Acanthosis nigricans – a common significant disorder usually unassociated with malignancy

Acanthosis nigricans – częsta choroba, niezwiązana na ogół z procesami złośliwymi

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ABSTRACT

Acanthosis nigricans (AN) can be a highly significant cutaneous finding and is usually unrelated to cancer. It is most often evident as velvety thickening of axillae, posterior neck fold, flexor skin surfaces and umbilicus. It is common in obesity, which is seen increasing in children and adolescents, and can serve as a cutaneous marker of insulin resistance. It is most often associated with hyperinsulinemia, which may result from insulin receptor gene defects causing insulin resistance, and less frequently due to mutations in fibroblast growth factor receptors. In this work non malignancy-associated AN types will be emphasized, particularly the association of AN with insulin-resistance, itself a potential threat to life.

STRESZCZENIE

Acanthosis nigricans (AN) jest ważnym skórnym objawem wielu schorzeń i zespołów chorobowych, najczęściej niezwiązanych z nowotworami. Tylko jedna z ośmiu odmian AN jest uznanym zespołem paraneoplastycznym, natomiast pozostałe są najczęściej markerem oporności na insulinę i towarzyszy im hiperinsulinemia. Etiopatogeneza AN wydaje się związana z aktywacją 3 różnych receptorów czynników wzrostu – naskórkowego, insulinopodobnego i czynnika wzrostu fibroblastów – należących do rodziny receptorów kinazy tyrozynowej.

Charakterystyczne zmiany skórne lokalizują się głównie w dołach pachowych, na karku, w zgięciach stawowych oraz w pępku. Obraz histopatologiczny AN ma cechy charakterystyczne, a różnicowanie dotyczy głównie zmian zapalnych przebiegających ze świądem oraz powierzchownych infekcji grzybiczych.

Najczęściej występującą odmianą AN niezwiązaną z nowotworami jest *acanthosis nigricans benigna*, która może być obecna przy urodzeniu albo rozwija się w dzieciństwie lub w wieku młodzieńczym i współistnieje z opornością na insulinę. Inna odmiana, związana z otyłością, występuje na całym świecie, zarówno u dorosłych, jak i u dzieci. Zmiany mogą ustąpić wraz z normalizacją masy ciała. *Acanthosis nigricans* może być również główną cechą fenotypową lub objawem wielu zespołów, m.in. zespołu HAIR-AN (hiperandrogenizm, insulinooporność typu A i AN) oraz zespołu oporności na insulinę typu B, w którym objawy AN występują w okolicy oczodołów. U osób z tym zespołem często stwierdza się choroby autoimmunologiczne. **Akralna**

odmiana AN dotyczy łokci, kolan, skóry nad stawami śródręczno-paliczkowymi oraz grzbietów stóp i występuje u osób zdrowych. **Jednostronna AN** ma charakter newoidalny – może być odmianą znamienia naskórkowego lub prekursorem dwustronnej AN. Objawy skórne występują w dzieciństwie lub w wieku późniejszym, są aktywne przez 4–5 lat, a następnie utrzymują się bez zmian. Różnicowanie dotyczy znamion naskórkowych. Odmiana ta nie ma związku z zaburzeniami endokrynologicznymi lub chorobami/zespołami układowymi. **Odmianę lekową AN** wywołuje wiele leków, najczęściej statyny i kwas nikotynowy – leki, które powodują również insulinooporność. Zmiany dotyczą skóry brzucha oraz zgięć stawowych i ustępują w ciągu 4–10 tygodni po odstawieniu leku wywołującego.

Podsumowując – AN, szczególnie u otyłych dzieci, jest ważnym markerem oporności na insulinę, którego obecność jest wskazaniem do wczesnej interwencji medycznej zapobiegającej ciężkim powikłaniom, w tym cukrzycy typu 2 i chorobom układu krążenia.

INTRODUCTION

Acanthosis nigricans (AN) was originally noted as an important cutaneous finding signifying an internal malignancy. Pollitzer and Unna [1] first characterized it in 1890 in a patient who most likely had a gastrointestinal cancer. Most early accounts of acanthosis nigricans illuminated the rare fulminant form with malignancy [1-4], rather than the common types are unassociated with it [5, 6]. Acanthosis nigricans has been classified into eight types [4]. They are benign (non-syndromic, insulin resistance-associated AN), obesity-related, syndromic, malignant (paraneoplastic), unilateral, acral, drug-induced, and mixed AN, a combination of two or more of the above.

The most salient cause of AN is obesity and compensatory hyperinsulinemia [4-6]. While AN may be a significant indicator of insulin sensitivity independent of body mass index, body mass index percentile may be more sensitive than acanthosis nigricans, at least in screening Native American children for diabetes risk [7]. In addition, AN was shown to be a significant predictor of metabolic syndrome in polycystic ovary syndrome, occurring in 65.6% of South Asian women with this syndrome [8]. Children in Chicago 8 to 14 years of age with AN were found to have severe insulin resistance, with more than 1 in 4 already having abnormal glucose homeostasis [9]. Thus, AN identified a high-risk population, for whom appropriate interventions may be pivotal.

PATHOGENESIS

Acanthosis nigricans occurs most commonly in association with hyperinsulinemia, a result of insulin receptor gene defects causing insulin resistance, and less frequently due to mutations in fibroblast growth factor receptors (FGFR). The latter is most evident with AN and lipodystrophic disorders [6]. Type A insulin resistance syndrome results from primary insulin receptor defects, many mutations of which have been described. Type B results from antibodies to the receptor. The mechanism of AN due to insulin resistance is by activation of the insulin-like growth factor 1 receptor due to high levels of circulating insulin. A family was described associating AN with a mutation of the FGFR3 gene located at 4p16.3 [10]. Thus, these genetic syndromes may be divided into insulin resistance syndromes and fibroblast growth factor (FGF) defects [6].

Acanthosis nigricans presumably results from growth factor stimulation of keratinocytes and dermal fibroblasts. Tyrosine kinase growth factor receptor signaling may be pivotal in the pathogenesis of AN [6]. AN appears to result from activation of three distinct sets of cellular receptors, epidermal growth factor receptor, insulin-like growth factor receptors and FGF receptors, all part of the tyrosine kinase receptor superfamily.

CLINICAL MANIFESTATIONS

The diagnosis of AN is usually clinically evident [3-5, 11]. It typically has symmetric, hyperpigmented, hypertophic, verruccous and at times papillomatous patches or plaques that confer a velvety texture to the skin and are usually brownish-black in color. The most commonly affected areas include the axillae, posterior neck fold, flexor surfaces of the upper and lower extremities, umbilicus, groin, inframam-

mary folds, face, and perioral and perianal surfaces. In obese individuals, involvement of the maxillary and periorbital skin surfaces may be noted, but this is more common in patients with generalized or malignancy-associated AN. AN becomes first evident with hyperpigmentation first evident in the axillae or posterior neck fold. Involvement of the mucosal surfaces of the conjunctivae, lips, oral cavity and vulva may occur, often with a papillomatous appearance more prominent than hyperpigmentation.

BENIGN ACANTHOSIS NIGRICANS

Benign acanthosis nigricans is non-syndromic, insulin resistance-associated AN. It is usually congenital or develops during childhood or adolescence [4, 11-16]. It may be inherited as an autosomal dominant trait with variable penetrance. Early AN can be unilateral, with extension of clinical involvement associated with puberty sometimes to become generalized. AN has been delineated in one family, all of whom tested had a mutation of the FGFR3 gene [10]. It was inherited in an autosomal dominant manner with no obvious associated skeletal or neurological abnormalities save for short stature. A few other families with isolated nonsyndromic, noninsulin resistance–associated familial AN have been described, inherited autosomal dominantly with variable penetrance. This familial form of AN tends to appear in infancy, matures and stabilizes at puberty, and is not associated with obesity or diabetes mellitus.

OBESITY-ASSOCIATED ACANTHOSIS NIGRICANS

This is the most common cause of AN in children and adults worldwide [4, 19-23]. The cutaneous manifestations are usually evident after puberty, but may occur at any age (Fig. 1, 2). Progressive hyperinsulinemia leads to a rapid progression of acanthotic changes during the pubertal years, and slows thereafter [17, 18]. Full regression of the skin lesions may occur with weight loss. A lineage between intrahepatic fat deposition and insulin resistance in adolescence has been described and may be significant [19].

SYNDROMIC ACANTHOSIS NIGRICANS

There are numerous syndromic disorders that feature AN as a key phenotype or an associated sign [4, 23-28]. The type A insulin resistance syndrome is also known as HAIR-AN syndrome, a constellation of hyperandrogenism, insulin resistance and AN. This commonly affects young black females, who

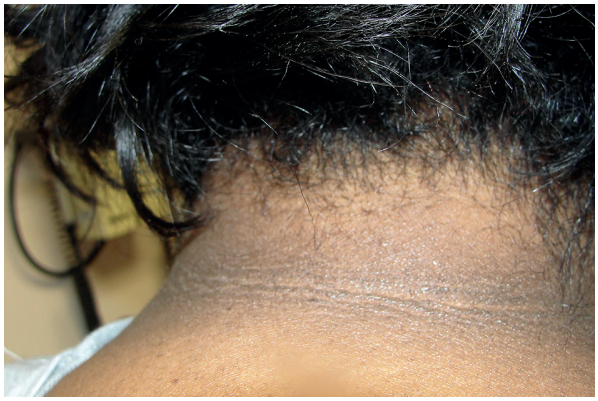

Figure. 1. Acanthosis nigricans in a patient with obesity
Rycina. 1 Acanthosis nigricans u pacjenta z otyłością

Figure 2. Acanthosis nigricans in a patient with obesity, accentuating the velvety thickening
Rycina 2. Acanthosis nigricans u pacjenta z otyłością, charakterystyczne zmiany skórne

demonstrate more severe lesions in early childhood [28]. Associated polycystic ovaries and signs of virilization may also be noted.

Patients with the type B insulin resistance syndrome are generally hyperinsulinemic African-American females who manifest acanthosis nigricans in the 4th decade of life [28, 29]. Periocular acanthosis nigricans is a remarkable attribute in the type B syndrome [17]. Hyperandrogenism may be an important component feature in this syndrome, particularly in women of reproductive age. These patients often have other autoimmune diseases, most often systemic lupus erythematosus, but also Sjögren syndrome, progressive systemic sclerosis, Hashimoto's thyroiditis, and autoimmune thrombocytopenia.

Other syndromic associations are noteworthy [4, 6, 30-32]. These include Lawrence-Seip syndrome of congenital or acquired generalized lipodystrophy, a generalized absence of subcutaneous fat, which may be associated with acanthosis nigricans, owing to extreme insulin resistance and hyperandrogenism, as well as Hirschowitz's syndrome, polycystic ovarian syndrome, Donohue's syndrome (leprechaunism),

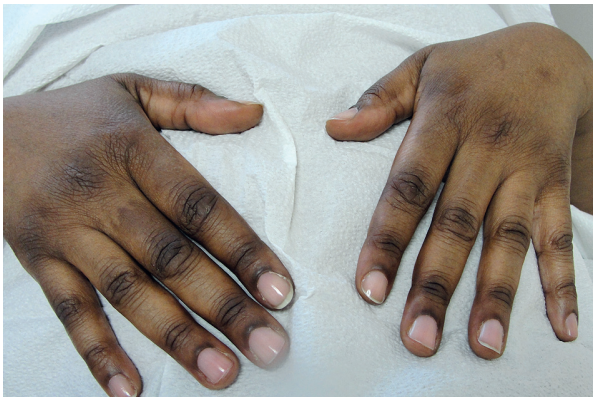

Figure 3. Healthy individual with acral acanthosis nigricans
Rycina 3. Osoba zdrowa z akralną odmianą acanthosis nigricans

Rabson-Mendenhall syndrome, Alström's syndrome, and Lelis syndrome of ectodermal dysplasia with hypotrichosis, hypohidrosis and AN [31, 32].

ACRAL ACANTHOSIS NIGRICANS

Acral AN, also known as acral acanthotic anomaly, affects the elbows, knees, knuckles, and dorsal surfaces of the feet in otherwise healthy individuals with axillae and other intertriginous regions appearing normal [4, 33, 34] (Fig. 3). Knuckle hyperpigmentation may be most prominent. This is common in patients of Subsaharian African lineage who are otherwise usually healthy. It was originally described in 1981 by Schwartz [33]. The name acral AN emphasizes that it is a type of AN, the term acral acanthotic anomic stresses its uniqueness. This relatively common disorder is seen as velvety hyperpigmented plaques in individuals with dark complexions. Although one patient with possible acral AN and dermatofibrosarcoma has been described, acral AN alone is not an indication to evaluate a patient for an internal malignancy. The cause of acral AN remains elusive.

UNILATERAL ACANTHOSIS NIGRICANS

Unilateral AN is an epidermal nevoid condition that may represent a unilateral epidermal nevus or be a precursor to bilateral AN [4, 35-40]. Unilateral AN may also be inherited in an autosomal dominant fashion with variable penetrance [4]. Unilateral AN has a unilateral or localized distribution manifesting during childhood or later, a short period of activity for 4-5 years and remains stable, with no tendency to resolve. It is not associated with systemic, endocrine or syndromic conditions and, unlike classical AN, there does not appear to be documentation of familial involvement in unilateral AN. Since its first description in 1991 by Krishnaram [35], less than 10 others have been documented in the world literature [37, 38]. AN may occur with both unilateral linear and symmetrical nonlinear changes, probably a result of early loss of heterozygosity causing the segmental skin lesions superimposed on less pronounced nonsegmental AN [40].

Epidermal nevi and unilateral AN share clinical and histopathological features [38]. Unilateral AN has a late onset with velvety thickening of the skin and ill-defined margins merging with normal skin. The streaky, curvilinear pattern so commonly seen in epidermal nevi is absent. Although the histopathology of AN is not diagnostic, lack of significant acanthosis excluded EN. Unilateral AN does not have a predilection for intertrigenous areas. Most cases have their origin from the midline with unilateral distribution.

DRUG-INDUCED ACANTHOSIS NIGRICANS

Acanthosis nigricans can be induced by pharmacologic agents [40-45]. Nicotinic acid, an anti-hyperlipidemic agent that also induces insulin-resistance, is the common one with plaques of AN typically developing on the abdomen and flexor surfaces of the skin and resolving within 4-10 weeks of stopping the medication. Insulin injection sites may develop localized AN [44]. It may also develop following long-term use of oral contraceptives, diethylstilbestrol, heroin, corticosteroids, methyltestosterone, fusidic acid, and hydantoin-like derivatives. Additionally, estrogens, niacin, triazinate, and somatotrophin have been linked. Palifermin, a modified human keratinocyte growth factor, was linked with AN in a cancer patient [45], a speculative association at best.

HISTOPATHOLOGY

Acanthosis nigricans is characterized by epidermal hyperkeratosis and minimal to mild acanthosis [4]. There is an associated upward projection of the dermal papillae into a thinned overlying epidermis; keratinaceous debris may fill the regions between the ridges. Hyperpigmentation evident clinically is usually the result of epidermal hyperkeratosis, but it sometimes may be due to an increased number of melanosomes in the stratum corneum [46]. Mucosal acanthosis nigricans also exhibits epidermal hyperkeratosis and papillomatosis along with parakeratosis.

DIFFERENTIAL DIAGNOSIS

Acanthosis nigricans may initially resemble an inflammatory dermatitis with pruritic and erythe-

matous patches, superficial fungal infections, confluent and reticulated papillomomatosis, and the continuum of acanthosis nigricans, the sign of Leser-Trélat and florid cutaneous papillomatosis (Schwartz-Burgess syndrome) [47, 48]. Ichthyosis hystrix, generalized epidermal nevi, and diffuse lichenification of atopic dermatitis may also occasionally require distinction.

CONCLUSION

Acanthosis nigricans is often an important cutaneous marker of insulin resistance that is more commonly being diagnosed in obese children and adolescents worldwide. Early intervention with dietary modification and achievement of endocrinologic hormone balance is vital to avert the potentially devastating future complications associated with these conditions, including type 2 diabetes mellitus and cardiovascular disease.

References

1. **Pollitzer S.:** Acanthosis nigricans, a symptom of a disorder of the abdominal sympathetic. JAMA 1909, 53, 1369-1373.
2. **Curth H.O.:** Cancer associated with acanthosis nigricans, review of literature and report of a case of acanthosis nigricans with cancer of the breast. Arch Surg 1943, 47, 517-552.
3. **Sinha S., Schwartz R.A.:** Juvenile acanthosis nigricans. J Am Acad Dermatol 2007, 57, 502-508.
4. **Schwartz R.A.:** Acanthosis nigricans. J Am Acad Dermatol 1994, 31, 1-19.
5. **Schwartz R.A., Janniger C.K.:** Childhood acanthosis nigricans. Cutis 1995, 55, 337-341.
6. **Torley D., Bellus G.A., Munro C.S.:** Genes, growth factors and acanthosis nigricans. Br J Dermatol 2002, 147, 1096-1101.
7. **Nsiah-Kumi P.A., Beals J., Lasley S., Whiting M., Brushbreaker C., Erickson J. et al.:** Body mass index percentile more sensitive than acanthosis nigricans for screening Native American children for diabetes risk. J Natl Med Assoc 2010, 102, 944-949.
8. **Wijeyaratne C.N. Seneviratne R.D., Dahanayake S., Kumarapeli V., Palipane E., Kuruppu N. et al.:** Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS), results of a large database from a specialist Endocrine Clinic. Hum Reprod 2010, 26, 202-213.
9. **Brickman W.J., Huang J., Silverman B.L., Metzger B.E.:** Acanthosis nigricans identifies youth at high risk for metabolic abnormalities. J Pediatr 2010, 156, 87-92.
10. **Berk D.R., Spector E.B., Bayliss S.J.:** Familial acanthosis nigricans due to K650T FGFR3 mutation. Arch Dermatol 2007, 143, 1153-1156.
11. **Schwartz R.A.:** Acanthosis nigricans. In, Clinical Dermatology. 18th edn. D.J. Demis (Ed.), JB Lippincott, Philadelphia, 1999, (Unit 12-26), 1-11.
12. **Chuang S.D., Jee S.H., Chiu H.C., Lin J.T.:** Familial acanthosis nigricans with madarosis. Br J Dermatol 1995, 133, 104-108.
13. **Tasjian D., Jarratt M.:** Familial acanthosis nigricans. Arch Dermatol 1984, 120, 1351-1354.
14. **Inamadar A.C., Palit P.:** Generalized acanthosis nigricans in childhood. Pediatr Dermatol 2004, 21, 277-279.
15. **Skiljevic D.S., Nikolic M.M., Jakovljevic A., Dobrosavljevic D.D.:** Generalized acanthosis nigricans in early childhood. Pediatr Dermatol 2001, 18, 213-216.
16. **Friedman C.I., Richards S., Kim M.H.:** Familial acanthosis nigricans, a longitudinal study. J Reprod Med 1987, 32, 531-536.
17. **Arioglu E., Andewelt A., Diabo C., Bell M., Taylor S.I., Gorden P.:** Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance), a 25-year perspective. Medicine 2002, 81, 87-100.
18. **Eberting C.L., Javor E., Gorden P., Turner M.L., Cowen E.W.:** Insulin resistance, acanthosis nigricans, and hypertriglyceridemia. J Am Acad Dermatol 2005, 52, 341-344.
19. **Springer F., Nguyen H.P., Machann J., Schweizer R., Ranke M.B., Binder G. et al.:** DISKUS Study Group. Normal-weight 14-year-old girl with acanthosis nigricans and markedly increased hepatic steatosis, evidence for the important role of ectopic fat deposition in the pathogenesis of insulin resistance in childhood and adolescence. Horm Res Paediatr 2010, 74, 376-380.
20. **Sadeghian G., Ziaie H., Amini M., Ali Nilfroushzadeh M.:** Evaluation of insulin resistance in obese women with and without acanthosis nigricans. J Dermatol 2009, 36, 209-212.
21. **Wang C.H., Lin W.D., Bau D.T., Chou I.C., Tsai C.H., Tsai F.J.:** The involvement of insulin receptor genotypes in pre- and co-obese acanthosis nigricans children and adolescent. J Pediatr Endocrinol Metab 2010, 23, 653-660.
22. **Chang Y., Woo H.Y., Sung E., Kim C.H., Kang H., Ju Y.S. et al.:** Prevalence of acanthosis nigricans in relation to anthropometric measures, community-based cross-sectional study in Korean pre-adolescent school children. Pediatr Int 2008, 50, 667-673.
23. **Brickman W.J., Binns H.J., Jovanovic B.D., Kolesky S., Mancini A.J., Metzger B.E.:** Pediatric Practice Research Group. Acanthosis nigricans, a common finding in overweight youth. Pediatr Dermatol 2007, 24, 601-606.
24. **Malek R., Chong A.Y., Lupsa B.C., Lungu A.O., Cochran E.K., Soos M.A. et al.:** Treatment of type B insulin resistance, a novel approach to reduce insulin receptor autoantibodies. J Clin Endocrinol Metab 2010, 95, 3641-3647.
25. **Takahashi I., Yamada Y., Kadowaki H., Horikoshi M., Kadowaki T., Narita T. et al.:** Phenotypical variety of insulin resistance in a family with a novel mutation of the insulin receptor gene. Endocr J 2010, 57, 509-516.
26. **Regan F.M., Williams R.M., McDonald A., Umpleby A.M., Acerini C.L., O'Rahilly S. et al.:** Treatment with recombinant human insulin-like growth factor (rhIGF)-I/rhIGF binding protein-3 complex improves metabolic control in subjects with severe insulin resistance. J Clin Endocrinol Metab 2010, 95, 2113-2122.
27. **Bhattacharya S.M.** Insulin resistance and overweight-obese women with polycystic ovary syndrome. Gynecol Endocrinol 2010, 26, 344-347.
28. **Kahn C.R., Flier J.S., Bar R.S., Archer J.A., Gorden .P, Martin M.M. et al.:** The syndromes of insulin resistance and acanthosis nigricans, insulin-receptor disorders in man. N Engl J Med 1976, 294, 739-745.
29. **Malek R., Chong A.Y., Lupsa B.C., Lungu A.O., Cochran E.K, Soos M.A. et al.:** Treatment of type B insulin resistance, a novel approach to reduce insulin receptor autoantibodies. J Clin Endocrinol Metab 2010, 95, 3641-3647.
30. **Bhattacharya S.M.:** Insulin resistance and overweight-obese women with polycystic ovary syndrome. Gynecol Endocrinol 2010, 26, 344-347.

31. **Yoshimura A.M., Velho P.E., Magalhães R.F., de Souza E.M.:** Lelis' syndrome, treatment with acitretin. Int J Dermatol. 2008, 47, 1330-1331.
32. **Lelis J.:** Autosomal recessive ectodermal dysplasia. Cutis 1992, 49, 435-437.
33. **Schwartz R.A.:** Acral acanthotic anomaly. J Amer Acad Dermatol 1981, 5, 345-346.
34. **Schwartz R.A.:** Acral acanthosis nigricans (acral acanthotic anomaly). J Am Acad Dermatol 2007, 56, 349-350.
35. **Krishnaram A.S.:** Unilateral nevoid acanthosis nigricans. Int J Dermatol 1991, 30, 452-453.
36. **Curth H.O.:** Unilateral epidermal naevus resembling acanthosis nigricans. Br J Dermatol 1976, 95, 433-436.
37. **Krishnaram A.S.:** Unilateral nevoid acanthosis nigricans and neurofibromatosis 1, an unusual association. Indian J Dermatol Venereol Leprol 2010, 76, 715-717.
38. **Das J.K., Sengupta S., Gangopadhyay A.:** Nevoid acanthosis nigricans. Indian J Dermatol Venereol Leprol 2008, 74, 279-280.
39. **de Waal A.C., van Rossum M.M., Bovenschen H.J.:** Extensive segmental acanthosis nigricans form of epidermal nevus. Dermatol Online J 2010, 16, 7.
40. **Happle R.:** Type 2 segmental acanthosis nigricans, a historical case explained by a new concept. Arch Dermatol 2008, 144, 1637.
41. **Stals H., Vercammen C., Peeters C., Morren M.A.:** Acanthosis nigricans caused by nicotinic acid, case report and review of the literature. Dermatology 1994, 189, 203-206.
42. **Elgart M.L.:** Correspondence, acanthosis nigricans and nicotinic acid. J Am Acad Dermatol 1981, 5, 709-710.
43. **Curth H.O.:** Acanthosis nigricans following use of oral contraceptives (Letter to the editor). Arch Dermatol 1975, 111, 1069.
44. **Fleming M.G., Simon S.I.:** Cutaneous insulin reaction resembling acanthosis nigricans. Arch Dermatol 1986, 122, 1054-1056.
45. **Lee M., Grassi M.:** Acanthosis nigricans in a patient treated with palifermin. Cutis 2010, 86, 136-137.
46. **Hall J.M., Moreland A., Cox G.J., Wade T.R.:** Oral acanthosis nigricans, report of a case and comparison of oral and cutaneous pathology. Am J Dermatopathol 1988, 10, 68-73.
47. **Schwartz R.A.:** Confluent and reticulated papillomatosis. eMedicine from WebMD. Updated 2010. Available at: http//emedicine.medscape.com/article/1106748-overview.
48. **Schwartz R.A.:** Acanthosis nigricans, florid cutaneous papillomatosis, and the sign of Leser-Trélat. Cutis 1981, 28, 319-334.
49. **Janniger E.J., Schwartz R.A.:** Florid cutaneous papillomatosis. J Surg Oncol 2010, 102, 709-712.

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