

Basal Cell Naevus Syndrome

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The patient had two sisters and one brother. They appeared to be normal. Her mother died at the age of 55. The death was sudden and the cause was unclear. The patient remembered that her mother had similar facial features as she. Her father had diabetes mellitus, Parkinson's disease and old stroke.

CASE SUMMARY

History

A 31-year-old lady presented with a right cheek swelling for one year. She was diagnosed to have an odontogenic keratocyst in a dental hospital. Surgical enucleation was performed. She also complained of multiple papules at the trunk and right axilla for one year. The lesion at the left lower abdomen was itchy. She was referred to the dermatological clinic for further assessment.

The patient had epilepsy since the age of 12 and oral anticonvulsant was given for 6 years. The treatment was stopped at the age of 18 because of absence of further attack. The menstrual cycle was normal and the patient was a university graduate.

Physical examination

The patient had a large body build compared with her siblings. Dysmorphic facial features including frontal bossing, broad nasal bridge and hypertelorism were noted (Figure 1). There were palmar pits (Figure 2). A pigmented papule, 3.5 mm in diameter was noted at right axilla. Similar lesions, 3 mm and 5 mm in diameters with regular borders, were noted in left lower abdomen and vertex of the scalp.

Investigations

Multiple excisional skin biopsies were performed. Scalp lesion showed skin infiltrated by masses and clusters of tumour cells with a peripheral palisade of the nuclei. Peritumoural cleft was noted. The tumour cells had large, oval, elongated nuclei and scanty



Figure 1: Dysmorphic facial features include broad nasal bridge, hypertelorism and frontal bossing



Figure 2: Palmer pits

cytoplasm. The histology was diagnostic of basal cell carcinoma. The biopsies at right axilla and left lower abdomen showed similar features.

Diagnosis

The diagnosis was basal cell naevus syndrome (BCNS) because of the typical dysmorphic features, history of dental cyst and abnormal skin lesions compatible with basal cell carcinoma.

Management

The patient was advised to avoid sun exposure. Regular follow-up would be necessary to check for basal cell carcinoma, and suspicious lesions should be removed. Genetic counseling was given. She was also referred to the medical clinic for screening of other potential complications of the disease. Examinations of other family members were offered.

REVIEW ON BASAL CELL NAEVUS SYNDROME

Basal cell naevus syndrome is also known as Gorlin syndrome and naevoid basal cell carcinoma syndrome. It is an autosomal dominant disorder although new

mutations can arise. The prevalence is 1 per 56,000, and 1-2% of medulloblastoma¹ and 0.5% of basal cell carcinoma are due to BCNS.²

Clinical features

More than 40 abnormalities have been reported in this disorder.³ However these abnormalities can be grouped into two categories, namely developmental anomalies and postnatal tumours. None of these abnormalities is unique to this syndrome. Four characteristics are frequently found and these include basal cell carcinomas, pits at palms and soles, jaw cysts and tissue overgrowth.

Basal cell carcinomas in patients with BCNS cannot be distinguished individually from those in sporadic cases. Their appearance in large numbers at an early age is however distinguishing.³ They may be banal-appearing and confused grossly with melanocytic naevus and hence the name "basal cell naevus" is adopted in this syndrome. Most of the basal cell carcinomas are locally invasive but pulmonary metastasis has been reported.⁴ Sunlight accelerates the formation of basal cell carcinomas, therefore avoidance of sun exposure is important in the management of patients with BCNS.

Palmoplantar pits are tiny defects in stratum corneum. They may be pink or dark; the latter is due to

the accumulation of dirt. Jaw cysts are often the first detectable abnormality and they may be asymptomatic or cause pain, swelling and loss of teeth.³ Tissue overgrowth is manifested by a bigger overall size, longer limbs with Marfanoid appearance, large head circumference and frontal bossing.

Underlying molecular defect

Numerous investigations have been done to find out the underlying molecular defect in BCNS. The prominence of developmental defects makes this syndrome unusual among autosomal dominant disorders predisposing to cancer.⁵

Mutations in tumour suppressor genes appear to be the mechanism for the majority of autosomal dominant cancer predisposition syndromes. Except those on the X and Y chromosomes, there are two copies of each tumour suppressor genes in every normal cell. Mutational inactivation of one copy of a tumour suppressor gene has very little effect because the second copy is sufficient to maintain the normal cell growth. But if both copies are not functioning, there will be a powerful growth promoting effect. Germline mutation of one homolog of a tumour suppressor can cause an autosomal dominant syndrome of cancer predisposition because the remaining homolog is likely to be lost in a proportion of susceptible cells through somatic events.⁵

Recently, screening for allelic loss in sporadic and hereditary basal cell carcinomas, hereditary ovarian fibromas, and sporadic medulloblastomas provided evidence for a tumour suppressor gene on chromosome 9q, which is important in all three tumour types.⁵ Demonstration of a chromosome 9q deletion in an unusual patient with this syndrome and genetic linkage studies in large kindreds indicated that the naevoid basal cell carcinoma syndrome gene maps to the loss of alleles in the region 9q22-q31.⁶

These data support the hypothesis that BCNS is caused by mutation in a tumour suppressor gene on chromosome 9, which plays an important role both in normal development and in the growth control of the precursor cells for basal cell carcinomas and other tumours.⁵ In BCNS, the precursor cells contain a hereditary "first hit", and the allelic loss represents loss of the normal allele. Sporadic basal cell carcinomas may

arise from cells in which two somatic "hits" have occurred.

The majority of neoplasm analyzed, both sporadic and hereditary, showed allelic loss for chromosome 9q22-q31.⁵ Because homozygous inactivation of tumour suppressor genes can occur through several mechanisms, not all of which result in loss of heterozygosity; it is possible that the relevant gene is inactive in all basal cell carcinomas even though genetic alterations are seen in only 2/3 of sporadic tumours. Point mutations, which are not manifested as allelic loss, are a likely mechanism of inactivation in sporadic cases.⁵ The gene for BCNS was recently identified as the PATCHED.^{7,8} This gene is the human homologue of the *Drosophila* patched gene, which is essential for the establishment of normal patterning of the body and limb in the developing fly embryo.

Tumour suppressor gene and developmental defects

The gene plays a role in both normal embryogenesis and continued control of cell growth and differentiation. It is possible that some of the defects in BCNS can be explained by a two-hit mechanism similar to the two-hit mechanism of neoplasia.⁵ The multiple and scattered developmental defects may be explained by a second hit in an early progenitor cell of the relevant tissue. However, other symmetric generalised features of the syndrome (for example, overgrowth) suggest that loss of just one copy of the gene exerts an effect on growth.

Learning points:

Basal cell naevus syndrome is an autosomal disorder caused by mutations at the patched gene which resides on chromosome 9q. The tumour formation and some of the developmental abnormalities can be explained by the two-hit mechanism.

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<http://www.medicine.org.hk/hksdv/>

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The Homepage of the Asian Dermatological Association

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