Gorlin syndrome associated with basal cell carcinoma of the vulva: A case report

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Summary

Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), is a hereditary condition transmitted as an autosomal dominant trait with high penetrance and variable expressivity. The syndrome is characterized by numerous manifestations: basal cell carcinomas (BCCs) and odontogenic keratocysts (OKCs) are the leading ones.

In this article a typical Gorlin syndrome case associated with basal cell carcinoma of the vulva is described.

Key words: Gorlin syndrome; NBCCS; PTCH gene; Basal cell carcinoma; Odontogenic keratocyst; Carcinoma of the vulva; Lymphadenectomy.

Introduction

The prevalence of Gorlin syndrome is one case of 55,600 inhabitants and race and sex do not influence it. The disease envolves during the first three decades of life but it can be diagnosed in older people as well. Its etiology is unknown but the onset is correlated with the PTCH gene mutation. PTCH is a tumor suppressor gene located on 9q22.3 [1].

The genetic alteration is inherited by patients (50-65%) as an autosomal dominant trait, nonetheless in 30-50% of cases the mutation develops spontaneously [2].

The patched gene product is a transmembrane glycoprotein and acts as a receptor for sonic hedgehog signal (SHH): SHH binds to PTCH and induces enzymatic cascade activation which is not completely understood. The Hedgehog pathway function is to regulate cell proliferation and differentiation [3-5].

While germline mutations of PTCH genes are characteristic of nevoid basal cell carcinomas (BCCs), somatic mutations have been found in sporadic BCCs occurring in the general population; the loss of heterozygosity of chromosome 9q is associated with both conditions [6].

The phenotypical effects of Hedgehog pathway block are cutaneous BCCs and other malformations of disparate organic structures that can be involved in various ways and are linked to the expressivity variation of gene mutations (Figure 1) [7-10].

BCCs, odontogenic keratocysts, palmar and plantar pits and ectopic calcifications of falx cerebri are the most common epiphenomena of Gorlin syndrome.

Diagnosis of NBCCS can be established when two major or one major and two minor criteria are present (Table 1) [7-11].

Case Report

We report a case of an 80-year-old caucasian woman with a history of cardiopathy and hypertension and more than 15 BCCs excised from the face, neck and back during the past 40 years.

On January 2005 she was referred for the progressive onset of numerous and diffuse cutaneous neoformations, with similar dimensions and clinical aspects, and also a large tumefaction of the jaw.

Thus the patient was readmitted to our hospital and submitted to surgical excision. Histologic tests were similar for all BCCs. These lesions presented the following characteristics:

1) Neoformation jutting out of the cutaneous plane, colored dark red with irregular edges and previous ulceration localized on the lateral right auricle surface (Figure 2A).

2) Red neoformation with regular edges and an ulcerated central umbilication in the right temporal area (Figure 2B).

3) Ovoidal neoformation, 0.5 cm maximum diameter, smooth rose colored surfaces with peripheral microtealangectasis which developed on the inferior right eyelid (Figure 2C).

4) Neoformation (4 x 1 cm), ulcerated in the central part with inregular edges and prominent borders, and diffuse teleangectasis localized in the right axillary cavum.

During hospitalization, an outbreak of external body symptomatology and abnormal vaginal bleeding required gynecologic referral.

Pelvic ultrasonography and pap tests were negative. Colposcopy with a Colposcope Plus (ZEISS-Germany) and photographic device – Contex 167MT – revealed the cervix and vaginal mucosal integrity and also two vulvar neoformations with different sizes and aspects.

In detail, the superior and medium third of the left labium majus presented a raised ulcerated area with bleeding in the central part and two prominent borders with nacreous-like crust adhering to the back. The lesion was painful upon pressure. This ovoidal area (3.5 x 2.5 cm) presented a small region where it was possible to see expansion arrested at 1 cm from the clitoris.

On the inferior third of the right labium majus, a second neoformation presented at the major axis of the oblique (2 x 1 cm), with pigmented prominent borders and non bleeding ulcerated central region (Figure 3).

Due to the clinical aspect and positivity of the superficial

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Table 1. — *Diagnotic criteria.*

Major criteria
Multiple (< 2) BCCs or one under age 20
OKCs of the jaws proven by histology
Palmar or plantar pits (3 or more)
Bilamellar calcification of the falx cerebri
Bifid, fused or markedly splayed ribs
First-degree relative with NBCCS
Minor criteria
Macrocephaly determined after adjustment for height
Congenital malformation
Other skeletal abnormalities
Radiological abnormalities
Ovarian fibroma
Medulloblastoma

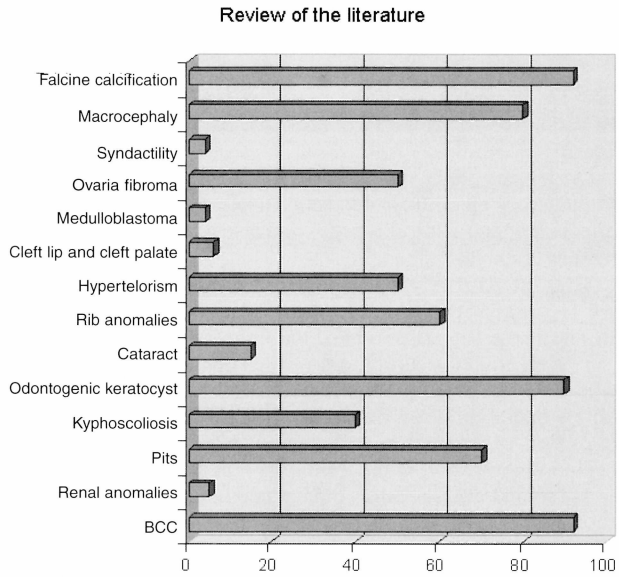


Figure 1. — Incidence of the most common manifestations of Gorlin syndrome.

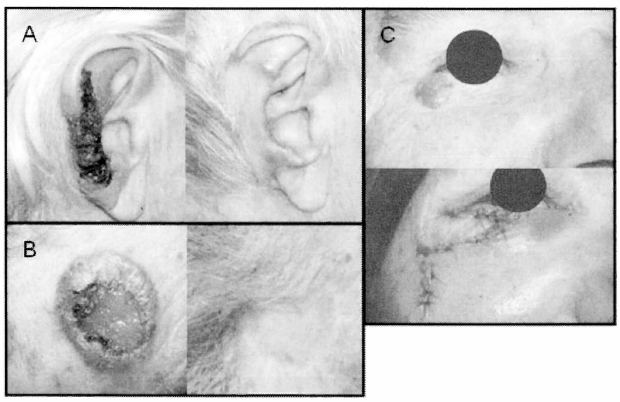


Figure 2. — Preoperatory and postoperatory aspect of cutaneous lesions.

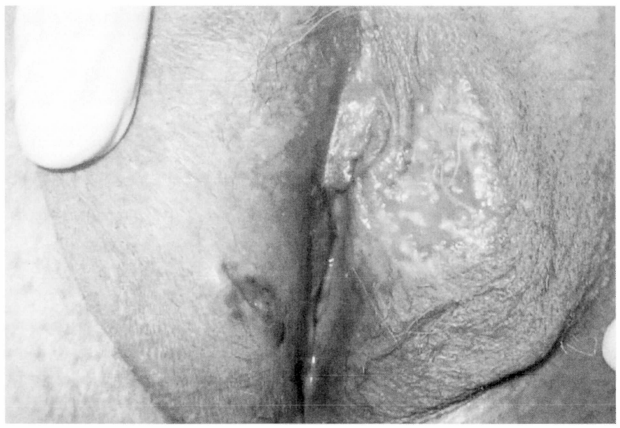


Figure 3. — Preoperative aspect of vulvar BCCs.

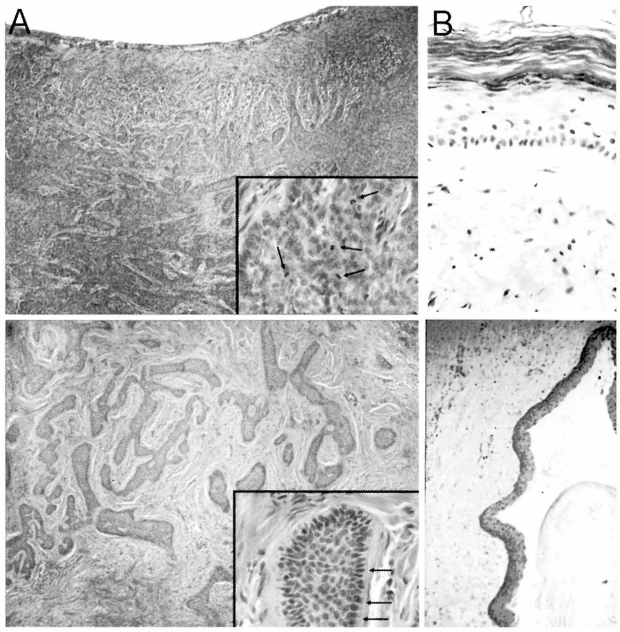


Figure 4. — A) Histologic aspect of the vulvar lesion. The upper photo represents the surface of an ulcerated neoformation (the arrows point out mitosis). The lower one shows neoplastic tissue infiltrating the derma. The arrows show the palisade disposition that is characteristic of basal cell carcinoma. B) Histologic aspect of odontogenic keratosis (two different blowups): stratified pavement epithelium with keratin.

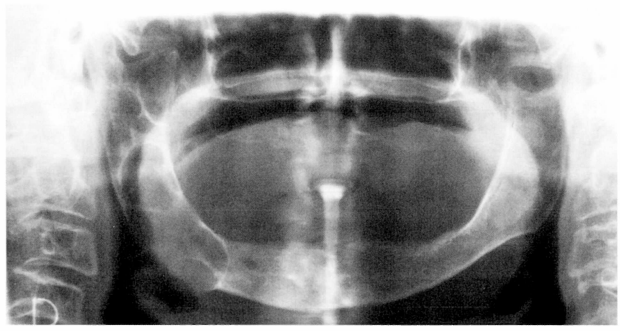
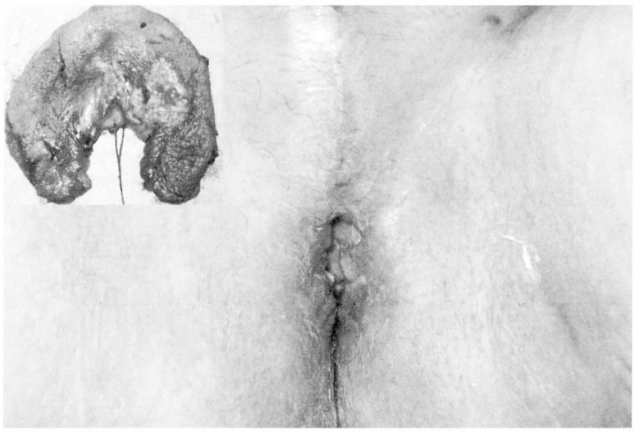


Figure 5. — The upright ramus, angle and transverse portion of the right hemimandible are interested by voluminous and numerous lacunar areas. A thin sclerosis edge limits them.



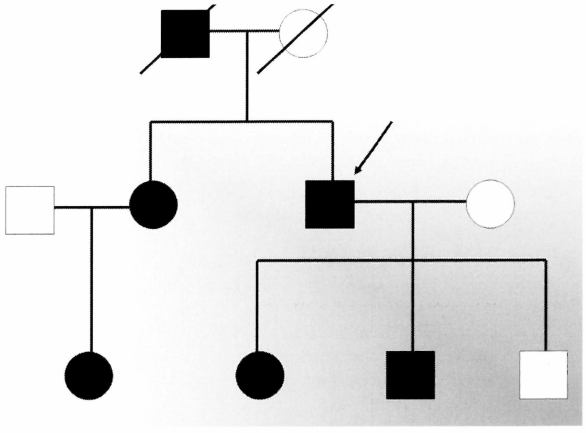


Figure 6. — In the upper left the anatomical part is present. It was removed totally and we chose the forward commissure as a finder point. The photo was taken 90 days after surgery (during the patient's first control). There is total absence of the outer lips, good cutaneous adhesion and healing by the first intention. There are no visible relapses.

Figure 7. — Familial diagram - arrow indicates our patient. A son (57 years old), a daughter (60 years old) and her brother (73) presented with the same clinical aspect as our case. Her nephew (48) has at present only BCC. From the anamnestic data we know that the patient's mother had the same lesions. She died 22 years ago but we do not know the cause of death.

lymph node palpation a vulvar microphoto and two microbiopsies were done using radiofrequency ansa (4 mm) under colposcope control.

Histology was BCC for both the right and left lesions (Figure 4A).

Before surgery a CT scan was performed for staging purposes. Localized disease without metatstatic diffusion was revealed. An orthopanoramic X-ray revealed numerous lacunar areas in the upright ramus and in the angle of the right hemimandible (Figure 5).

Materials and Method

Cutaneous neoplasias were submitted to surgical treatment. The procedures were chosen according to location and lesion dimensions.

A simple excision was performed with rotation flaps or Thiersch-Ollier cutaneous graft for healing by first intention. The jaw cyst was removed by cystotomy and microscopic examination showed odontogenic keratocysts (OKCs) (Figure 4B).

Preoperative clinical and instrumental staging of the vulvar neoformation revealed disease in Stage III (FIGO) and the probable involvement of the superficial left inguinal lymph nodes.

For the vulvar lesions the DiSaia and Creasman (three in one) procedure was used: for the first procedure two inguinal surgical incisions about 8 cm in length were performed. After the campers fascia was cut local lymph nodes between campers and cribriform fascia were removed. An extemporaneous histologic test was negative for metastasis.

The second operation was radical surgery without radical vulvectomy (Figure 6).

The neoplastic tissue was analyzed by LOH analysis (using SR8 and D9S287 as the microsatellite markers). The test result was loss of homozygosity for the PTCH gene.

LOH analysis recognized the identical genetic alteration in her son (Figure 7).

The postoperative course was unremarkable and the patient was discharged in good condition.

Conclusion

Gorlin syndrome, linked to PTCH gene mutation, can be transmited by parents or can occur spontaneously. It is typified by multiple BCCs, odontogenic keratocystis and other organic and tissue abnormalities.

In our case the diagnosis, therapeutic process and follow-up were difficult.

During the diagnosis, because of the repeated onset of cutaneous neoformations, we suspected that our patient was suffering from a rare syndrome. The presence of jaw tumefaction and the histologic result of the OKCs allowed us to diagnose Gorlin syndrome in concordance with the international licterature.

In our case a third major diagnostic criteria was satisfied: three first-degree relatives, a brother, a daughter and a son with the same clinical aspect.

BCCs with OKCs represent the typical manifestations. Cutaneous tumors in Gorlin syndrome can be localized on the head, neck, limbs and on the trunk but they have never been described on the genitals. This last localization is most frequent in sporadic BCC [12].

To our knowledge this case is the only one described in which two basal cell carcinomas are present on the genitals. Preoperative staging did not confirm the clinical suspicion. Considering the patient's age a vulvectomy up to Colles' fascia was performed. Lymphadenectomy of 16 superficial inguinal sites was carried out to have major prognostic safety. We did not foresee treatment for FIGO Stage III because there were no metastatic lesions; extemporaneous histological examination of the lymph nodes was negative and the patient refused radical surgery.

In follow-up the patient has sustained three clinical controls for a meticulous clinical and instrumental screening to look for new lesions. Currently after the third hospital stay she is disease-free.

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