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Gorlin syndrome

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Naevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is an autosomal dominant syndrome of developmental anomalies associated with an increased risk of malignancies. Patients have multiple lesions, which may be subtle, and the diagnosis can easily be missed, leading to sub-optimal follow-up. Despite its infrequency clinicians may benefit from familiarity with the syndrome, as these patients are hypersensitive to radiation and prone to develop multiple malignancies. Patients can present to paediatricians, oncologists, maxillofacial surgeons, radiation oncologists and dermatologists, and it will be to the benefit of the patient with this syndrome for these specialists to have a working knowledge of this rare but fascinating disorder.

Case report

A 13-year-old girl was referred with an ovarian mass. She gave a 3-month history of episodic abdominal pain. Her menstrual cycle had previously been regular with normal flow, but had become increasingly heavier. An abdominal ultrasound scan showed a large, complex mass in the left ovary with both solid and cystic components, and free fluid in the abdomen. Two years before this presentation, she had had a growth removed from her jaw at another hospital. Her maternal grandmother had been diagnosed with breast cancer, and there was no known history of malignancies in other family members.

The patient had hypertelorism, epicanthic folds and macrocephaly (Fig. 1). A cystic mass was found in the right antecubital fossa and she had small pits in her palms and soles. Her abdomen was distended, with a large mass easily seen arising from the pelvis. On palpation it was firm with cystic areas, and measured 15 cm in diameter. The genitalia were normal for age. Serum tumour markers (α-fetoprotein and β-HCG) were not raised.

A contrast computed tomography scan of the abdomen showed a large multilobulated mass arising from the pelvis (Fig. 2). The exact organ of origin could not be determined. The mass had cystic areas and features suggestive of necrosis with some calcification, and impinged on both ureters, causing bilateral hydronephrosis.
At laparotomy, the patient was found to have large tumours arising from both ovaries. A bilateral oophorectomy was performed, and peritoneal washout was done. The histopathological features of both tumours were those of sex cord stromal tumour with morphological features of a fibroma (Fig. 3). The pathologist noted that it was rare for a patient to have bilateral ovarian tumours containing calcification at such a young age, and suspected Gorlin syndrome. The jaw mass that had been removed previously was reviewed and confirmed to be an odontogenic keratocyst. Together with the hypertelorism and palmar pits, the cluster of signs and pathologies fitted the diagnosis of naevoid basal cell carcinoma syndrome (NBCCS), or Gorlin syndrome. Radiographs of the skull and vertebrae helped to confirm the diagnosis, showing calcification of the falx cerebri (Fig. 4) and mild scoliosis (Fig. 5).

Fig. 1. Hypertelorism and epicanthic folds (image used with permission of the patient and her mother).

The patient recovered well from surgery and was started on hormone replacement therapy. Follow-up will include surveillance for the other malignancies associated with this syndrome.

Discussion

Gorlin syndrome was described in 1960[1] and has been known by a range of names, but NBCCS is currently the most widely accepted and accurate description. It has been found to be caused by a specific gene mutation.[2] Inheritance is autosomal dominant, with complete penetrance but variable expressivity,[3] although approximately 40% of cases represent new mutations. The gene responsible for the disease has been mapped to the long arm of chromosome 9, and the normal product of this gene is thought to act as a tumour suppressor. However, when the tumour suppressor function is altered, malignancies occur. The variety of malformations found in this syndrome suggests that the gene also has an essential role in controlling development of normal tissues.[3]

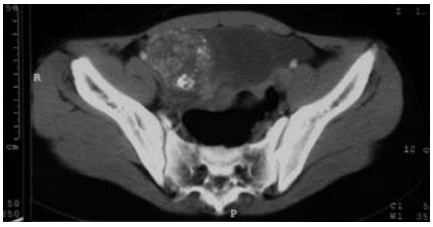

Fig. 2. Axial computed tomography scan of the pelvis showing large multilobulated mass. Cystic material, necrosis and calcification are present.

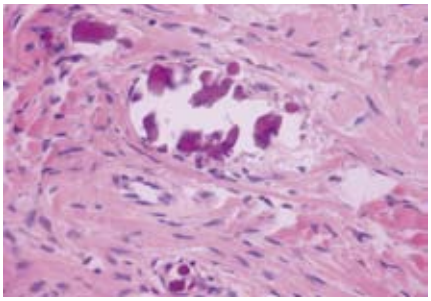

Fig. 3. Foci of dystrophic calcification with surrounding bland spindle cell proliferation.

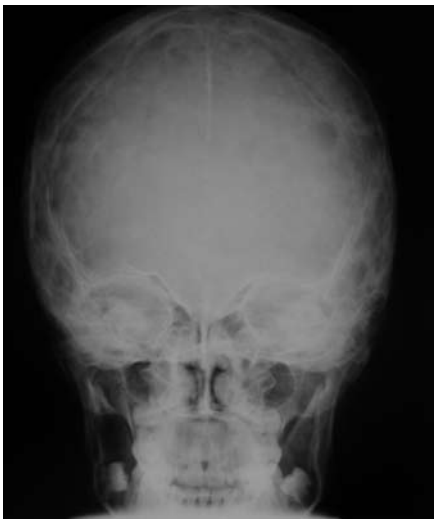

Fig. 4. Plain film skull radiograph showing calcification of the falx cerebri.

Amended diagnostic criteria have been proposed, with a diagnosis of Gorlin syndrome being made when **two major** or **one major and two minor** criteria are present.[4]

Major criteria

- Two or more basal cell carcinomas in persons younger than 20 years
- Odontogenic keratocysts of the jaw
- Three or more palmar or plantar pits
- Bilamellar calcification of the falx cerebri
- Bifid, fused or markedly splayed ribs
- First-degree relative with Gorlin syndrome.

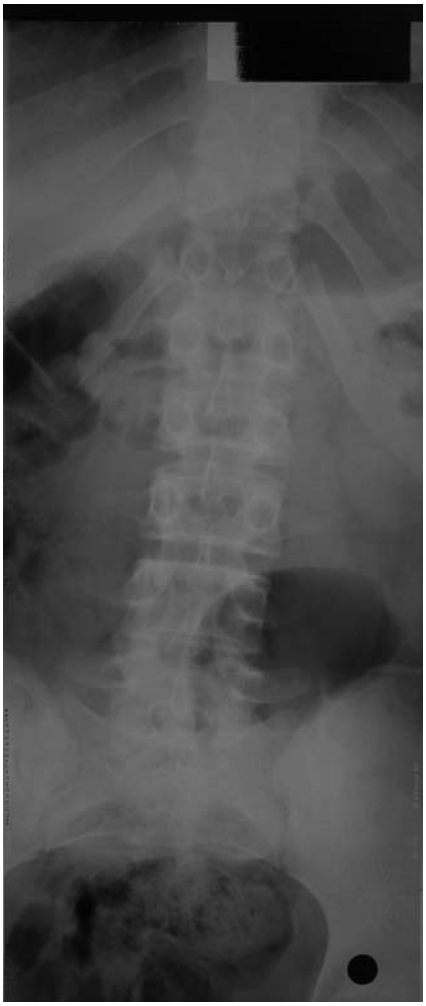

Fig. 5. Plain film radiograph showing mild scoliosis..

Minor criteria

- Macrocephaly
- Congenital malformations (e.g. cleft lip or palate, frontal bossing, hypertelorism)
- Other skeletal abnormalities (e.g. Sprengel deformity, marked pectus deformity, syndactyly of digits)
- Radiological abnormalities (e.g. bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion/elongation of the vertebral bodies, modelling defects of the hands and feet, flame-shaped lucencies of the hands or feet)
- Ovarian fibroma
- Medulloblastoma.

Black African patients are less likely than Caucasians to develop basal cell carcinomas (BCCs),[5] which can arise as early as 3 years of age. These skin cancers can be very pleomorphic and may look like haemangiomas, ulcers or flesh-coloured papules. These BCCs usually occur in areas exposed to sunlight but may also be found in areas protected from sun exposure, and are more prevalent in areas exposed to therapeutic radiation. In patients who develop medulloblastomas and are treated with radiation, it is mandatory that they be monitored for the development of BCCs in the radiation field.

Management of a patient or family with this syndrome should include genetic counselling and neurological evaluations to detect medulloblastoma until the age of 7, after which time medulloblastoma is unlikely to occur. As radiation should be avoided if possible, magnetic resonance imaging of the brain is recommended if a medulloblastoma is suspected on clinical grounds. Current recommendations are to perform neurological examinations every 6 months rather than scheduled, elective imaging.

Patients should avoid excessive ultraviolet radiation as well as other forms of ionising radiation, and should have regular skin examination to detect BCCs. Repeated screening radiographic studies are not recommended owing to sensitivity to the effects of radiation, although panoramic dental X-rays may be required if odontogenic cysts are suspected.

Gorlin syndrome is often not diagnosed in childhood as many of the characteristic features develop later in life, and patients may present to various specialists with different problems. In addition, the variable expressivity of the gene abnormality translates in clinical practice to affected patients having either very obvious features or subtle ones such as coarse facies, hypertelorism and bifid ribs, which may never be detected. For this reason careful follow-up is essential, and co-operation from members of various specialities will ensure optimal treatment and follow-up.

We thank the patient and her mother for their permission to publish the accompanying images.

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