CLINICAL QUIZ (p118-119) ANSWER

Gorlin syndrome (OMIM# #109400): Our proband has mandibular odontogenic keratocyst, palmer pits, calcifications at anterior cerebral falx and tentorium, macrocephaly (2 cm above than 97th percentile line), medulloblastoma and congenital chest abnormalities. The first 3 phenotypes are considered as major phenotypes and the latter three are considered as minor from the diagnostic criteria in Table 1.[1,2] These strongly suggest a diagnosis of Gorlin syndrome since it is diagnosed clinically when at least two major phenotypes or one major and two minor phenotypes are present.[3] The clinical findings are then confirmed by targeted sequencing of the *PTCH1* gene. (PreventionGenetics, USA) Results showed a two nucleotide deletion in nucleotide positions 665 and 666 (c.665_666delAT). This deletion changes the tyrosine at position 222 to serine, and at the same time causing a frameshift of the protein, leading to a premature stop after 29 amino acids (p.Tyr222Serfs*29). Although this mutation has not been reported before, however it is expected to be pathogenic and is consistent with diagnosis of Gorlin syndrome. Parental testing has not been done yet.

Gorlin syndrome was first reported by Gorlin and Goltz in 1960,[4] although it was reported in as early as 1894.[5] It is a condition that affects many areas of the body and has a predisposition in developing tumours, whether cancerous or noncancerous. The most common type of cancer found in Gorlin syndrome is a common form of skin cancer called basal cell carcinoma hence Gorlin syndrome is also called nevoid basal cell carcinoma syndrome. The prevalence of

Table 1 Diagnostic Criteria for Gorlin Syndrome and phenotypes presented in our proband. (Modified from Basal Cell Carcinoma Nevus Syndrome Life Support Network webpage and Kimonis et al, 1997)[1,2]

Diagnostic criteria	Our proband
Major phenotypes	
Basal cell carcinoma	–
Keratocystic odontogenic tumors or odontogenic keratocysts	√
Palmar and/or plantar pits	√
Calcification of the *dura mater*	√
Bifid, fused or splay ribs	-
First degree relative with Gorlin syndrome	-
Minor phenotypes	
Macrocephaly	√
Frontal bossing	-
Cleft lip and palate	-
Hypertelorism	-
Sprengel deformity	-
Pectus	-
Syndactyly/polydactyly	√
Hemivertebrae	-
Hamartoma	-
Ovarian fibroma	-
Medulloblastoma	√
Other common phenotypes	
Hyperpneumatisation of paranasal sinuses	-
Skin tags	-
Spina bifida	-
Seizures	-
Inguinal hernia	-

Gorlin syndrome varies amongst different populations, from 1 in 30,827 in the United Kingdom,[6] to 1 in 164,000 in Australia,[7] to 1 in 235,800 recently reported in Japan.[8] The true prevalence of Gorlin syndrome may be even higher due to increased awareness leading to increased diagnosis as well as presence of mild cases which are difficult to detect in clinical settings.[9]

At birth, patients with Gorlin syndrome usually are found to have macrocephaly and/or ribs anomalies. Pits will become more evident in palms and soles of the feet as the patients age. Small number of patients will develop medulloblastoma at around 2 years of age and jaw keratocyst are found at around 10 years of age.[8] By around 20 years of age, basal cell carcinoma may develop on the body, especially in the eye lids. Other tumours for example cardiac fibromas, meningioma and ovarian fibroma in females are also associated with Gorlin syndrome. Other important non-tumour features may include falx calcification, cleft lip/palate, frontal bossing, digits anomalies and ocular anomalies. Please see Table 1 for more features of Gorlin syndrome.[1,2] Apart from the predisposition to tumours, life expectancy of patients with Gorlin syndrome does not significantly deviate from the average population.[9]

Gorlin syndrome, the "fifth phakomatosis", involves multiple systems and gives rise to interesting findings in different imaging modalities. The radiologic protocol for the diagnosis of this syndrome may include panoramic radiography to detect multiple keratocystic odontic tumours; skull X-ray (XR) for the evaluation of calcification; chest X-ray (CXR) to detect rib anomalies; computed tomography (CT) as well as magnetic resonance (MR) and ultrasound (USG) images to find further abnormalities. Premature ectopic calcification of the central nervous system (CNS) in form of calcifications along falx cerebri (70-80%), tentorium (20-40%), diaphragm sellae (60 to 80%) with bridging of sella turcica are very common abnormalities seen in CT brain of these patients.[10] It is also associated with CNS neoplasms, mostly medulloblastoma (in 10% of cases). However, other CNS neoplasms like meningioma, astrocytoma and craniopharyngioma have also been reported with Gorlin syndrome. Apart from CNS tumours, US examinations of the pelvis of female patients may reveal ovarian fibromas. Cardiac echocardiography and Cardiac MR may be used to look for cardiac fibroma (relatively rare).

Keratocystic odontic tumours (KCOTs), formerly identified as odontogenic keratocysts, are one of the most consistent (appears in more than 90% of the cases) and early manifestations (usually in the second decade) of this syndrome.[11] They usually present as uni- or multi-locular cysts, which may have a smooth or scalloped borders.[10,12] The mandible is more commonly involved than maxilla and posterior involvement is more common than anterior. When in the mandible, they typically grow along the length of the bone. In the maxilla, they expand into the maxillary sinus. They are often associated with an impacted tooth, mimicking a dentigerous cyst.

Another common abnormality found in patients with Gorlin syndrome is rib anomalies include bifid, hypoplastic, fused, partially missing, or splayed ribs in 38-60% of patients; with the 3rd, 4th and 5th ribs most commonly affected and it may be unilateral or bilateral. Other skeletal anomalies including kyphoscoliosis, blocked vertebrae, hemivertebrae and spina bifida occulta, short fourth metacarpals, pectus deformity and Sprengel's deformity may be noted in other XRs. Flame shaped lucencies in phalanges, which are small, pseudocystic, lytic bone lesions, can also be seen on XR hands (30%) and feet (17%).[13,14] Detailed radiological features detectable in Gorlin syndrome are summarised in Table 2.

The *patched 1* (*PTCH1*; OMIM# *601309) gene is responsible for Gorlin syndrome and is located in the long arm of chromosome 9 (9q22.32). *PTCH1* encodes for patched 1 which is the receptor protein of the sonic hedgehog (SHH) protein. When SHH binds to patched 1, a downstream protein smoothened (SMOH) is de-inhibited which in turns releases transcription factors Gli 1, 2 and 3 from the suppressor of fused homolog (SUFU) inhibitory protein.[15] Gli1 is an activator and its level is found to be increased in brain and skin tumours.[16] Gli2 is also an activator and is found to promote G1 to S phase transition in keratinocytes which may promote tumour development.[17] Unlike the first two, Gli3 is a repressor and it is shown to repress the dHand and GREMLIN proteins which are involved in digits development.[18] Mutation or absence of *PTCH1* gene means absence of a functional patched 1 protein. The knock on effect causes uninhibited SMOH activity and continual up regulation of all 3 Gli transcription factors, causing tumour development as well as digit anomalies. Hence *PTCH1* is regarded as a tumour suppressor gene.[19] SHH signalling pathway via patched-1 is shown in Figure 3.[15]

Table 2 Radiological features detectable in Gorlin syndrome

Imaging examinations	Findings
CT or MR Brain	Premature ectopic calcification • falxcerebri (70-80%) • tentorium (20-40%) • diaphragmsellae (60 to 80%) with bridging of sellaturcica CNS neoplasms • medulloblastoma (in 10% of cases) • meningioma • astrocytoma • craniopharyngioma
Dental XR or XR Maxilla & Mandible	Keratocystic odontic tumours (KCOTs), previously known as odontogenic keratocysts
CXR	Bifid, fused, or markedly splayed ribs Cervical ribs Pectus carinatum or pectus excavatum Sprengel's deformity
XR Spine	Kyphoscoliosis Blocked vertebrae Hemivertebrae Spina bifida occulta
XR Hand & Foot	Short fourth metacarpals Flame shaped lucencies in phalanges
USG Pelvis	Ovarian fibroma
Echocardiogram or Cardiac MR	Cardiac fibroma

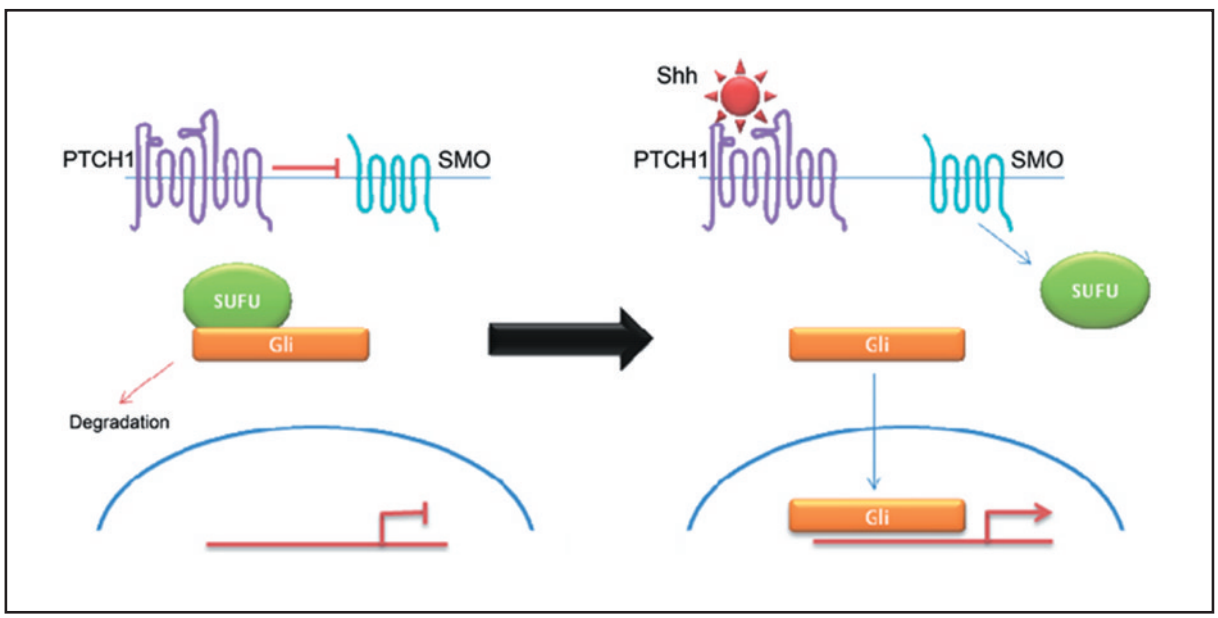

Figure 3 SHH signalling pathway via patched-1 (Modified from DeSouza et al. 2014)[15]

Management

Diagnosis of Gorlin syndrome is usually established in a clinical setting and diagnostic criteria have been published.[2,3] A modified version of these criteria can be seen in Table 1.[1,2] Both Evans, Ladusans et al (1993) and Kimonis, Goldstein et al (1997) proposed that Gorlin syndrome can be clinically confirmed when 2 major or 1 major and 2 minor phenotypes are present from the diagnostic criteria. Once a diagnosis has been made clinically, molecular testing can be used for confirmation. Targeted sequencing of *PTCH1* gene is usually the first approach where exons 1 to 23 of *PTCH1* gene are sequenced and has a detection rate of 50-85%.[9] If sequencing analysis fails to detect the mutation, deletion/duplication analysis for large gene deletions can be considered and it has a detection rate of 6%-21%. However there have been cases where *PTCH1* gene analysis found no mutation, and analysis of another component of the SHH pathway revealed a mutation in the *SUFU* gene found in chromosome 10q24.32.[20] And it has been shown that cases with nodular or desmoplastic medulloblastoma caused by *SUFU* mutation exhibits some features of Gorlin syndrome.[21] A non-functional SUFU protein from a mutated *SUFU* gene may cause uninhibited Gli transcription factors functions similar to that of *PTCH1* mutation. The testing strategy is similar to *PTCH1* where sequencing analysis is performed first followed by deletion/duplication analysis.

Treatments for Gorlin syndrome are usually supportive, aiming to reduce the presenting symptoms rather than curing them. An experienced specialist should be involved. One such treatment is the treatment for basal cell carcinomas which early treatment is essential to prevent long term cosmetic problems, especially for basal cell carcinomas found on the face. The aim is to completely eradicate aggressive basal cell carcinomas while persevering normal tissues to prevent disfigurement. Accompanying surgical treatments are cryotherapy and laser treatment for early lesions and photodynamic therapy. Moh's microsurgery has been proven to be particularly effective.[22] Another presenting symptom that requires surgical treatment is keratocyst. Although they may be a painless swelling, if untreated, keratocysts may lead to major tooth disruption and jaw fracture. Due to the sensitively of basal cell carcinomas to radiography, thousands of basal cell carcinomas may develop at the radiation field and therefore radiotherapy should be avoid at all cost, especially in childhood.[23] However if no other option is available, radiotherapy should be used with as few skin ports as possible.[9] Diagnostic X-rays may also trigger development of basal cell carcinomas, therefore it should be used sparingly. Individuals are also advised to avoid direct sun exposure and administrate precautions since excessive sun exposed may trigger basal cell carcinomas. Precautions may include wearing long sleeves, high collars, and hats and complete sunblock should be used. Full discussion on treatment and management suggestions of Gorlin syndrome is beyond the scope of this clinical quiz. For more details, readers are suggested to read the guideline published by Bree and Shah (2011).[24]

Apart from clinical managements, proper genetic counselling should also be provided to the patients as well as the families. Gorlin syndrome is inherited in an autosomal dominant pattern. Only one copy of the genes in chromosome 9 has to be mutated in an affected individual and they have 50% chance of passing on the mutated gene to their offspring. Although at least one parent of affected children is affected in 70%-80% of cases, the remaining 20%-30% of cases are reported to have a *de novo* mutation.[9] The siblings of patients also have 50% chance of being affected as well. Therefore genetic testing should be provided for the patients as well as the whole family.

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