Generalized Familial Acanthosis Nigricans Associated With Hypochondroplasia

R. Pardavila, E. Rosón, C. de la Torre, and M. Cruces
Servicio de Dermatología, Complejo Hospitalario de Pontevedra, Pontevedra, Spain

To the Editor:
Acanthosis nigricans (AN) is a proliferative epidermal disorder expressed clinically in the form of velvety brown plaques in skin folds, although other parts of the skin and mucosa can occasionally be affected.

New associations and peculiar clinical forms have been added to classifications of the disease since Pollitzer1 and Janovskys2 first reported cases of AN associated with neoplasia. There are currently 8 accepted types of AN, listed by Schwartz3 as: benign, associated with obesity (pseudoacanthosis nigricans), syndromic, paraneoplastic, acral, unilateral, drug-induced, and mixed. Generalized AN is not considered to be a specific form, but rather an extensive manifestation of other forms of the disease. The condition is mostly associated with internal malignancy in adults, but benign generalized cases have been described in childhood.4-6

We present a case of generalized benign familial AN associated with small stature resulting from hypochondroplasia. The patient was a 33-year-old woman who consulted for a check-up of a nevus. Examination revealed brown velvety skin coloration in the central thoracic region, on the sides of the abdomen (Figure 1), the middle of the back, the neck, and armpits. These asymptomatic lesions had been present since infancy, increasing in number until puberty and remaining stable ever since. She reported that 3 of her sisters, a niece and her oldest child have similar lesions, as probably did her late father. We had the opportunity to confirm this affirmation in 1 sister and her niece.

None of them reported any illness or habitual use of medication.

We observed that all 3 patients examined presented small stature, with short limbs. The patient reported that all except 1 of her siblings were of small stature, as was 1 of her children. Radiological examinations of the patient revealed shortened long bones diagnostic of hypochondroplasia and similar results were seen in her son.

Skin biopsy revealed hyperkeratosis and papillomatosis with moderate irregular acanthosis (Figure 2).

In order to rule out any systemic disease associated with acanthosis nigricans and papillomatosis with moderate irregular acanthosis (Figure 2).

In order to rule out any systemic disease associated with acanthosis nigricans, studies were requested for the patient, sister, and niece, including: blood tests, coagulation and general biochemistry, insulin and C-peptide, testosterone, dehydroepiandrosterone sulfate levels, and tumor markers. All the results were completely within normal ranges.

Benign familial AN is characterized by presence at birth and progression in early infancy, with cutaneous changes becoming more prominent in puberty and then stabilizing or diminishing later. Lesions tend to be located in folds, although in some cases they reach an unusual extension and intensity—probably when onset occurs early with the ensuing long period of development. Pruritis is uncommon.7 The condition is transmitted in autosomal dominant form with variable penetrance and it is not normally associated with any endocrine or congenital abnormality.

We present a case of benign familial AN, with the classic clinical characteristics, associated with hypochondroplasia. Although we could not examine all the cases in this family, autosomal dominant inheritance appears to be present (Figure 3) as is normally the case. Benign familial AN is 1 of the usual classifications of the disease, although very few cases have been described. This could be due to the absence or minimal extent of associated symptoms and the hereditary nature of the disorder whereby patients do not consider the condition relevant or worthy of reporting to a physician. Even though there are generally no associated systemic alterations patients should be
given a physical examination and a full medical history should be taken. Hyperandrogenism and insulin resistance should be ruled out whenever these appear to be present. As far as we are aware, no association with hypochondroplasia has been previously reported. The characteristic phenotype of this disease means that a general physical examination will be sufficient to guide the choice of complementary examinations given to patients.

References


Primary Kaposi Sarcoma of the Penis in an HIV-Negative Patient

P. Hernández-Bel, J. López, J.L. Sánchez, J.J. Vilata, and V. Alegre
Servicio de Dermatología, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

To the Editor:

Kaposi sarcoma is a vascular tumor of multifocal origin first described by Moritz Kaposi in 1872.1 In the Mediterranean area, the classic form is mainly seen on the lower limbs of the elderly.2 Isolated involvement of the penis is rare, and although it is seen in AIDS patients—where it is the initial manifestation in 2-3% of cases—it is extremely uncommon in human immunodeficiency virus (HIV)-negative patients.3 In the last 20 years, only 15 cases of immunocompetent patients with primary Kaposi sarcoma of the penis have been described in English-language journals.4 We present the case of an 80-year-old man, with no relevant history, presenting a rapidly growing asymptomatic tumor on the penis that had developed 2 weeks earlier. The patient had no history of local trauma, immunosuppression, intravenous drug addiction, blood transfusions, or homosexual acts. Physical examination revealed a soft pink pedunculated nodule of 10 mm in diameter on the coronal sulcus. He also presented a second clearly circumscribed painless red-violaceous lesion of 4 mm in diameter that had been present for several years (Figure 1). There was no evidence of inguinal gland involvement, hepatosplenomegaly, or other
mucocutaneous lesions. Histological studies of the larger lesion showed a multinodular tumoral proliferation made up of fusiform cells with lengthened hyperchromatic nuclei and occasional mitosis. Bundles of these cells formed disruptions containing red blood cells (Figures 2 and 3). Several areas of eosinophilic globular bodies and hemosiderin deposits could also be seen. Immunohistochemical staining proved positive for CD31 and CD34. On removal, the second lesion showed similar histopathological abnormalities. Complete blood count, coagulation, and T-cell count results did not provide any relevant findings, and the patient was seronegative for HIV in 2 tests. Primary Kaposi sarcoma of the penis in an immunocompetent patient was the final diagnosis. A year later, the patient remains stable with no further lesions.

The pathogenesis of Kaposi sarcoma is unknown, although the epidemiological characteristics probably indicate an infectious cause. Human herpes virus type 8 (HHV8) is implicated in vascular hyperplasia, but while a necessary factor, it is not sufficient in itself. The high seroprevalence of HHV8 in individuals with high risk sexual activity would appear to support this form of transmission in adults; however, the detection of HHV8 antibodies in children suggests there are other nonsexual means of transmission, probably through saliva.2,3

Kaposi sarcoma of the penis is clinically identified by painless red-violaceous colored nodules. Other less common forms of presentation include multiple papules, plaques, or rapidly growing pedunculate tumors.1 Most cases consist of 1 or 2 isolated lesions4 most commonly found on the glans, although the foreskin, coronal surcus, urethral meatus, and scrotum can also be affected.4

The histological pattern for Kaposi sarcoma of the penis is similar to that seen in other anatomical locations. In the tumor phase, nodules containing a network of blood-filled vascular spaces appear along with fascicles of fusiform cells. These fusiform cells have a clearly defined cytoplasm and an ovoid nucleus and are characteristically CD34 positive.6 In some areas, differential diagnosis with pyogenic granuloma and spindle-cell hemangioendothelioma might be necessary. Spindle-cell tumor proliferation with the presence of abnormal cells and the formation of disruptions would not support a diagnosis of pyogenic granuloma. Spindle-cell hemangioma would be clearly shown by marked cytoplasmic vacuolization and an absence of atypical cells.7

Primary Kaposi sarcoma of the penis can be treated by local surgery, radiotherapy, electrocoagulation, laser therapy, and injection of interferon α into the lesion, although there are no established treatment guidelines. Surgery is recommended for small or solitary lesions. Radiotherapy is used in larger lesions and systemic chemotherapy is reserved for more advanced cases with visceral involvement or widespread lesions. The clinical course of primary Kaposi sarcoma of the penis is variable and local recurrence is uncommon if the primary tumor is completely eliminated.3

We would like to stress that although primary KS of the penis is extremely uncommon in immunocompetent subjects it must be considered in the differential diagnosis of nonspecific lesions in the genital area. Histological examination is advisable in unclear cases where no clinical characteristics are available to establish a definitive diagnosis.

**References**

To the Editor:

Neonatal syphilis is one of the most serious infections transmitted from mother to fetus.

The World Health Organization estimates that maternal syphilis is responsible worldwide for 460,000 stillbirths or miscarriages, 270,000 cases of congenital syphilis, and 270,000 of underweight or premature newborns.

Transmission occurs after uteroplacental circulation is established; however, the manifestations do not appear until the fourth month and consist of abnormal organogenesis and immunologic abnormalities, often leading to late-term abortion.

We describe an infant born at 30 weeks of gestation, the first common child of a young couple (Spanish father, Romanian mother). A single prenatal visit had been performed, although our hospital had no record of this visit.

The examination revealed an infant with a noteworthy clinical picture at birth, including perceptible abdominal distention on palpation, which also showed considerable liver and spleen enlargement. The most striking observation, however, were large bullous lesions that varied in size between 1 and 5 cm and occupied virtually the entire surface of the palms and soles (Figure 1), as well as other isolated lesions of creamy-white content on the legs and forearms. Further examination showed that the skin was extremely fragile, particularly on the left foot and the third toe of the right foot, and peeled off like the finger of a glove (Figure 2).

The rest of the body was covered with erythematous-desquamative, macular, papular lesions, some of which were actually crusty. The lesions were mainly located on the head between the eyebrows, perinasal, and circumoral region, as well as on the trunk, buttocks, and perianal area (Figure 3). Spoke-like cicatricial atrophic striae could also be seen in the circumoral and perianal area.

Because perinatal infection (congenital syphilis) was suspected, the child was transferred to the neonatal intensive care unit, but died 3 hours later.

Serologic results received 2 days later confirmed the diagnosis. In the case of the newborn, rapid plasma reagin (RPR) was 1/128, Treponema pallidum hemagglutination assay (TPHA) was 1/81,920, and anti-Treponema pallidum immunoglobulin (Ig) M, 2.9. In the mother, RPR was 1/32, TPHA was 1/81,920, absorption of fluorescent Treponema antibodies, 1/200, and anti-Treponema pallidum IgM, 1.519. All other serology tests were negative.

Congenital syphilis can occur if a woman with syphilis gets pregnant or if the mother is infected during pregnancy. According to Thomas, the longer the duration of untreated maternal syphilis before pregnancy occurs, the lower the risk will be for the fetus. If the mother acquires the infection in an advanced stage of pregnancy, the newborn may be normal and the clinical manifestations may not appear until weeks or months later. Conversely, if infection occurs during early pregnancy, it can lead to abortion or serious symptoms in the infant.

Pemphigus syphiliticus is a rare condition in Spain, but is on the rise, particularly in developing countries and in Eastern Europe. Industrialized nations are being affected by population changes caused by immigration from underdeveloped countries, particularly from Central Africa, but also from Eastern Europe. These immigrants bring with them certain ideas and habits and some of these groups may find themselves in precarious employment situations.

Prevalences of 3% to 19% have been reported among pregnant women in developing countries; the highest figures are from southeast Africa and southern Sahara. In Zambia, 42% of fetal deaths have been attributed to syphilis and 30% of all perinatal deaths are associated with neonatal syphilis.
In Spain, syphilis rates in adulthood increased by about 75% between 1999 and 2004; the total number of cases was 675 per 100,000 inhabitants in 1999 and 1,156 in 2004. Cases of congenital syphilis have increased 700%, rising from 2 in 1999 to 16 in 2004, with 9 cases reported in 2000, 8 in 2001, 15 in 2002, and 4 in 2003.

In 2004 the number of reports has continued to climb, with 12 cases described in the province of Malaga alone. In 2005, cases of neurosyphilis in Madrid and malignant syphilis in Galicia and Madrid have been published. The latest study on an epidemiologic outbreak was conducted in Las Palmas de Gran Canaria, in the Canary Islands.

Because of the recent rise of syphilis in Europe, closer control consisting of early screening and treatment of affected pregnant women is necessary, since neonatal syphilis can be prevented through education programs focused on sexually transmitted diseases and good prenatal care (compulsory Venereal Disease Research Laboratory screening in pregnant women).

References

Letters to the Editor

Classic Kaposi Sarcoma Associated With Lymphedema Following Arterial Catheterization

D. Barco, M. Alegre, and A. Alomar
Servicio de Dermatología, Hospital de Sant Pau, Barcelona, Spain

To the Editor:

Classic Kaposi sarcoma (CKS) is a vascular neoproliferation typically seen on the lower limbs of elderly patients. The condition is associated with human herpes virus 8 (HHV8); however, its high prevalence in Mediterranean countries suggests that other environmental factors may be relevant in its etiology.

We describe a 59-year-old man with asymptomatic violaceous plaques and nodules present from 1 year earlier on the right leg (Figure 1). The lymphedema observed had been present since a femoral artery catheterization performed 6 years earlier for intestinal bleeding. The histologic study of the lesion showed vascular proliferation of fusiform cells with erythrocytes dissecting the collagen bundles, consistent with Kaposi sarcoma (KS). The immunohistochemical study was positive for HHV8. Contrast-enhanced magnetic resonance angiography showed no vascular abnormalities or arteriovenous fistulas in the lower limbs. Ten cycles of liposomal doxorubicin of 20 mg/m2/3 wk were administered, and complete clinical remission was achieved (Figure 2).

The classic variant of KS is characterized by violaceous papules or...
nodules in the distal part of the limbs of older men, with a slow course. It appears that HHV8 is a necessary factor: regardless of the tumor variant, more than 95% of neoplastic cells are infected with this virus. This virus is responsible for coding proteins similar to human oncogenes that modify the cell cycle and proliferation, apoptosis, angiogenesis, and T-helper cell-mediated immune response. Viral oncogenes are tumor promoters that induce the synthesis of angiogenic molecules, such as the viral G-protein-coupled receptor (vGPCR), vascular endothelial growth factor (VEGF), and the expression of kinase insert domain-containing receptor (KDR), vascular endothelial growth factor receptor 1 (VEGFR-1), and vascular endothelial growth factor receptor 2 (VEGFR-2). vGPCR, viral G-protein-coupled receptor.

Figure 3. Molecular mechanisms of action in human herpes virus 8 (HHV8) in cell conversion and in the secretion of angiogenic factors and receptors. VEGFR-1 indicates vascular endothelial growth factor receptor 1; VEGFR-2, vascular endothelial growth factor receptor 2; vGPCR, viral G-protein-coupled receptor.

Letters to the Editor

Abnormal vascular drainage would promote autocrine secretion of VEGF and its receptor (KDR), promoting the proliferation of endothelial cells infected with HHV8. An increase in VEGF that stimulates angiogenesis has been described in both thrombosis and lymphedema. The appearance of KS in areas affected by circulatory disorders and lymph vessels without arteriovenous fistulas supports the pathogenic role of local immune abnormalities and the secretion of vascular growth factors such as VEGF. Viral oncogenes act on this factor, as well as on other angiogenic agents, and play a role in KS genesis that is increasingly more apparent. The Köebner phenomenon and the secondary secretion of angiogenic molecules could explain the appearance of KS in areas affected by trauma caused by invasive tests. In patients most susceptible to KS, such as those infected with HIV, invasive procedures pose a risk for this neoplasm. In conclusion, it appears that lymphatic stasis can lead to vascular neoplasms such as CKS via physical and immunologic mechanisms, as well as by secretion of angiogenic agents.
References