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clinical practice

Nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Case report

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SUMMARY: **Nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Case report.**

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Gorlin-Goltz syndrome or nevoid basal cell carcinoma syndrome (NBCCS) comprises multiple basal cell carcinomas, keratocysts of the jaw, palmar/plantar pits, spine and rib anomalies, calcifications of the falx cerebri etc. The diagnosis is made according to clinical criteria (Kimonis Criteria) and genetic ones. We studied one family where father and then his sun resulted affected by each syndrome. Gorlin-Goltz syndrome is a rare disease diagnosed according to clinical criteria sometimes difficult to integrate. The family case we presented shows how you can get diagnosis even in older age and after numerous surgeries. Patients should be given special attention and therefore should be monitorized and need multidisciplinary treatments continued in time, even a trivial change of signs and symptoms may be an important indicator of a precipitating event which puts the patient's life under threat.

KEY WORDS: Nevoid basal cell carcinoma syndrome - Gorlin-Goltz Syndrome
Basal cell carcinoma - Mandibular keratocysts - Surgery.

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome, is an inherited autosomal dominant condition with high penetrance and variable expressivity. It was first described in 1960 by Gorlin and Goltz in a patient with multiple dermatological lesions associated with jaw cysts, subsequently defined as primordial (1-3).

Estimates of the incidence of NBCCS in the general population vary between 1:57,000 and 1:150,000 (4). This variability is undoubtedly due to the wide range of clinical signs associated with the syndrome. A typical characteristic of NBCCS is the development of multiple basal cell carcinomas (BCC), with up to 100 or more arising in the same individual; 0.4% of all cases of basal cell carcinoma arise in patients with this syndrome (5).

We report a case of NBCCS diagnosed in an adult man and subsequently, through genetic analysis, in one of his two children.

Case report

The patient, CR, was a 68-year-old man referred to us due to the recent onset of tenderness and paraesthesia in the left jaw. He had undergone a number of surgical procedures to remove skin lesions, that were probably cancerous, and jaw cysts, but it was not possible to gather precise information on the procedures or the histology of the removed lesions.

Physical examination revealed sequelae of a right mandibulectomy (resection of the *ramus mandibulae* and condylectomy, reconstruction with the iliac crest) with evident facial disfigurement, numerous surgical scars, hypertelorism and mild lagophthalmos bilaterally with epiphora and lack of lower eyelashes (Fig. 1). There was also a skin lesion of the left auricle, suspected to be basal cell carcinoma. Neurological examination confirmed dysethesia of the left side of the face in the area of the trigeminal innervation.

Orthopantamogram (Fig. 2) and facial CT scan (Fig. 3) bolstered the suspected diagnosis of NBCCS. In fact, in addition to the sequelae of the previous surgical procedures, instrumental investigations also revealed some cystic formations in the sinus cavities, leading to thinning of the contiguous walls of the orbital, maxillae and nasal cavities, while a satellite cyst in the angle of the left mandible had caused initial osteolytic lesions of the contiguous cortical bone. There were also calcifications of the *cerebri falx*.

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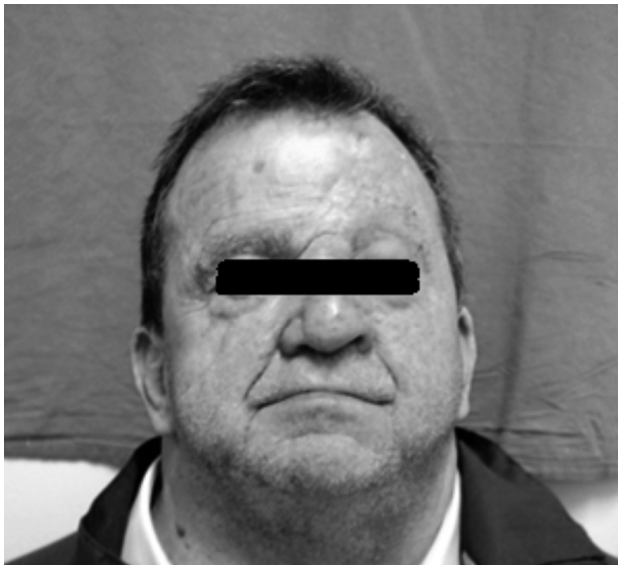

Fig. 1 - Patient in frontal vision.

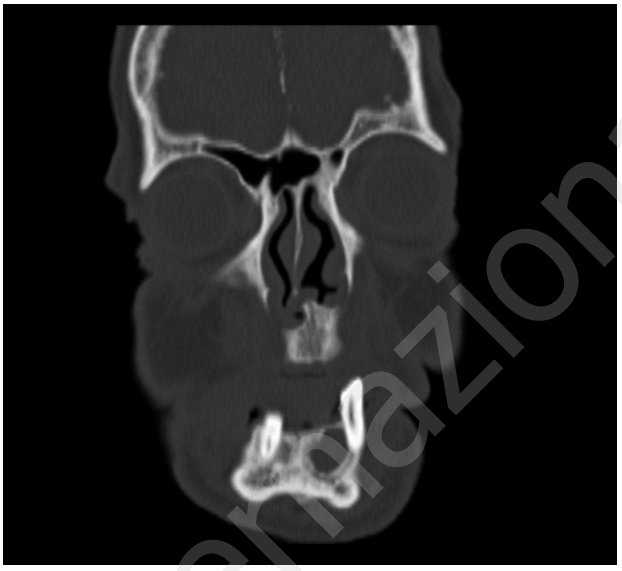

Fig. 3 - Facial CT scan (coronal projection) of the patient.

The patient underwent surgery to enucleate the satellite cyst and remove the auricular skin growth. Histological examination of the cyst suggested a benign lesion surrounded by squamous epithelial cells (odontogenetic or mandibular keratocyst, a so-called primordial cyst), while the auricular growth was diagnosed as basal cell carcinoma.

The patient was then discharged and recommended to undergo intensive clinical and instrumental follow-up and to avoid prolonged unprotected exposure to sunlight. Finally, we invited the patient's two children to undergo focused diagnostic testing. The significance of the blood relationship between the patient's parents (who are cousins) is unknown.

The son, who reported having undergone orchidopexy in early infancy, underwent orthopantogram and CT scanning of the dental arches, which revealed mild hypertelorism and, above all, jaw cysts (Figs. 4, 5). Genetic analysis confirmed the specific mutation and thus the diagnosis of NBCCS. Given the absence at that time of any signs or symptoms attributable to the syndrome, it was decided not to perform surgery for the jaw cysts. Instead, the son was recommended to go for intensive clinical and instrumental monitoring and to avoid unprotected exposure to sunlight. In contrast, the daughter showed no signs of the syndrome and genetic testing was negative.

Discussion

NBCCS is an inherited syndrome caused by a mutation on the long arm of chromosome 9q22.3 in the area of the PTCH (Protein patched homolog) gene, a homolog of the Drosophila patched (PTC) gene, which encodes a transmembrane receptor protein (6). This protein binds a soluble hedgehog (Hh) family factor, thus activating the Smo (smoothened) receptor, that unblocks the transcription of various growth factors. The PTCH gene is thus an oncosuppressor forming part of the Sonic Hedgehog Homolog (Shh) signaling pathway and is crucial in embryonal development, the control of cell division

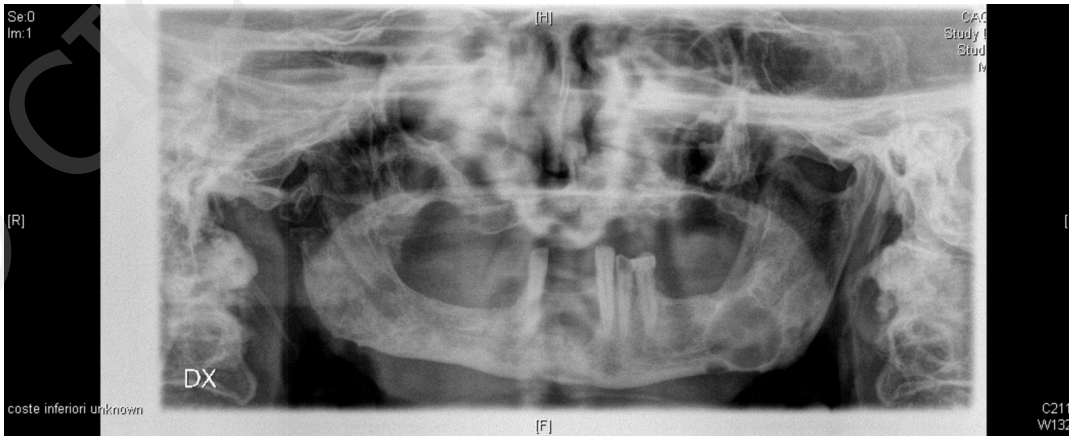

Fig. 2 - Orthopantogram of the patient.

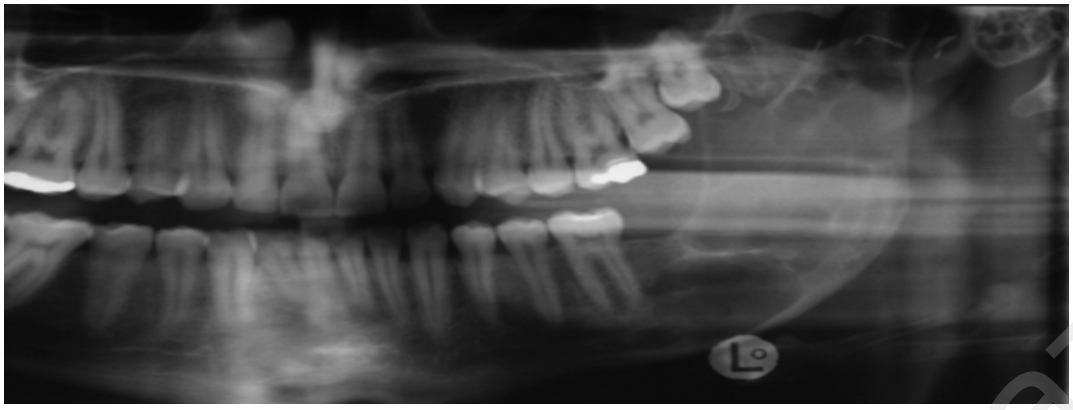

Fig. 4 - Orthopantogram of the patient's son.

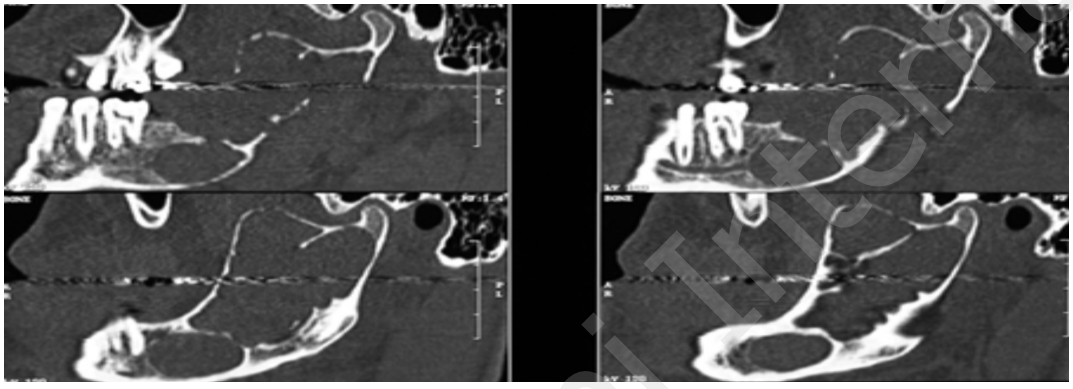

Fig. 5 - CT scan of the dental arches of the patient's son.

and the growth of tumors (7). Mutations of this gene have been found in 50% of NBCCS patients (8).

The relative rarity and phenotypic variability of NBCCS mean that its diagnosis is often delayed. The coexistence of basal cell carcinomas and jaw keratocysts are practically pathognomonic. The pathogenesis of BCC is thought to involve a greater sensitivity to ultraviolet sunlight, i.e. inefficacy of the mechanisms that repair UV-induced DNA damage. However, this theory is not shared by all authors, as BCCs also appear in areas that have not been exposed to sunlight. In any case, NBCCS patients, especially children, undergoing radiotherapy for other cancers have been shown to be at an increased risk of radiation-induced BCCs (9). Jaw keratocysts, characterized by a thin surrounding layer of epithelial cells, are found in 50% of NBCCS patients (10). These cysts tend to recur locally after removal in 6-60% of cases. It should thus be carefully considered if surgery is really indicated, taking into account the possibility of intensive clinical and instrumental monitoring alone (11).

There are numerous other possible signs of NBCCS (12). These include:

- palmar and plantar ulcers, appearing as shallow pits, caused by the partial or total absence of the corneal layer. Rarely, these may also appear along the sides of the hands and the fingers, and sometimes even on the tongue;
- spina bifida, often misdiagnosed or an incidental finding (1-3, 12);
- medulloblastoma, which, especially in patients under the age of five years, may be epiphenomenal to NBCCS (13, 14);
- cardiac tumors, including fibromas and ventricular histiocytomas, that are often congenital and, if they cannot be enucleated, an indication for heart transplant (15);
- ameloblastoma, although this is rare, with only four cases reported in the literature (16, 17).

As reported by Kimonis et al. (12), the diagnosis of NBCCS requires the coexistence of at least two major criteria or one major and two minor criteria from those listed in Table 1.

Conclusions

The difficulty in diagnosing NBCCS is justified by its rarity and phenotypic variability. Diagnosis is often delayed, especially in less severe forms, such as in our case. Once diagnosis has been made, family screening, including genetic testing, is indicated.

TABLE 1 - DIAGNOSTIC CRITERIA FOR NBCCS - FROM KIMONIS VE, ET AL. (11).

Major criteria	
1. More than 2 BCCs or one under the age of 20 years.	2. Congenital malformations: cleft lip or palate, frontal bossing, "coarse face" moderate or severe hypertelorism.
2. Odontogenic keratocysts of the jaw proven by histology.	3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
3. Three or more palmar or plantar pits.	4. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame shaped lucencies of the hands or feet.
4. Bilamellar calcification of the falx cerebri.	5. Ovarian fibroma.
5. Bifid, fused or markedly splayed ribs.	6. Medulloblastoma.
6. First degree relative with NBCC syndrome.	
Minor criteria	
Any one of the following features	
1. Macrocephaly determined after adjustment for height.	

For doubtful lesions a biopsy can be performed (18). In line with literature evidence, we believe that surgery is indicated only in the presence of symptomatic jaw cysts. Naturally, a more aggressive approach is also necessary if BCCs are suspected. Then, depending from the site of the lesion and the kind of surgery, reconstruction can be performed (19-22). Sometimes alloplastic materials can be used for the maxillofacial reconstruction (23).

In general, patients with NBCCS require long-term integrated multi-specialty follow-up, aiming particularly at the early diagnosis of any life-threatening lesions.

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