กลุ่มอาการนีวอยด์เบซัลเซลล์คาร์ซิโนมา: รายงานผู้ป่วย 1 ราย

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บทคัดย่อ

กลุ่มอาการนีวอยด์เบซัลเซลล์คาร์ซิโนมา (nevoid basal cell carcinoma syndrome, NBCCS) หรือกลุ่มอาการกอร์ลิน (Gorlin syndrome) เป็นโรคทางพันธุกรรมที่พบได้ยาก ถ่ายทอดผ่านทางยีนเด่น (autosomal dominant) สาเหตุหลักเกิดจากการกลายพันธุ์ของยีน patched tumor suppressor gene (PTCH1) อัตราความชุกแตกต่างกันออกไปในแต่ละพื้นที่ กลุ่มอาการนี้มีลักษณะเฉพาะคือ มะเร็งผิวหนังชนิดเบซัลเซลล์หลายตำแหน่ง (multiple basal cell carcinomas, BCC) ถุงน้ำโอดอนโตเจนิกเคอราโตซิส (odontogenic keratocyst, OKC) ในกระดูกขากรรไกร และความผิดปกติอื่นๆ ที่เกี่ยวข้องกับโครงกระดูก ระบบประสาทส่วนกลาง ตา ต่อมไร้ท่อ และระบบสืบพันธุ์ กลุ่มอาการนี้อาจได้รับการวินิจฉัยโดยศัลยแพทย์ตกแต่งหรือแพทย์ผู้เชี่ยวชาญด้านโรคผิวหนังด้วยมะเร็งผิวหนังชนิดเบซัลเซลล์หลายตำแหน่ง หรือวินิจฉัยโดยทันตแพทย์ด้วยถุงน้ำโอดอนโตเจนิกเคอราโตซิส การวินิจฉัยที่รวดเร็วและการดูแลรักษาจากสหวิชาชีพอย่างถูกต้องจะช่วยลดโอกาสการดำเนินโรค และช่วยให้ผู้ป่วยได้รับการรักษาที่ถูกต้องและมีคุณภาพชีวิตที่ดี บทความนี้รายงานผู้ป่วยกลุ่มอาการนีวอยด์เบซัลเซลล์คาร์ซิโนมาในชายไทยอายุ 38 ปี ที่สงสัยเนื้องอกในสมองไกลโอมาชนิดร้ายแรง

คำสำคัญ: กลุ่มอาการนีวอยด์เบซัลเซลล์คาร์ซิโนมา; กลุ่มอาการกอร์ลิน; มะเร็งผิวหนังชนิดเบซัลเซลล์; ถุงน้ำโอดอนโตเจนิกเคอราโตซิส

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Nevoid basal cell carcinoma syndrome: A case report

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Abstract

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is a rare autosomal dominant inherited condition mainly caused by mutations in the patched tumor suppressor gene (PTCH1). Prevalence rates vary by region. This syndrome is characterized by multiple basal cell carcinomas, as well as odontogenic keratocysts (OKC) in the jaw and other abnormalities involving the skeletal, central nervous system, ophthalmic, endocrine, and genital systems. This syndrome may be diagnosed by a plastic surgeon or dermatologist in patients who present with multiple basal cell carcinomas or by a dentist in patients who present with OKC. Early diagnosis and a multidisciplinary approach to treatment are important for decreasing the progression and severity of this syndrome, as well as improving the patient's quality of life. Here, we report a case of nevoid basal cell carcinoma syndrome with a suspected high-grade glioma in a 38-year-old Thai man.

Keywords: nevoid basal cell carcinoma syndrome; Gorlin syndrome; basal cell carcinoma; odontogenic keratocyst

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Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin syndrome was first reported by Gorlin and Goltz in 1960.[1] The syndrome is a rare autosomal dominant inherited condition mainly caused by mutations in the patched tumor suppressor gene (PTCH1), located on chromosome 9q22.3.[2] This gene has a fundamental role in controlling the growth and development of normal tissues. Incidences may vary by region, though they can also occur spontaneously. While it may arise in all ethnic groups, most cases involve Caucasians. Males and females are equally affected. There are three major reports concerning the epidemiology of this syndrome; in the UK, Australia and Japan. Prevalence rates were reported as 1 in 30,827 in the UK[3], 1 in 164,000 in Australia[4] and 1 in 235,800 in Japan.[5] The syndrome is defined as a condition characterized by the triad of basal cell carcinomas (BCC), as well as odontogenic keratocyst (OKC) in the jaw and skeletal anomalies. A spectrum of other neurological, ophthalmic, endocrine and genital manifestations is known to be variably associated with this triad.[6] Early diagnosis and a multidisciplinary approach to treatment are important for decreasing the progression and severity of this syndrome as well as improving the patient's quality of life. This study reports on a particular case of nevoid basal cell carcinoma syndrome.

Case report

A 38-year-old man was referred from a rural hospital with a chief complaint of generalized tonic-clonic seizure and alteration of consciousness. He was admitted to the internal medicine department and underwent investigations for the cause of his seizure and alteration of consciousness. Brain computerized tomography (CT) revealed a well-defined heterogeneous hypodense lesion at the left frontal lobe, measuring approximately 5.6x3.5x5.3 cm with perilesional subtle increased leptomeningeal enhancement. The patient had been diagnosed with a brain abscess and had received treatment with intravenous (IV) antibiotics. After the completion of the IV antibiotics treatment, brain CT was repeated, which showed there was no significant change in the size of the brain lesion. The possible diagnosis for a brain lesion could be a brain tumor. Therefore, an internist consulted with a neurosurgeon and arranged for additional examination using magnetic resonance imaging (MRI), which revealed high-grade glioma. Upon a review of the patient's history and a physical examination, multiple heterogenous hyperpigmentation papules, plaques and nodules were found to be present on his face since the age of 20. The lesions had persisted and gradually increased in size during the past year. A plastic surgeon was consulted for further assessment.

A general physical examination showed dysmorphic facial features including a coarse face, prominent brow, facial milia and multiple shiny blue-black papules, plaques and nodule of various sizes scattered on the face, particularly in the periorbital areas. Some lesions showed a raised and rolled border with central ulceration (Figure 1). Ophthalmic examination revealed multiple firm yellow papules on both upper and lower eyelids, protruding from palpebral conjunctiva, fixed to tarsus (Figure 2). Intraoral examination showed a permanent complement of teeth. There was mild swelling of the oral mucosa in the left mandibular ramus area.

Figure 1 Facial appearance of the patient showing dysmorphic facial features, coarse face, prominent brow, facial milia and multiple shiny blue-black papules, plaques and nodule of various sizes scattered on the face, particularly in the periorbital areas. Some lesions showed a raised and rolled border with central ulceration.

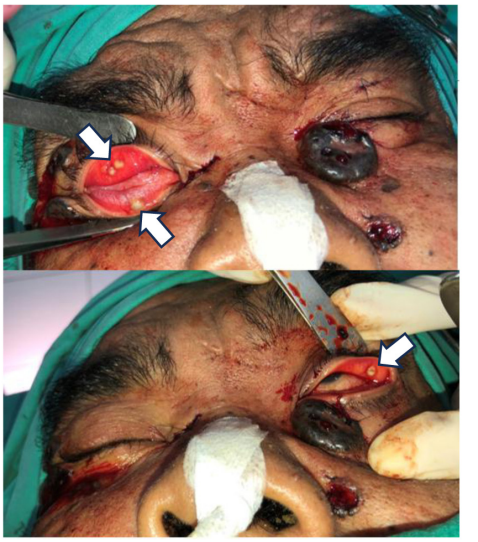

Figure 2 Ophthalmic examination showing multiple firm yellow papules on both upper and lower eyelids, protruding from palpebral conjunctiva, fixed to tarsus (indicated by the white arrow)

The patient was subjected to various radiographic examinations as follows. Panoramic radiography for orthodontic purposes showed radiolucent lesions suggestive of jaw cysts in both the mandible and maxilla (Figure 3). Other radiographic examinations were also performed, which included posteroanterior (PA) and lateral view of the skull, chest (CXR), anteroposterior (AP) and lateral view of the whole spine radiographs, CT and MRI of the brain. The CT and MRI of the brain revealed high-grade glioma at the parasagittal of the left high frontal lobe (Figure 4), linear calcification of the falx cerebri (Figure 5), CXR and whole spine radiographs observed no osseous anomalies. The patient was then evaluated systemically for other anomalies of the skeletal and cardiovascular system, but there were no other anomalies observed. An oral and maxillofacial surgeon and neurosurgeon advised the patient to undergo incisional biopsy as well as removal of the jaw cysts and removal of glioma, but he refused to do so. Anticonvulsant and analgesic drugs were used to control his seizure and headache symptoms.

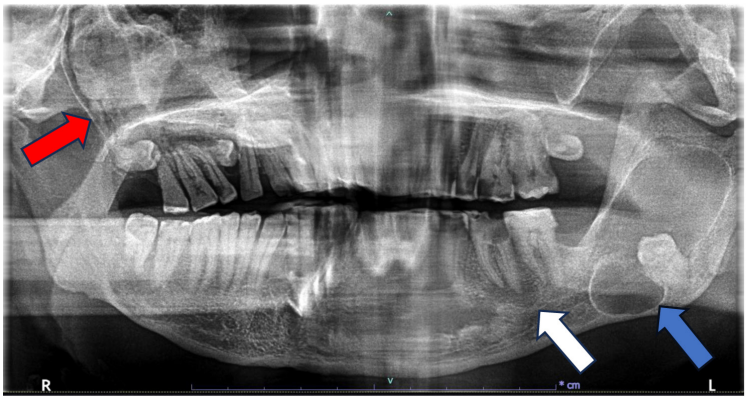

Figure 3 Panoramic radiography showing radiolucent lesions associated with an impacted mandibular and maxillary molar tooth. The left mandibular lesion extended from angle to the ramus of the mandible (indicated by the blue arrow). The right maxillary lesion, associated with a horizontally impacted molar in the right maxilla, extended up to the right maxillary sinus (indicated by the red arrow). Moreover, the patient had another lesion associated with a radiolucent area on left mandibular body involving the first premolar tooth (indicated by the white arrow). All lesions are suggestive of jaw cysts.

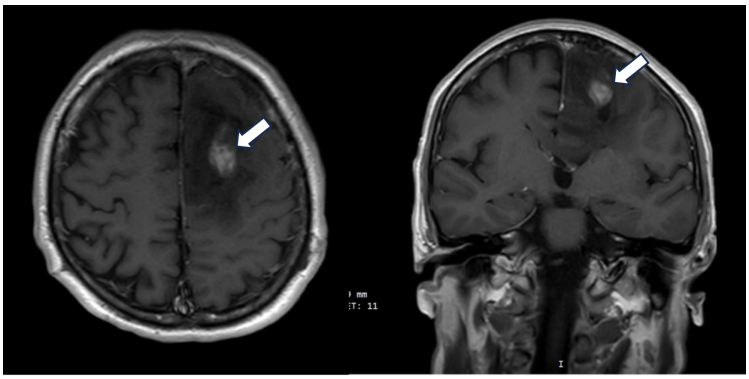

Figure 4 Brain MRI showing high-grade glioma at the left frontal lobe (indicated by the white arrow)

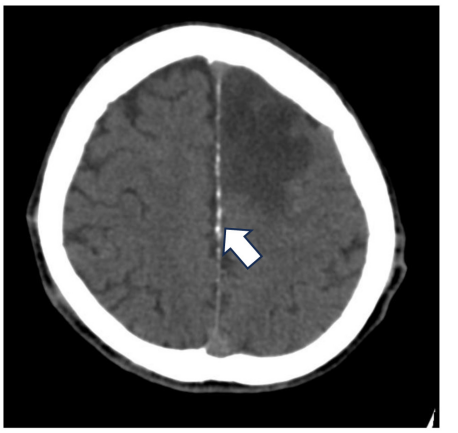

Figure 5 Brain CT scan showing linear calcification of the falx cerebri (indicated by the white arrow)

Based on the history and clinical findings, the provisional diagnosis was nevoid basal cell carcinoma syndrome. An incisional biopsy was performed on the patient to assess all hyperpigmentation papules, plaques and nodules on the face and bilateral intratarsal eyelid lesions; pathologic reports were BCC for the face lesions (Figure 6) and keratin flakes for the eyelid lesions. Since the two major criteria; excessive numbers of BCCs out of proportion to prior sun exposure and skin type, lamellar calcification of the falx cerebri were present; the final diagnosis was nevoid basal cell carcinoma syndrome.[7] All the cancers on the face were surgically removed in one session through a wide excision with a local flap and/or primary closure technique. Pathology reports were BCC, superficial and nodular subtypes. During follow-up, intratarsal keratinous papules were resolved spontaneously.

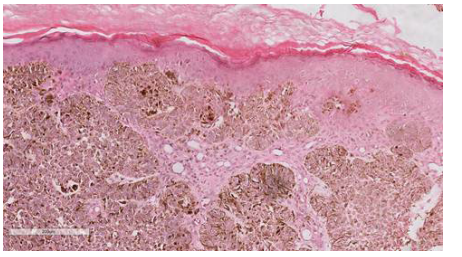

Figure 6 Pathological report of skin from the lower left eyelid; pigmented BCC, nodular subtype. The section shows a moderately cellular tumor with deposition of pigmentation throughout the tumor and the surrounding stroma, peripheral nuclear palisading, and a cleft artifact. Mitotic figures are frequently seen. All resection margins are free.

The patient is receiving follow-up regularly and no recurrences of the BCC or intratarsal keratinous papules have been observed in one and a half years (Figure 7).

Figure 7 Facial appearance of the patient showing no recurrence of BCC after follow-up for one and a half years

Regarding the jaw cysts, the patient did not experience jaw pain or swelling. However, for the high-grade glioma, the patient underwent repeated brain MRI scans, which showed an increase in size and extension of the infiltrative tumor involving the left frontal lobe. The patient also experienced generalized tonic-clonic seizures approximately five times a month, which were controlled by medications.

Discussion

Nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin syndrome was first reported by Gorlin and Goltz in 1960. The syndrome is a rare autosomal dominant inherited condition characterized by a predisposition to neoplasms and other developmental abnormalities that are mainly caused by mutations in the patched tumor suppressor gene (PTCH1), located in chromosome 9q22.3. PTCH1 is the receptor for sonic hedgehog (SHH), a signaling molecule that plays crucial roles in embryonic development and tumorigenesis. When SHH binds PTCH1, smoothened (SMO) is released and signals cell proliferation.[8] However, mutations in other genes such as Patched 2 (PTCH2), Sonic hedgehog and Smoothened have been reported in isolated cases of medulloblastoma and BCC.[5,9] Although it is a genetic disorder, this syndrome can also occur spontaneously.[10] Genetic testing for PTCH1 is suggested in the following three situations: (1) diagnosis confirmation is insufficient using

clinical diagnostic criteria; (2) predictive testing for patients at risk, even if they do not meet the clinical criteria but have an affected family member; (3) prenatal testing if there is a known familial mutation.[10] Although it can appear in all ethnic groups, Caucasians are the most affected. Males and females are equally affected. There are three major reports concerning the epidemiology of this syndrome; in the UK, Australia and Japan. The prevalence rates were reported as 1 in 30,824 in the UK[3,11], 1 in 164,000 in Australia[4] and 1 in 235,800 in Japan.[5] There is now general agreement that the prevalence is about 1 per 60,000.[2] Diagnosis of NBCCS can be established when (1) one major criterion and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria are present, as described in Table 1.[7]

Table 1 Diagnostic criteria of NBCCS

The major criteria	The minor criteria
(1) BCC prior to 20 years old or excessive numbers of BCCs out of proportion to prior sun exposure and skin type	(1) Rib anomalies
(2) Odontogenic keratocyst of the jaw prior to 20 years of age	(2) Other specific skeletal malformations and radiologic changes (i.e., vertebral anomolies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)
(3) Palmar or plantar pitting	(3) Macrocephaly
(4) Lamellar calcification of the falx cerebri	(4) Cleft/lip palate
(5) Medulloblastoma, typically desmoplastic	(5) Ovarian/cardiac fibroma
(6) First degree relative with BCNS	(6) Lymphomesenteric cysts
	(7) Ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)

BCC: Basal cell carcinoma, BCNS: basal cell nevus syndrome

The classical triad consists of multiple BCC, OKC in the jaw, and skeletal anomalies. Early diagnosis can reduce the severity of complications and death, such as skin cancer, brain tumors, and maxillofacial deformities related to multiple jaw cysts. The treatment of NBCCS involves a multidisciplinary approach to its clinical findings.

NBCCS is highly sensitive to ionizing radiation, which can cause DNA damage, mutations, or cell death through pathways involving p53 protein. As a result, radiation therapy is contraindicated for patients with NBCCS.[12]

The present case is interesting because the patient presented with generalized tonic-clonic seizure. Along with physical examination and further investigations findings consistent with NBCCS, this led to the diagnosis. However, seizures are not considered a common clinical

manifestation in NBCCS. They have been rarely reported in the literature, with previous studies documenting 10 cases involving epilepsy.[13]

BCC is a slow-growing malignant tumor for which metastases are rare. It is derived from non-keratinizing cells that originate in the basal layer of the epidermis and rarely develops on the mucous membranes or palms and soles. BCC is the most common type of skin cancer. The development of BCC in most individuals is multifactorial. BCC typically occurs in middle-aged to elderly patients and is less common in younger individuals, After puberty, they can become aggressive and locally invasive. BCC is seen in 50-97% of patients with NBCCS.[14] Highly suspicious NBCCS is also possible, especially in younger ages and those less than 20 years old. BCC typically presents as a pearl-liked, pink- or flesh-colored papule or nodule with surface telangiectasia. The tumor may enlarge and ulcerate, giving a rolled border or rodent ulcer appearance. A more recent treatment for patients with advanced or metastatic BCC that is untreatable with conventional therapeutic methods is Hedgehog pathway inhibitors. The FDA approved Vismodegib in 2012.[15] A second inhibitor, Sonidegib, was also approved.[16]

Another feature of NBCCS is the occurrence of multiple OKC of the jaw. The literature reports a wide variation in the incidence of OKC in NBCCS patients, ranging from 62% to 100%. This association has been found to be 100% in the case series of Lata et al.[17] OKC associated with NBCCS are more common in the mandible (69%) than the maxilla (31%)[18,19] Similarly, in our case, there were more jaw cysts observed on the mandible than on the maxilla.

Patients with NBCCS experience various ophthalmic problems. The most common is periocular BCC, followed by intratarsal keratinous cyst; small, very transient keratin-filled cysts (milia) found on the palpebral conjunctivae in approximately 40%[20] of patients and tend to occur bilaterally as multiple eyelid cysts (80%) at an earlier age (mean age 40).[21] Other problems include hypertelorism, congenital cataracts, microphthalmia, orbital cysts, coloboma of the iris, choroid and optic nerve, strabismus, and nystagmus. The histopathologic features of intratarsal keratinous cysts are characterized by a stratified squamous parakeratinized epithelium with a palisading pattern of columnar cells along with keratin flakes resembling the histopathology of OKC.[22] Complete excision of the cyst with surrounding tarsus and avoiding destruction of the eyelid anatomy is usually recommended for treatment to prevent recurrence. In our case, the incisional biopsy performed in the intratarsal area showed keratin flakes, but there was no information about the cyst wall, and the lesion disappeared spontaneously. Therefore, it cannot be concluded whether it is a keratinous cyst or not.

In the present case, the syndrome did not affect the patient's parents. It is possible that the patient has a sporadic case. NBCCS can also arise from a spontaneous mutation (without any family history) in 35% to 50% of

the cases.[2] A negative family history could impede the early clinical recognition of patients with NBCCS. However, there was a history of neurofibromatosis type 1 (NF1) in his aunt, which was an autosomal dominant disorder from an NF1 gene mutation. The gene mutation for PTCH1 in his family was not carried out because the test was unable to be conducted in Thailand.

Conclusion

Nevoid basal cell carcinoma syndrome is a rare autosomal dominant inherited condition characterized by the triad of basal cell carcinomas (BCC), odontogenic keratocyst (OKC) in the jaw and skeletal anomalies. A spectrum of other neurological, ophthalmic, endocrine and genital manifestations is known to be variably associated with this triad. Despite this syndrome being potentially life-threatening, correct and timely diagnoses can lead to appropriate treatment by a multidisciplinary team, which can reduce complications, lower mortality rates, and improve the quality of life for patients.

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Conflicts of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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