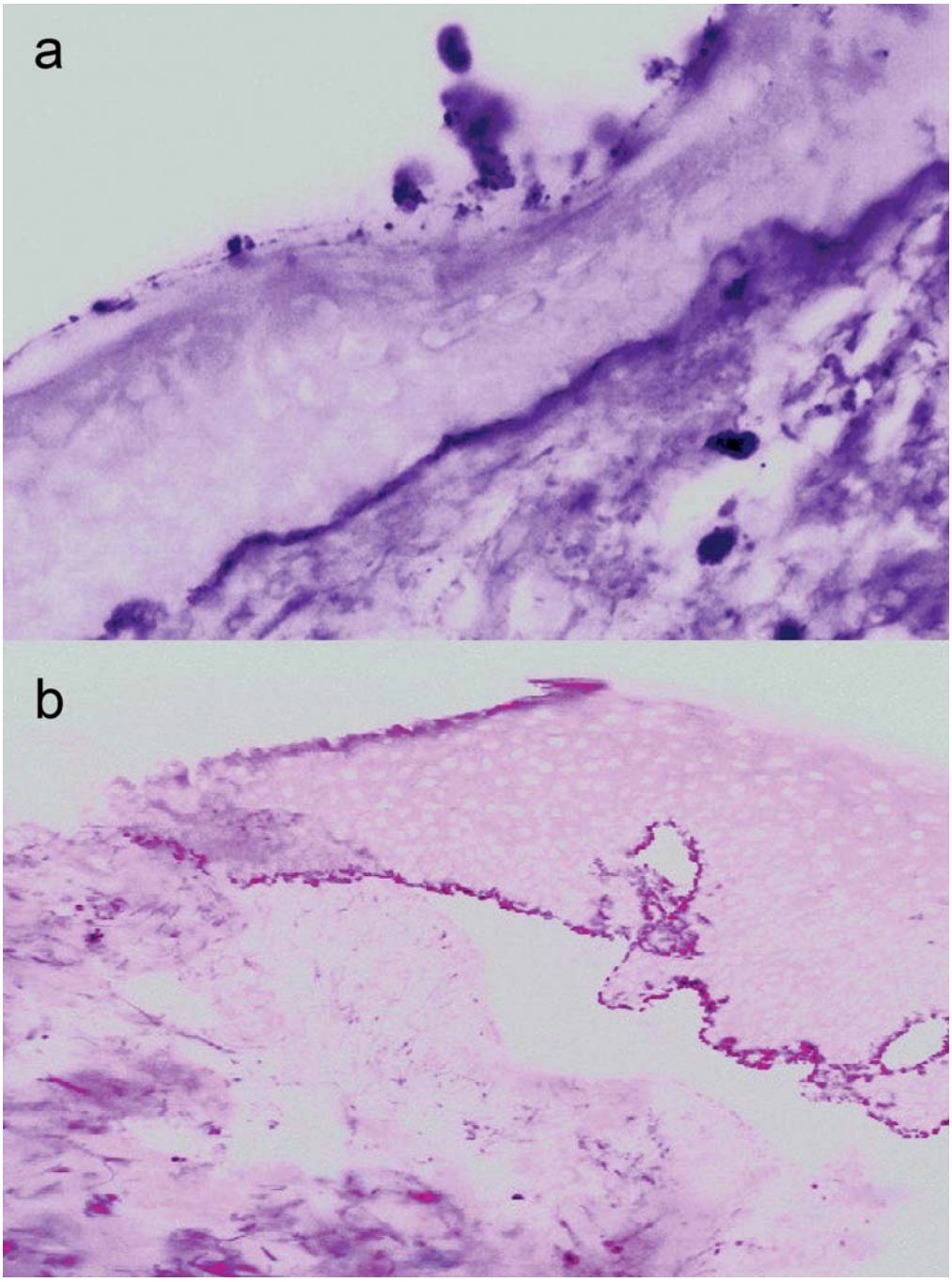

Figure 2. Direct immunofluorescence microscopy of perilesional skin showing IgG and C3c deposits at the epidermal-dermal junction; (b) Direct immunofluorescence on salt-split skin shows IgG and C3c deposits confined to the epidermal side of the split skin

Another possibility is observed when localized lesions develop in a patient with pre-existing generalized BP in remission, leading to conclusion that BP can be exacerbated by trauma (13). In this particular sense, trauma includes the following: radiotherapy and phototherapy (either UVB or psoralen with UVA) (14); thermal or chemical burns (6); skin grafting (15); simple skin biopsy (13); cellulitis (16). Cases of

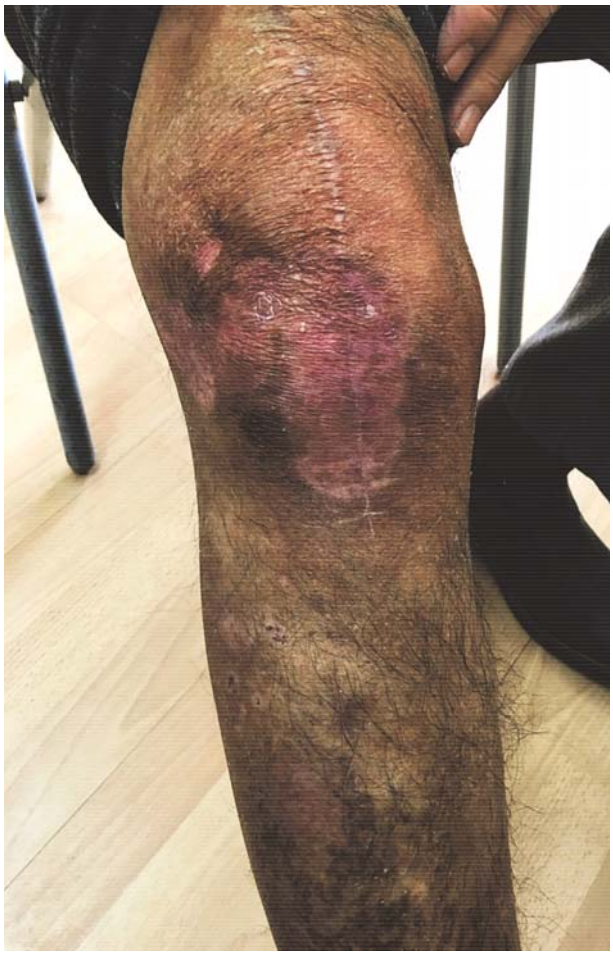

Figure 3. Complete resolution of bullous lesions at the follow-up visit eight weeks later

BP after surgical procedures such as arthroplasty as in our case (2,3), internal fixation of skeletal fractures (17), amputation stumps (13), incisional hernia (14), vascular grafting (7), percutaneous gastrostomy or urostomy (2) etc., are well documented in the literature. Time elapsed from the injury and development of skin lesions varies greatly, ranging from as little as few hours (6) to over 20 years (16).

Several hypotheses have been proposed regarding the pathogenesis of trauma-induced BP. One point of view is that the injury may ′uncover′ BP antigens which were previously inaccessible to the immune system (13), or alters these antigens in BMZ, which becomes alien to immune cells (3). If this latter happens, this enhanced antigenicity of the basement membrane constituents leads to ′de novo′ synthesis of autoreactive antibodies. On the other hand, some researchers propose a different, more likely theory which advocates that these patients already have autoantibodies directed towards BMZ components in low titers, insufficient to induce immunologic response (6). Complement system activation due to antigen-antibody binding is possible only in a pro-inflammatory milieu (2). If the tissue is injured, this prerequisite is met leading to blister formation because of the following: innate immune cells (such as macrophages, neutrophils and mast cells) are activated by non-antigen-specific pathways and heavily infiltrate the site; cytokines and chemokines are secreted; vasodilation increases concentration of autoantibodies (simultaneously increasing the affinity for binding to antigens); complement system is activated and matrix metalloproteinase 9 is released by leukocytes (2,6,11). However, both of these two opposing hypotheses, the first advocating induction of autoimmunity, the second unmasking latent BP, are yet to be proven.

Interestingly enough, one might consider LBP arising in surgical scars, actually, in any traumatized site, as a real-life example of novel concept in dermatology, so called "*immunocompromised district*" (ICD) (4). Ruocco et al. were the first to introduce this term in 2009, as an expansion of an older concept of "*locus minorisresistentiae*" (LMR) 18. The previously described concept of LMR suggests that a certain body region is more prone to some diseases due to innate or acquired defense dysregulation, and that is why certain regions represent opportunistic localizations for a number of skin conditions thanks to pre-existing favoring conditions (19). Even more specific example of LMR would be Wolf′s "*isotopic response*", where sites previously affected by herpes simplex virus, become susceptible to other infections, tumors or different immune dysregulation (20). As Ruocco described, ICD represents a site in which one disease predisposes development of a different, unrelated disease due to regional destabilization of neuro-immuno-cutaneous system (18), which can vary immensely in lapse of time, but is typically confined to the same area (4). It is important to point out that the term ′immunocompromised′ indicates merely immunedysregulation (in either directions) and cannot be equaled with its reduction of it (19). In short, any interference with signaling pathways between nerve fibers, neuropeptides,

neurotransmitters and immune cell receptors can alter regional immune response, and even though the affected area may look clinically normal after the causing agent has disappeared, this alteration can be permanent (19). Most often implicated exogenous factors that contribute to ICD are regional chronic lymphedema, herpetic infections, vaccinations, ionizing and ultraviolet radiation, thermal burns and different types of other physical injuries (2,19).

In our opinion, in our patient, one ´disease´ or rather tissue injury (surgery), caused immunological alteration that led to secondary disease (LBP), which would be another good example of ICD. Finally, we feel that this case demonstrates the need for clinicians' awareness of LBP which should be included in the differential diagnosis of localized bullous eruptions, especially if bullae are confined to surgical scars.

Conclusion

We presented a case of an otherwise healthy male adult with a rare localized variant of bullous pemphigoid around the surgical scar which developed 9 months after knee arthroplasty. BP was successfully treated with a topical corticosteroid.

Abbreviations

LBP - localized bullous pemphigoid
BP - bullous pemphigoid
DIF - direct immunofluorescence
BMZ - basement membrane zone
DIF-SS - direct immunofluorescence using salt-split skin
Hb - hemoglobin
UVA - ultraviolet light A
UVB - ultraviolet light B
ICD - immunocompromised district
LMR - locus minorisresistentiae

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Lokalizovani bulozni pemfigoid na mestu izvedene artroplastike kolena: prikaz slučaja

Sažetak

Uvod. Lokalizovani bulozni pemfigoid (LBP) predstavlja retku varijantu buloznog pemfigoida čija tačna patogeneza još uvek nije razjašnjena.

Prikaz slučaja. Prikazujemo 74-godišnjeg pacijenta sa kutanim lezijama u trajanju od 3 meseca, kojesu se pojavile 9 meseci nakon artroplastike zgloba kolena. Pri pregledu, bile su uočljive bule napetog krova na desnom kolenu, lokalizovane oko operativnog cikatriksa, kao I erozije prekrivene krustama, uz pruritus na mestu lezija. Dijagnoza LBP postavljena je na osnovu direktnog imunofluorescentnog testa (konvencionalnog i na hemijski rascepljenoj koži). Primenjena je potentna topikalna kortikosteroidna terapija, što je dovelo do potpune rezolucije kožnih promena.

Diskusija. Smatramo da se pojava LBP kod našeg pacijenta može objasniti konceptom „imunokompromitovanog područja", u kome jedna bolest (hirurškaintervencija) dovodi do izmene imunskog odgovora, što stvara preduslov za razvoj druge bolesti na istom mestu, u našem slučaju lokalizovanog buloznog pemfigoida.

Zaključak. U radu je prikazan slučaj inače zdrave muške osobe kod koje su se na mestu operativnog ožiljka, devet meseci nakon artroplastike kolenog zgloba, pojavile promene retkog lokalizovanog oblika buloznog pemfigoida, koje su uspešno lečene isključivo lokalnim kortikosteroidima.

Ključne reči

Bulozni pemfigoid; Kožne bolesti; Ožiljak; Imunokompromitovani bolesnici; Clobetasol; Artroplastika zgloba kolena

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Condyloma Latum on the Lower Lip as an Isolated Manifestation of Secondary Syphilis – a Case Report

Milan BJEKIĆ[1]*, Kiro IVANOVSKI[2]

[1]City Institute for Skin and Venereal Diseases, Belgrade, Republic of Serbia
[2] Periodontology and Oral Pathology Department, Faculty of Dentistry, University St Cyril and Methodius, Skopje, Republic of Macedonia

*Correspondence: Milan Bjekić, E-mail: milinkovski@gmail.com

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Abstract

Oral lesions are described in all stages of syphilis, except in the latent stage. During the secondary stage of infection, oral lesions, saliva and blood of infected person are very contagious. The aim of this case report was to point to the secondary syphilis in differential diagnosis of oral diseases.

A 30-year-old homosexual man presented with a three-week history of a painless verrucous lesion on his lower lip. Physical examination revealed a hypertrophic painless papillomatous lesion on the lower lip. The lesion was partly split with peripheral fissures. There were no generalized lymphadenopathies and no evidence of systemic disease. Further examination showed no other mucous membrane or cutaneous lesions elsewhere on the body. The external genitalia were normal. The patient was HIV-negative and otherwise healthy. A review of his medical history was significant for previous well documented treatment of anal chancre, which was successfully commenced at our Institute in 2010. It also revealed a history of a single unprotected receptive oral sex with an unknown partner 3 months before the onset of lesion. The diagnosis of condyloma latum on the lower lip was considered on clinical grounds. Laboratory findings, including complete blood count and blood chemistry were within normal limits. The VDRL (venereal disease research laboratory) test was positive with a titre of 1 : 128. Treponema pallidum hemagglutination assay (TPHA) was positive. HIV serology was non-reactive.

The final diagnosis of solitary condyloma latum on the lower lip, as the only sign of secondary syphilis, was confirmed by positive results of routine serologic tests for syphilis. The patient was diagnosed with secondary syphilis and treated with a single intramuscular injection of benzathine penicillin, 2.4 million units. The lesion regressed completely within 2 weeks. Three months later the VDRL titer had fallen to 1 : 8 and HIV serology remained negative.

Polymorphic oral manifestations in syphilis indicate that this disease should not be overlooked in the differential diagnosis of not only benign, but even malignant oral lesions.

In conclusion, as far as the world literature available to us is concerned, this would be the first report of isolated solitary condyloma latum on the oral lip that, in the absence of any other clinical signs or symptoms of the disease, led to the diagnosis of secondary syphilis.

Key words

Syphilis, Cutaneous; Lip Diseases; Treponema pallidum; Diagnosis, Differential; Treatment Outcome; Signs and Symptoms; Case Reports

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*. The disease is known as a multi-stage disease and it is characterized by diverse and wide-range clinical manifestations. If untreated, syphilis progresses through four stages: primary (chancre), secondary (mucocutaneous lesions and/or lymphadenopathy with or without organ involvement), latent (asymptomatic) and late; in 25% of those who are untreated, the disease takes a chronic course. Oral lesions are described in all stages, except in the latent stage. Oral ulcers may be seen at any stage, but particularly in secondary syphilis, during

the secondary stage of infection; oral lesions, saliva and blood of infected person are very contagious (1, 2)

In this report, we present a rare case of a solitary oral lesion, as an isolated manifestation as well as a diagnostic clue of secondary stage syphilis. It also underlines the importance of taking into consideration this "great imitator" in the differential diagnosis of oral diseases and reviews oral manifestations of infectious syphilis.

Case report

A 30-year-old homosexual man presented with a three-week history of a painless verrucous lesion on his lower lip. Physical examination revealed a well-defined, round flat-topped, white in colour, non-ulcerated hypertrophic painless papillomatous lesion on the lower lip. The lesion was partly split with peripheral fissures (Figure 1). There were no generalized lymphadenopathies and no evidence of systemic disease. Further examination showed no other mucous membranes or cutaneous lesions elsewhere on the body. The external genitalia were normal. The patient was HIV-negative and otherwise healthy. A review of his medical history was significant for previous well documented treatment of anal chancre, which was successfully commenced at our Institute in 2010. It also revealed a history of a single unprotected receptive oral sex with an unknown partner 3 months before the onset of lesion. The diagnosis of condyloma latum (CL) on the lower lip was considered on clinical grounds.

Laboratory findings, including complete blood count and blood chemistry were within normal limits. The VDRL (venereal disease research laboratory) test was positive with a titre of 1 : 128. *Treponema pallidum* hemagglutination assay (TPHA) was positive. HIV serology was non-reactive.

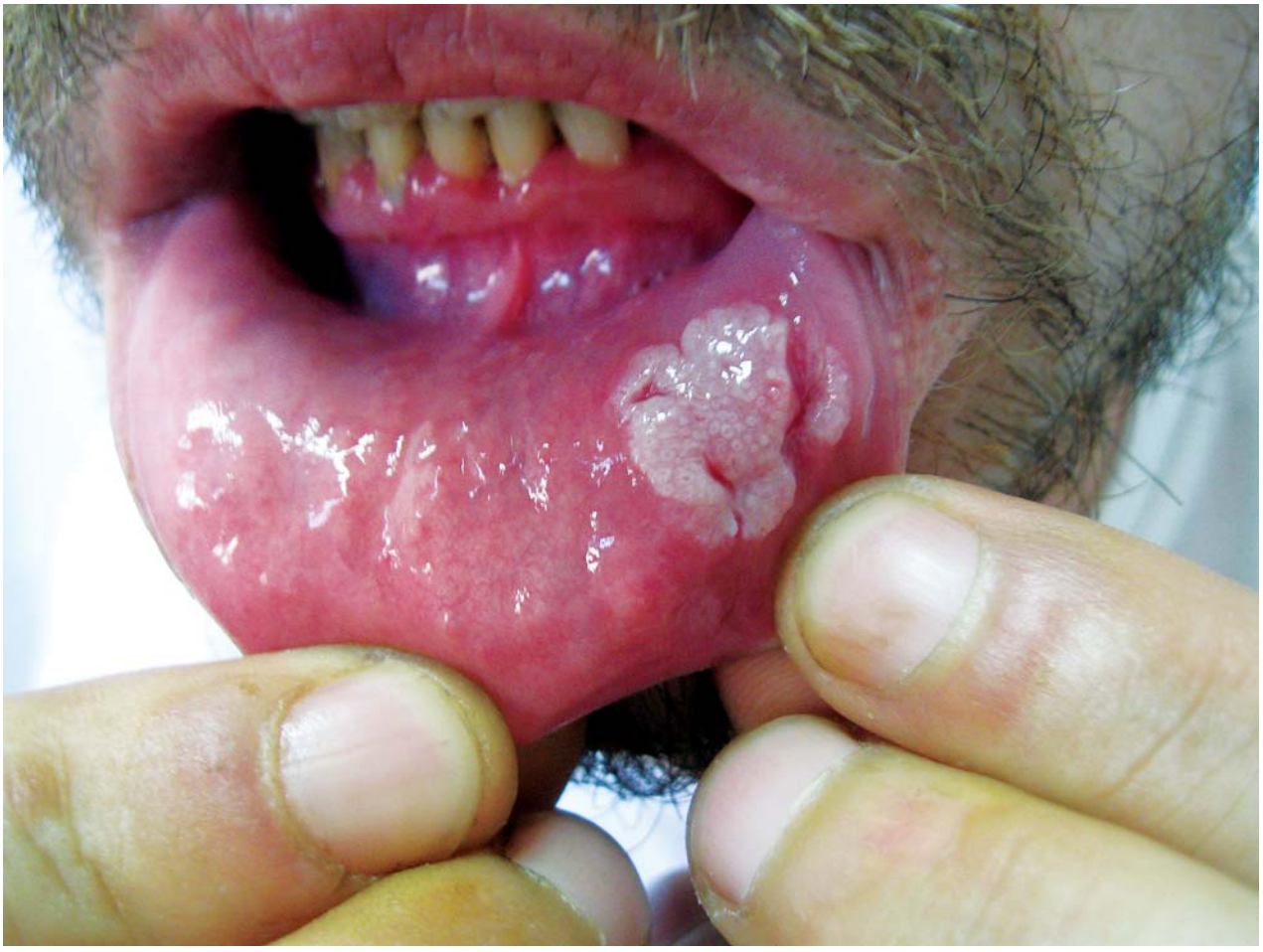

Figure 1. Hypertrophic, raised, papillomatous lesion on the lower lip partly split with peripheral fissures

The final diagnosis of solitary CL on the lower lip, as the only sign of secondary syphilis, was confirmed by positive results of routine serologic tests for syphilis. The patient was diagnosed with secondary syphilis and treated with a single injection of benzathine penicillin, 2.4 million units intramuscularly. The lesion regressed completely within 2 weeks. Three months later, the VDRL titer had fallen to 1 : 8 and HIV serology remained negative.

Discussion

The syphilitic infection is usually transmitted through sexual contact. It occurs through oral sex in at least 13% of cases and in one fifth to one third in men who have sex with men (2). Oral lesions are among clinical manifestations in infectious syphilis. In the primary stage of disease lesions are the result of unprotected oral intercourse. Oral sex is commonly practiced by sexually active male-female and same-gender couples of various ages, including adolescents. Oral sex involves both giving and receiving oral stimulation to the penis, the vagina, and/or the anus. Although the risk of HIV transmission by oral sex is small, other sexually transmitted diseases especially gonorrhea, syphilis and herpes are more easily transmissible through oro-genital contact (3). During an outbreak of early syphilis in Belgrade, about 60% of cases contracted the disease by oral sex (4).

The primary lesion develops at the site of inoculation about three weeks (range 10 - 90 days) after infection with *Treponema pallidum*. About 5% of all primary chancres are found in extra genital locations and the majority of them occur in the mouth (40 - 75%) although they can be observed on any part of the body (5). The lip is the most common extragenital site for primary syphilitic lesions. Most lip chancres in males tend to occur on the upper lip, in females on the lower lip. Primary syphilis of the mouth manifests as a solitary ulcer with irregular raised border, and usually on the lips or the tongue, accompanied by a cervical lymphadenopathy. Rare appearances of a chancre on the tonsils and the pharynx have been described, as well (6).

Without treatment, chancre resolves within 2 - 8 weeks. Lesions of secondary syphilis erupt 3 to 12 weeks after the appearance of the chancre, but may develop months later or in up to 15% of cases, before chancre disappears (2).

An extremely broad spectrum of skin and mucosal lesions are seen in patients with secondary syphilis (7). Mucous membrane lesions in secondary stage are extremely infectious. These are highly infectious and usually fairly painless ulcers (mucous patches and snail-track ulcers) (1). Nevertheless, the three manifestations are well recognized: condylomata lata (CL), mucous patches and macular lesions. The latter usually occur on the hard palate and are manifested as red flat to slightly raised lesions in the form of pharyngitis. Mucous patches are painless, oval or circular lesions covered with thin mucosa on which shalow, rounded erosions covered with macerated scaling and erythematous edge can be seen. Present in 7 - 12% of secondary syphilis cases, the lesions may appear anywhere in the mouth, commonly on the tongue and lips. Confluence of several denuded lesions may occur on the tongue. They may be seen also on the glans of the uncircumcised penis, inner vulva and anus. Split papules are elevated mucous patches with central fissures in the oral commissures. Furthermore, sometimes these patches make serpentine like lesions, so-called "snail track" ulcers (1, 2). Special papular lesions in secondary syphilis are very contagious CL, which have been reported in 9 - 44% of cases. CL may appear in two different forms: the first includes flat moist papules, and the second elevated verrucous or cauliflower-like papules or plaques usually located in the oral commissures. The later type, found in our patient, was described on the lower lip. CL consists of flesh-colored or hypopigmented macerated papules or plaques. Their surface may be smooth, papillated or covered with cauliflower-like vegetations. Lesions in intertriginous areas may erode or proliferate, forming elevated, brown, velvety plaques or grouped hyperthrophic nodular lesions that resemble raspberries (frambesiform syphilis). CL tend to develop at sites where two body surfaces are in apposition such as anogenital areas, scrotum, medial thighs and behind the ears. Constant moisture, friction and maceration at these sites facilitate coalescence and growth of syphilitic papules, resulting in development of plaque-like condylomas. The common sites are the genital and anal, less frequently, the oral commissures, face, nasolabial folds, axillae, inframammary folds, toe webs and umbilicus (8, 9). In secondary syphilis, moist, flat, papulonodular lesions of oral CL often

appear at the mucocutaneous junctions and on mucosal surfaces especially at the commissures of the lips (1).

The secondary stage of syphilis usually recedes in 2 to 12 weeks. However, the classic, above given description is present only in 60% of cases, and various deviations are common (2). An accurate and thorough patient history is important, since the diagnosis of secondary syphilis requires a high index of clinical suspicion, because the primary stage may go undiagnosed. Furthermore, the primary stage of syphilis may not develop in certain circumstances, such as in HIV positive patients (10). Not all patients present with classic symptoms and clinical findings. These may be subtile, transient, and easily overlooked. However, the infection is systemic, even in the absence of symptoms, despite the fact that the most common and recognizable manifestations are mucocutaneous (2). In ou patient the characteristic morphology of the lesion present on the lip, a well-defined, raised, round, flat-topped, white in colour, non-ulcerated hypertrophic painless papillomatous lesion on the lower lip suggested a clinical diagnosis of condyloma latum. Although the primary stage of infection has not been registered in our case, medical history and data indicated that the primary lesion may have been present. The obvious and largest distinction between chancre, and CL are ulcerations and papillomatosis, respectively. Moreover, it has been postulated that CL often develop within the vicinity of the primary chancre (10).

CL may mimic condylomata acuminata or bowenoid papulosis, which are associated with human papillomavirus infection. However, being not contagious, oral lesions are also described in the tertiary stage of syphilis (6). Gummas, destructive granulomas, usually occur on the hard palate and tongue. They can ulcerate and cause bone destruction or perforation of the palate. In contrast to CL, syphilitic leukoplakia is a large whitish homogenous area on the dorsal side of tongue and can show malignant alteration.

The diagnosis of CL is based on typical skin lesions and positive serologic tests for syphilis, as in our case. Dark field microscopy detects *Treponema pallidum* based on characteristic morphology and motility. It can be used both for primary and secondary lesions, and it is a very valuable tool: sensitive, inexpensive and may be performed at the point of care. Dark-fild examination is a diagnostic test of choice in chancre and most lesions of secondary syphilis, especially CL and mucous patches. Dark-field microscopy was not performed in our patient due to technical limitations. The test is invalid for oral lesions because saprophytic treponemas that can not be differentiated from *T. pallidum* are common in the mouth (2). In such cases, a lymph node aspirate can be examined by dark-field microscopy. If the diagnosis is otherwise unequivocal as a result of these examinations, or clinical evaluation of typical lesions coupled with reactive serologic results, skin biopsy is recommended. Oral syphilitic lesions are frequently seen as a diagnostic challenge to dentists, who are usually the first to examine oral lesions. Biopsies are occasionally the first examination performed, but histologic findings are considered nonspecific and the diagnosis is usually made through serologic tests (10). However, recently it has been suggested that the presence of plasma cell arteritis and plasma cell neuritis represent a combination that has not been reported in any other pathologic condition of the oral cavity and may be specific enough to direct the clinician toward the diagnosis of syphilis prior to clinical confirmation (11). Polymorphism of oral clinical findings in syphilis indicates that this disease should not be overlooked in the differential diagnosis of oral lesions such as oral hairy leukoplakia, lichen planus, oral condylomata acuminata, candidiasis and oral squamous cell carcinoma (1, 2, 11). Early detection of characteristic oral lesions facilitates the diagnosis and enables prompt treatment of syphilis.

CL in our patient was a solitary lesion and the only sign of secondarism, since there were no other mucous membrane or cutaneous lesions elsewhere on the body, as well as no generalized lymphadenopathies and no other evidence of systemic disease. There were several reports on cases of secondary syphilis with no other lesions but oral, and in each case oral lesions led to the diagnosis of secondary syphilis, without evidence of systemic disease, even without generalized lymphadenopathies (12). However, contrary to our case, the lesions were more extensive, multiple or rather erosive (12, 13). Solitary condyloma latum was reported, but on the umbilicus (9). In 2010, Vera et al, reported four patients with interdigital CL and reviewed the world literature since 1940, where 18 previously reported patients were found. Thus, in the total number

of 22 patients, they detected the following: an isolated interdigital space was affected in 50% of patients; besides the interdigital CL, 82% of patients presented with other secondary skin lesion; CL was the only manifestation only in 4 patients (18%) (8).

Conclusion

As far as the world literature available to us is concerned, this the first report of an isolated solitary condyloma latum on the lip that, in the absence of any other clinical signs or symptoms of the disease, led to the diagnosis of secondary syphilis.

Acknowledgement

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Abbreviations

HIV - human immunodeficiency virus
VDRL - venereal disease research laboratory
TPHA - *Treponema pallidum* hemagglutination assay
CL - condylomata lata

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Condyloma latum na donjoj usni kao jedina manifestacija sekundarnog sifilisa – prikaz slučaja

Sažetak

Uvod. Usna duplja može biti zahvaćena lezijama u svim stadijumima stečenog sifilisa.
Cilj rada bio je da ukaže na značaj lezija sekundarnog sifilisa u diferancijalnoj dijagnozi oralnih oboljenja.
Prikaz slučaja. U radu je dat prikaz tridesetogodišnjeg muškarca homoseksualne orijentacije koji se javio dermatologu zbog bezbolne verukozne promene na donjoj usni koja je trajala tri nedelje. Anamnestički podaci, klinička slika i pozitivni serološki testovi na sifilis ukazali su na sekundarni stadijum oboljenja u kojem je *condyloma latum* na donjoj usni u odsustvu drugih promena na koži i sluznicama, uključujući i odsustvo regionalne i generalizovane limfadenopatije, bio jedina klinička manifestacija infekcije. Nakon sprovedene terapije benzatin penicilinom G, promena se promptno u potpunosti povukla.
Diskusija. Polimorfizam kliničke slike u usnoj duplji kod obolelih od sifilisa upućuje na značaj ovog oboljenja u diferencijalnoj dijagnozi bolesti usne duplje poput čupaste oralne leukoplakije, lihena planus, kondiloma izazvanih humanim papiloma virusima, oralne kandidijaze i karcinoma skvamoznih ćelija usne duplje.
Zaključak. Prema nama dostupnoj literaturi, ovo bi bio

prvi objavljeni slučaj izolovanog solitarnog *condyloma latum* na sluznici donje usne, koji je u odsustvu bilo kog drugog znaka ili simptoma, predstavljao jedini klinički znak sekundarnog sifilisa.

Ključne reči

Kutani sifilis; Bolesti usana; Treponema pallidum; Diferencijalna dijagnoza; Ishod terapije; Simptomi i znaci; Prikazi slučajeva

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12-14 April, 2016	Dubai Derma 2016, Dubai, UAE	30 November, 2016	www.dubaiderma.com
15 April, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
7 May, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
19-22 May, 2016	13th EADV Spring Symposium, Athens, Greece	10 January, 2016	www.eadvathens2016.org
23-27 May, 2016	4th International Conference on Radiation and Applications in Various Fields of Research, Niš, Serbia	31 December, 2015	www.rad-conference.org
26-28 May, 2016	13th Congress of the European Society for Pediatric Dermatology, Paris, France	15 January, 2016	www.espd2016.com
11-15 June, 2016	Congress of the European Academy of Allergology and Clinical Immunology, Vienna, Austria	10 January, 2016	www.eaaci2016.org
13-15 June, 2016	7th European Dermatology Congress, Alicante, Spain	No submission deadline	www.dermatology.conferenceseries.com/europe
23-25 June, 2016	11th World Congress of the International Academy of Cosmetic Dermatology, Panama City, Panama	15 April, 2016	www.iacdpty2016.com
7-9 July, 2016	5th Congress of the Psoriasis International Network – Psoriasis 2016, Paris, France	12 February, 2016	www.pso2016.com
11-14 August, 2016	1st International Conference on Tropical Dermatology, Colombo, Sri Lanka	1 April, 2016	www.ictd2016.org
31 August – 3 September, 2016	16th World Congress on Cancers of the Skin, Vienna, Austria	31 July, 2016	www.wccs2016.com
8-11 September, 2016	3rd Regional Congress, Mostar, Bosnia and Herzegovina	1 August, 2016	www.derma-regional2016.org
15-17 September, 2016	IUSTI Europe 2016, Budapest, Hungary	15 May, 2016	www.iusti2016.com
28 September – 2 October, 2016	25th EADV Congress, Vienna, Austria	18 April, 2016	www.eadvvienna2016.org

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/.

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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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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

Accepted manuscripts are edited and returned to the corresponding author for approval. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

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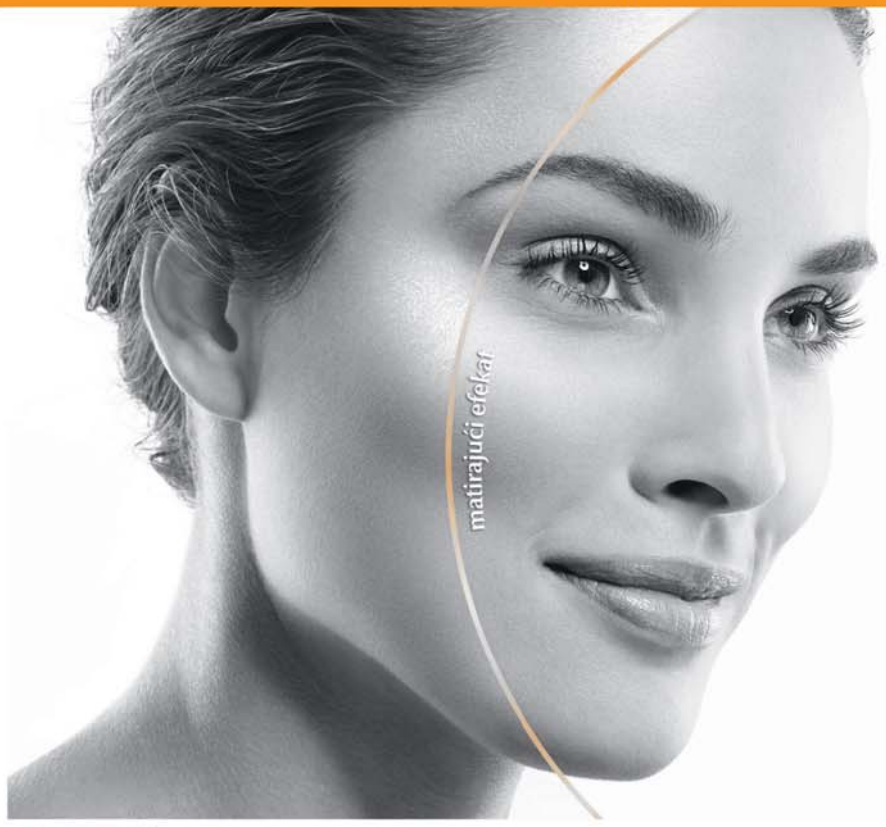

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