

Situs inversus in a patient with nevoid basal cell carcinoma syndrome: a histogenetic relationship?

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Abstract: Nevoid basal cell carcinoma syndrome (NBCCS) is an uncommon autosomal dominant inherited disorder with high penetrance and variable expressivity. It affects multiple organ systems, including the stomatological, skeletal, skin, eye, reproductive, and central nervous systems. It is caused by mutations in the patched tumor suppressor gene, *PTCHI*, located in the 9q22.3-q31 chromosome. To our knowledge, this is the first report of a patient with unusual radiological features, i. e. dextrocardia and situs inversus totalis, in conjunction with common features including multiple keratocystic odontogenic tumors, bifid ribs, palmar and plantar pits, bridging of the sella turcica and calcification of the falx cerebri. We examined whether these genetic conditions were associated, as both involve ciliary dysfunction. (J Oral Sci 53, 253-256, 2011)

Keywords: multiple jaw cysts; Gorlin-Goltz syndrome; basal cell nevus-Bifid syndrome; situs-inversus totalis.

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) affects multiple organ systems, including the stomatological, skeletal, skin, eye, reproductive, and central nervous systems. In 1960, Gorlin and Goltz defined the syndrome as a hereditary condition transmitted by an autosomal

dominant gene with high penetrance and variable expressivity (1). NBCCS is caused by mutations in the patched tumor suppressor gene, *PTCHI*. The gene responsible has been localized to chromosome 9q22.3-q31 (2). The prevalence of this condition is approximately 1 per 60,000 (3), and clinical manifestations include basal cell carcinomas (BCCs), which may appear as early as age 2 years (4), keratocystic odontogenic tumors that generally develop in the first, second, and third decades of life (5), palmar or plantar pits (which occur in 85% of patients over age 20 years) (6), ectopic calcification of the falx cerebri (70% to 85% of cases), complete or partial bony bridging of the sella turcica (25% of cases), ovarian cysts and fibromas (25% to 50% of affected women), and cardiac fibromas (3% to 5% of cases). These manifestations are considered the major criteria for diagnosis. NBCCS is also characterized by congenital skeletal abnormalities: macrocephaly with frontal bossing is frequent (70% of cases), and NBCCS also affects the shape of the ribs and bones of the vertebral column. Scoliosis is common, and spina bifida occulta of the cervical or thoracic vertebrae is observed in 60% of cases. Patients often have cleft lip or palate and eye anomalies such as hypertelorism (70% of cases), exophthalmus, rotatory nystagmus, internal strabismus, congenital cataracts, orbital cysts, coloboma of the iris, choroid, or optic nerve, microphthalmia, and chalazions. Less common are neoplasms such as medulloblastomas and meningiomas. Intellectual deficits are present in up to 5% of cases. We describe a patient with situs inversus totalis, along with other common features, including multiple keratocystic odontogenic tumors, bifid ribs, palmar and plantar pits, bridging of the sella turcica, and calcification of the falx cerebri.

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Case Report

Clinical presentation

A 13-year-old girl reported to the department of oral and maxillofacial surgery at our institution with painless swelling on the lower left side of her face. The swelling

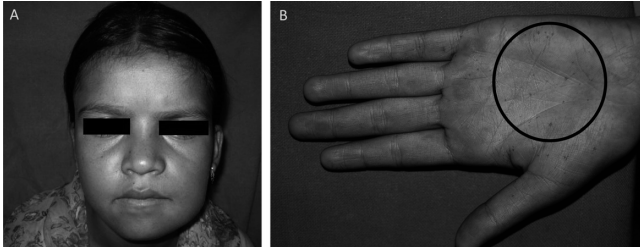


Fig. 1 Photographs showing (A) facial asymmetry due to swelling and (B) palmar keratosis.

had persisted for 3 years and the patient was otherwise relatively asymptomatic. The swelling measured 4×3 cm and was firm and non-tender. It extended anteroposteriorly from the angle of the mouth to the posterior border of the ramus of the mandible and lateromedially from the lower border of the mandible to the nasolabial fold. The surface of the swelling was smooth. Frontal bossing and a wide nasal bridge were also noted (Fig. 1A).

Intraoral examination revealed the absence of teeth 17, 13, 35, and 43, retention of teeth 63, 75, and 83, and overlap of teeth 22 and 23. A single swelling obliterating the buccal sulcus extending was present from region 33 to region 37. On palpation the lesion was fluctuant, cystic, and slightly tender. The mucosa was blanched but non-ulcerated. The involved teeth were slightly mobile, but vital.

Dermatological examination revealed no basal cell nevi,

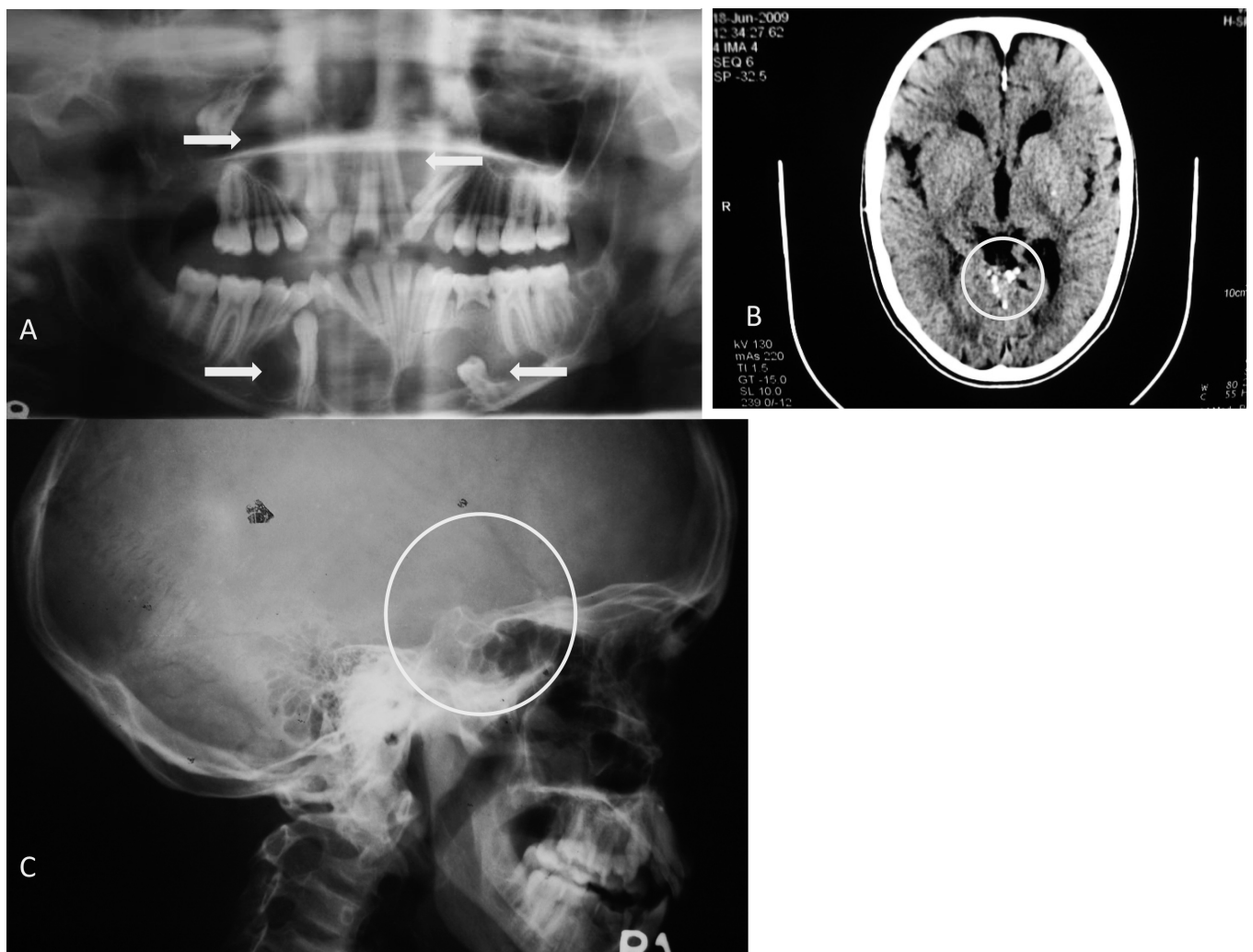


Fig. 2 (A) Orthopantomogram showing multiple expansile cystic lesions in the maxilla and mandible, (B) Axial CT scan showing calcification of the falx cerebri along venous sinuses, (C) Lateral view of skull showing bridging of the sella turcica.

but palmar and plantar pits and keratosis were present (Fig. 1B). Psychiatric consultation showed intellectual deficit, and ophthalmological examination revealed hypertelorism (Fig. 1A).

Radiological presentation

Orthopantomography showed multiple cystic lesions in the upper and lower jaws, which were associated with unerupted permanent teeth displaced from their normal positions (Fig. 2A). Axial computerized tomography showed calcification of the falx cerebri along the venous sinuses and small venous channels (Fig. 2B). Lateral views of the skull revealed bridging of the sella turcica (Fig. 2C). A chest radiograph showed bifid fourth and fifth ribs on the left side and dextrocardia, with the heart apex to the right side. (Fig. 3A). Ultrasound examination of the abdomen confirmed complete situs inversus; the liver was on the left, the spleen on the right side, and the stomach was transposed (Fig. 3B, C).

The clinical and radiological findings confirmed the diagnosis of NBCCS. The parents and siblings of the

patient were also examined clinically and radiographically; however, none had any characteristics of this syndrome.

Discussion

A review of the literature shows that NBCCS is associated with a wide variety of abnormalities. However, this is the first reported case of situs inversus totalis (the heart was located to the right of the thorax; the stomach and spleen were in the right abdomen, and the liver and gall bladder were on the left; the left lung was trilobed and the right lung bilobed, and blood vessels, nerves, lymphatics, and intestines were also transposed) combined with common features of NBCCS such as multiple keratocystic odontogenic tumors, bifid ribs, palmar and plantar pits, bridging of the sella turcica and calcification of the falx cerebri. Because situs inversus itself is asymptomatic, we cannot exclude the possibility that it has been overlooked in routine examinations of NBCCS patients by oral surgeons and dermatologists. However, the rarity of these two conditions (NBCCS incidence: 1 in 57,000; situs inversus incidence: 1 in 10,000) suggests that coincidental

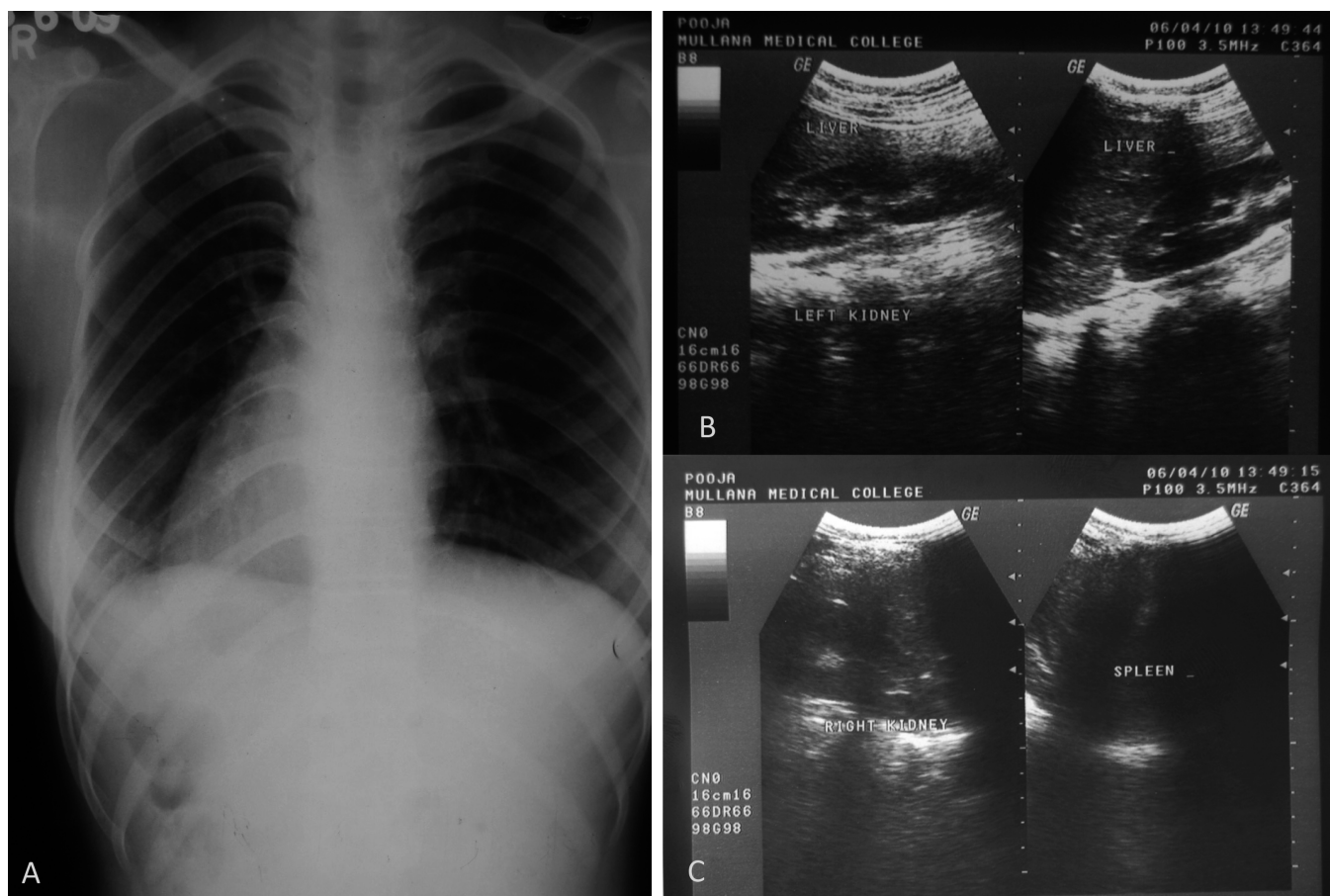


Fig. 3 (A) PA radiograph of chest showing bifid fourth and fifth ribs on the left side and dextrocardia, (B) Ultrasound image showing the liver in the left hypochondrium, (C) Ultrasound image showing the spleen in the right hypochondrium.

occurrence is unlikely. Thus, there is the intriguing possibility that these two clinical phenotypes are histogenetically linked to PTCH/hedgehog signaling.

The hedgehog (Hh) signaling pathway plays an important role both in embryonic development and adult stem cell function. Dysregulation of the pathway causes birth defects and cancer. NBCCS is known to be caused by mutations in the *PTCH1*, the receptor of hedgehog. *PTCH1* is localized to primary cilia and mediates key steps in the transduction of the hedgehog signal (7-9). It has been suggested that ciliary dysfunction via dysregulation of the hedgehog pathway is the underlying cause of situs inversus (10). Therefore, further research is warranted to determine if there is an association between these conditions. Because of the oral maxillofacial manifestations of this syndrome, it is essential to determine its characteristics to assist in diagnosis, early preventive treatment, and accurate genetic counseling. Many people with situs inversus totalis are unaware of their unusual anatomy. The transposition of organs may lead to confusion, as many signs and symptoms will be on the “wrong” side.

Thus, in examinations of patients with NBCCS, systemic findings must be ruled out by considering the possibility of situs inversus as another sign of the syndrome. The most common findings, ie, basal cell nevi on the skin and multiple keratocystic odontogenic tumors in the jaws, are observed early and should be treated at the earliest opportunity. In addition, possible complications must be explained to the patient. Most of the time, patients present to dental hospitals with jaw swelling. Evaluation and treatment of NBCCS requires a multidisciplinary approach involving dentists, maxillofacial surgeons, dermatologists, and neurologists; hence, the responsibility of proper diagnosis and development of a treatment plan rests with medical professionals. There should be a periodic follow-up at regular intervals of 6 months until age 10 years, with annual examinations thereafter. Finally, further research is needed to assess the genetic association between situs inversus and nevoid basal cell carcinoma syndrome.

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