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Original Research Paper

Pathology

GORLIN - GOLTZ SYNDROME - A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT Gorlin-Goltz syndrome(GGS)(NBCCS) (Nevoid basal cell carcinoma syndrome) is characterised by multiple basal cell carcinomas appearing at a younger age, associated with odontogenic keratocysts of the jaw, skeletal abnormalities, ectopic calcification, and pits of the hands and feet with equal sex predilection. A case of 48 year old male patient presented with Gorlin- Goltz syndrome is presented in this study. Our report emphases the clinical and pathological features of this syndrome for the early diagnosis and genetic counselling for the patients.

KEYWORDS : Gorlin Goltz syndrome, Basal cell carcinoma, Odontogenic Keratocyst.

INTRODUCTION

The name Gorlin syndrome is derived from the name of American oral pathologist and human geneticist Robert J Gorlin (1923-2006) and his co-author Robert W. Goltz (1923-2014), an American dermatologist. It was first described in 1960 by Gorlin and Goltz [1]. It is an autosomal dominant disorder with complete penetrance and variable expressivity. Gorlin - Goltz syndrome has rarely been reported from India. We report here one such patient diagnosed at our hospital.

CASE REPORT

48 year male presented with skin lesions in right eyebrow, (Fig.1) posterior surface of pinna of right ear (Fig.2) and on scalp (Fig.3). Detailed clinical examination revealed swelling in right and left jaw and multiple cutaneous lesions over face, apart from ocular hpertelorism, heavy fused eyebrows (Fig.4) and multiple palmar pits (Fig.5). An orthopantomogram (Fig.6) revealed multiple radiolucent cysts in right mandible, left mandible and left maxilla. Excision of the swellings, enucleation and chemical cauterisation of the cysts were done.

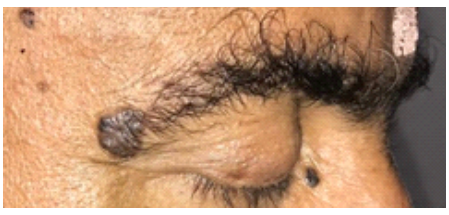

Fig.1 Swelling near right eyebrow

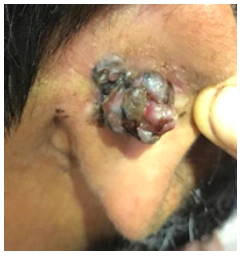

Fig. 2 Nodular swelling on posterior surface of pinna of right ear.

Fig.3 Swelling over scalp.

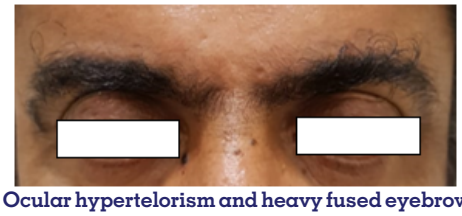

Fig 4. Ocular hypertelorism and heavy fused eyebrows.

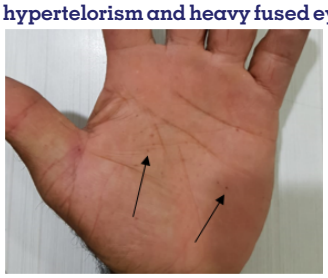

Fig.5 Multiple palmar pits.

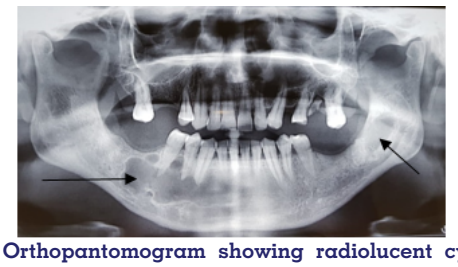

Fig.6 Orthopantomogram showing radiolucent cysts in right and left mandible.

Specimens were sent for histopathological examination. Sections from swelling in right eyebrow and ear show a malignant neoplasm arising from epidermis (Fig. 7) composed of lobules of basaloid cells with peripheral palisading (Fig.8) and retraction cleft between tumour lobules and stroma (Fig.9). Final diagnosis was basal cell carcinoma (nodulocystic type). Cysts from the jaw show odontogenic keratocyst (Fig.10).

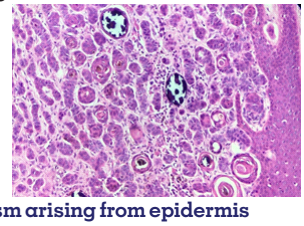

Fig.7 Neoplasm arising from epidermis

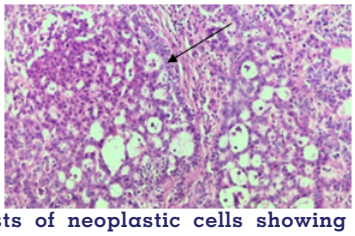

Fig. 8 Nests of neoplastic cells showing peripheral palisading.

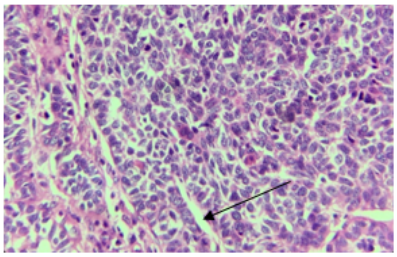

Fig.9 Artefactual cleft between stroma and neoplastic nests

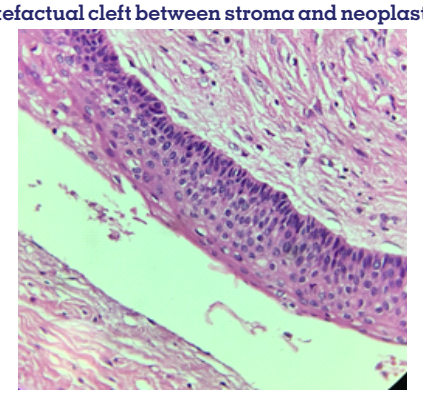

Fig.10 Odontogenic keratocyst.

DISCUSSION

NBCCS was first described by Jarish and White in 1894 and was later established as a unique syndrome by Gorlin-Goltz in 1960. Inheritance pattern is autosomal dominant with complete penetrance and variable expressivity. Significant number of cases show spontaneous germ cell mutations also. Genetic studies identified human homologue of Drosophila patched (PTCH) as the candidate gene mapped to chromosome 9q23.1-q31 [2].

Homozygous inactivation of the gene results in basal cell carcinomas whereas hemizygous germline mutations cause the numerous congenital abnormalities. This gene is part of the sonic hedgehog signaling pathway involved in control of cell proliferation and development of neural tube, pharyngeal pouches, somites, and limb buds in vertebrates. Gorlin - Goltz Syndrome is characterized mainly by the presence of multiple basal cell carcinomas (BCC), odontogenic keratocysts (OKCs) of the jaw, palmar pits and ectopic calcifications of the falx cerebri. More than 100 minor criteria have been described. The presence of two major and one minor criteria or one major and three minor criteria are necessary to establish a diagnosis.

Evans et al. [3] first established major and minor criteria for diagnosis of this rare entity, later modified by Kimonis et al. [4]. According to them diagnosis of GGS can be established when two major or one major and two minor features are present.

The major criteria are:

- Multiple Basal cell carcinoma or one occurring under the age of 20 years
- Histologically proven odontogenic keratocysts of the jaws.
- Palmar or plantar pits (three or more).
- Bilamellar calcification of the falx cerebri.
- Bifid, fused or markedly splayed ribs.
- First-degree relative with NBCCS.

The minor criteria are:

- Macrocephaly (adjusted for height).
- Congenital malformation: Cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism.
- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
- Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion of the vertebral bodies, modelling defects of the hands and feet.
- Ovarian fibroma.
- Medulloblastoma.

In the present case, the diagnosis of the Gorlin-Goltz syndrome was made due to the presence of three major criteria - multiple basal cell carcinomas (BCCs), multiple odontogenic keratocysts of the jaw bone and palmar pits along with minor criteria of hypertelorism.

Basal cell carcinomas usually develops in adolescent age group, some reports suggest that it could also develop during early childhood [5,6]. They have a variable appearance characterised by small flesh-coloured or brown dome-shaped papules, soft nodules or flat plaques measuring up to 1 cm in diameter associated with numerous milia. The larger tumours are usually pigmented, often ulcerate, and typically behave in an aggressive fashion affecting both exposed and covered sites. The central part of the face is commonly the first area to be involved, followed by the chest, back, and scalp and then other exposed sites [7]. Rarely genitals can be involved [8].

Patients may harbour up to thousands of basal cell carcinomas, but about 10% of adult patients do not manifest skin tumours. Rarely, the tumours have a unilateral distribution. Multiple large epidermoid cysts are also often evident on the trunk and limbs.

All variants of basal cell carcinoma may be seen, but the solid and superficial types are most common, with 30 % patients having two or more histological types of BCC and morpheaform tumors being rare. There are no particular distinguishing features by which they might be distinguished from ordinary basal cell carcinoma [9].

Odontogenic keratocysts of the jaws occur in up to 65-100% of patients, usually in childhood or adolescence [10]. They are commonly multiple and show a predilection for the premolar area and are associated with tooth displacement, pain, and swelling of the jaws. It is common for recurrence following a surgical procedure.

The jaw cysts are lined by stratified squamous epithelium with a thick fibrous capsule and may be associated with the development of spindle cell squamous carcinoma, myxoma, ameloblastoma, and fibrosarcoma.

Skeletal abnormalities, which are present in up to 75% of cases, include generalized overgrowth, macrocephaly, bridging of the sella turcica, high-arched palate, vertebral abnormalities, splayed, fused, missing or bifid ribs, kyphoscoliosis, spina bifida occulta, hyperplasia of the mandibular coronoid processes, and bone cysts. There is a characteristic 'dished' facial appearance due to frontal and biparietal bossing, broadening of the nasal root, and ocular hypertelorism.

Ectopic lamellar calcification of the falx cerebri (85-90%) and also of the diaphragma sellae (60-80%), tentorium cerebelli (40%), and petroclinoid ligaments (20%) are frequent

manifestations. Craniocerebral manifestations may be evident in utero with epilepsy being an occasional complication.

The shallow pits of the palms and soles are pathognomonic. Pits can be seen in 85% of the patients above 20 years [11]. They are asymptomatic, 1-3 mm deep and 2-3 mm across, [12] and may be present in their hundreds. The palmar and plantar pits show a diminution or loss of the keratin and granular layers, associated with a thinned underlying malpighian layer. Electron microscopic examination reveals incompletely discharged Odland bodies. The pits are therefore believed to develop as a result of reduced 'intral-amellar cement' resulting in diminished adherence between the keratin lamellae. The rete ridge pattern is irregular in size and shape and some pits may show basaloid proliferation. No BCC has been found to arise from these pits [13].

Patients with the nevoid basal cell carcinoma syndrome may have many other abnormalities, including congenital blindness, hypogonadism, ovarian fibromas (75% of females), cardiac fibromas, and an increased incidence of central nervous system tumors, including medulloblastoma and meningiomas.

Rare associations include eosinophilic pustular folliculitis, nevus sebaceous, microphthalmia, ulcerative colitis, unilateral renal agenesis, multiple acrochorda, ameloblas toma, thyroid neoplasia, prenatal chylothorax, hepatic mesenchymal tumor, fetal rhabdomyoma, lymphomatoid papulosis, primary ovarian leiomyosarcoma, rhabdomy osarcoma, and Wilms' tumor as well as undifferentiated sinonasal carcinoma.

Differential diagnosis-

The nevoid basal cell carcinoma syndrome should be distinguished from the linear unilateral basal cell nevus (Carney's) syndrome, which comprises an extensive unilateral lesion consisting of basaloid follicular hamartomas in addition to comedones, epidermoid cysts, and areas of epidermal atrophy. Patients may also have scoliosis, but there are no other significant internal abnormalities. Other differential diagnoses include Bazex syndrome, trichoepithelioma papulosum multiplex and Torre's syndrome (Muir-Torre's syndrome).

Bazex syndrome is characterized by multiple BCCs, milia, reduced sweating (hypohidrosis), abnormal loss of hair (hypotrichosis), and follicular atrophoderma, a skin condition involving breakdown of the follicles of the skin and causing lesions, especially on the arms and legs. In most affected individuals, BCCs develop in the 20s or 30s. Additional symptoms can vary greatly from one person to another.

Muir-Torre syndrome is characterized by a predisposition to skin cancer and certain low grade visceral cancers. BCCs have been reported in individuals with Muir-Torre syndrome.
Clinical diagnosis relies on the specific criteria. Gene mutation analysis confirms the diagnosis. Genetic counselling is mandatory. Antenatal diagnosis is feasible by means of ultrasound scans and analysis of DNA extracted from fetal cells (obtained by amniocentesis or chorionic villus sampling).

Patients with Gorlin syndrome may be hypersensitive to and contraindicated from receiving radiation therapy.

Life expectancy in NBCCS is not significantly altered but morbidity from complications can be substantial. Regular follow-up by a multi-specialist team (dermatologist, neurologist and odontologist) should be offered.

CONCLUSIONS

Nevoid basal cell carcinoma is a multisystem disorder. Diagnosis requires a multisystem approach by dermatologist, odontologist and neurologist.

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