CASE REPORT

Basal cell nevus syndrome in a 56-year old Filipino female: a case report

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Introduction: Basal cell nevus syndrome (BCNS) (Gorlin-Goltz syndrome or Nevoid basal cell carcinoma syndrome) is a rare inherited multisystem and tumor-predisposing disorder caused by the patched tumor suppressor gene mutations and suppressor of fused gene. Its diagnosis follows a set of criteria based on specific cutaneous features and radiologic findings. Although an autosomal dominant disorder with a high degree of penetrance, BCNS has variable expression making its diagnosis difficult. The limited epidemiologic data among Asians especially in the Philippines hamper early detection or cause frequent misdiagnosis of the condition.

Case report: A 56-year-old Filipino female with Fitzpatrick skin type V presented with early onset multiple basal cell carcinomas and bilateral palmoplantar pits. Radiologic investigation reveals odontogenic keratocyst, calcification of the falx cerebri, bridging of the sella turcica, bifid/splayed ribs and vertebral anomalies. The patient exhibits coarse facial features and bilateral cataracts. Cranial computed tomography scan shows cerebrocerebellar atrophy with ventricular dilatation. Management included wide excision of the nodular basal cell carcinomas (BCC), application of 5-flourouracil cream on the superficial BCC and electrodessication and curettage of the smaller lesions. Oral acitretin was also prescribed.

Conclusion: This is a case that highlights the approach to diagnosis, clinical features and management of BCNS in a Filipino patient. Since various phenotypic presentations may exist among dark-skinned individuals, early diagnosis poses a challenge among physicians. Epidemiologic and prevalence studies among Filipinos may be done to aid in the diagnosis and early management of this rare genodermatosis.

Keywords: Basal cell nevus syndrome, Gorlin-Goltz syndrome, Nevoid basal cell carcinoma syndrome, Basal Cell Carcinoma

INTRODUCTION

Basal cell nevus syndrome (BCNS) (Gorlin-Goltz syndrome or Nevoid basal cell carcinoma syndrome) is a rare inherited multisystem and tumor-predisposing disorder caused by the patched tumor suppressor gene (PTCH1) mutations, in most cases, and suppressor of fused (*SUFU*) gene. Diagnosis follows a set of criteria based on specific cutaneous features and radiologic findings. (Table 1) A patient must fulfill either two major criteria or 1 major and 1 minor criterion to make the diagnosis of BCNS.[2, 3,4]

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Table 1. Criteria for the diagnosis of Basal Cell Nevus Syndrome [2,3,5]

Major: • Calcification of the falx cerebri • Odontogenic keratocyst • 2 or more palmoplantar pits • Multiple basal cell carcinomas, BCCs (>5) or appearance before the age of 30 • First degree relatives (Autosomal Dominant) • PTCH gene mutation
Minor: • Macrocephaly • Childhood medulloblastoma • Lymphomesenteric pleural cyst • Congenital malformations: "Coarse face", Cleft lip/ Palate, moderate or severe hypertelorism • Skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of digits. • Radiologic abnormalities: Bridging of the sella turcica, Rib anomalies (Bifid/splayed), Vertebral anomalies, Flame-shaped lucencies of the hands and feet) • Ovarian fibromas • Ocular abnormalities (cataracts, developmental defects, pigmentary changes of retinal epithelium)

Although an autosomal dominant disorder with a high degree of penetrance is the usual mode of inheritance, BCNS has variable expression making its diagnosis difficult.[2,6] Disease onset and clinical presentation may vary among patients with different races.[3,4]Majority of reported cases involve Caucasians. Its limited epidemiologic data among Asians especially in the Philippines hamper early detection or cause frequent misdiagnosis of the condition.

We present a case of basal cell nevus syndrome in a 56-year old Filipino female with Fitzpatrick skin type V, the approach to diagnosis, its clinical features and management.

CASE REPORT

A 56-year old female sought consult due to a 26-year history of gradually enlarging multiple hyperpigmented, non-pruritic, non-tender and non-friable papules initially on the left cheek and the left ear, patches on the forehead and pedunculated, slightly pruritic papules on the neck and trunk with gradual increased in size and number. The patient manifested a hyperpigmented ulcerated and friable nodule on the left forearm, excised by private physician without a follow up histopathologic exam. The excised nodule recurred two years prior to this consult. She had not undergone immunosuppression, photosensitivity, radiation therapy and persistent ultraviolet light exposure.

The patient had a solitary well defined hyperpigmented ulcerated friable nodule on the left cheek with rolled border and multiple hyperpigmented non-friable, plaques and patches on the forehead and left ear (Fig 1) and multiple hyperpigmented, some pedunculated non-friable papules on the neck and trunk. Palmar pits were also seen (Figure 2). She had coarse facies, mandibular prognathis, broad nasal bridge and ptosis. (Figure 1)

Histopathologic examination of the nodules on the left forearm and left cheek showed nodular and micronodular basal cell carcinoma (BCC) and the hyperpigmented patch from the left lateral forehead showed superficial BCC (Figure 3).

Panoramic radiograph revealed two cystic structures in the mandible (Figure 4). Chest radiograph showed osteosclerosis of the ribs and clavicles with unremarkable cardiopulmonary findings. Plain skull radiography indicated macrocephaly with intracranial calcifications and calcification on the flax cerebri. Craniofacial non-enhanced computed tomography (NECT) scan revealed dense intracranial calcifications along the falx cerebri and tentorium cerebelli, hyperostosis of the

skull and thickened cranium (Figure 5). The sella turcica was deep with sellar bridging (Figure 6). Cerebrocerebellar atrophy with ventricular dilatation was also noted. Chest NECT scan showed bifid first set of ribs (Figure 10). The first set of ribs and the scapulae were at the same level.

Wide excision of all nodular basal cell carcinomas on the left cheek and left forearm was performed. Electrodessication and curettage were done to remove the multiple papules smaller than 1 cm on the neck and trunk. Superficial basal cell carcinomas were treated with 4% 5-flourouracil cream twice daily. The patient was further advised to take oral acitretin 20mg/day for six months. Lipid profile and liver enzyme levels were monitored for the first 2 months and every 2 to 3 months thereafter.

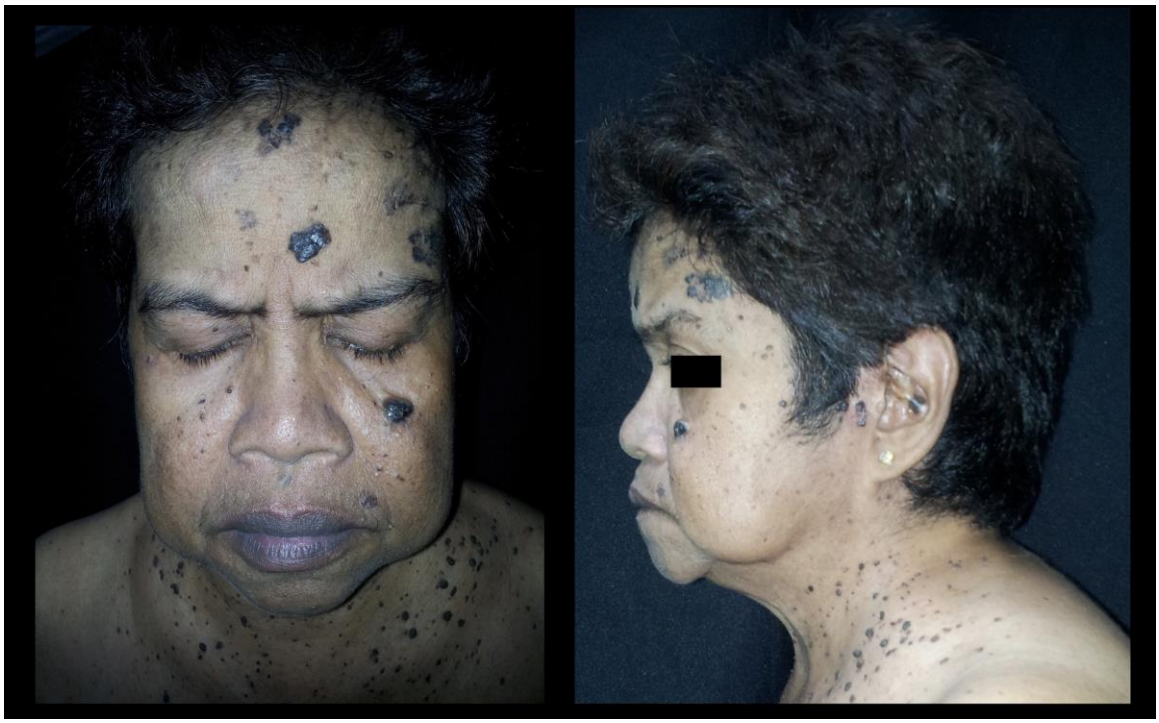

Figure 1. Solitary well defined hyperpigmented ulcerated friable nodule on the left cheek with rolled border and multiple hyperpigmented well-defined and ill- defined non-friable, plaques and patches on the forehead and on the left ear

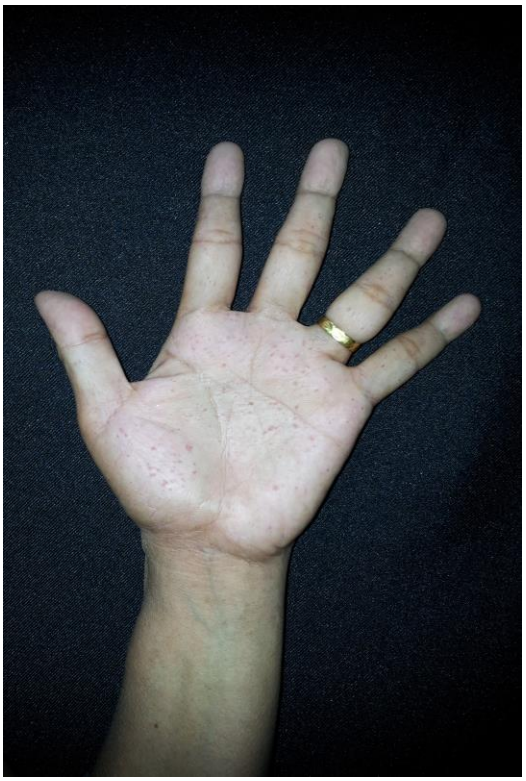

Figure 2. Palmar pits

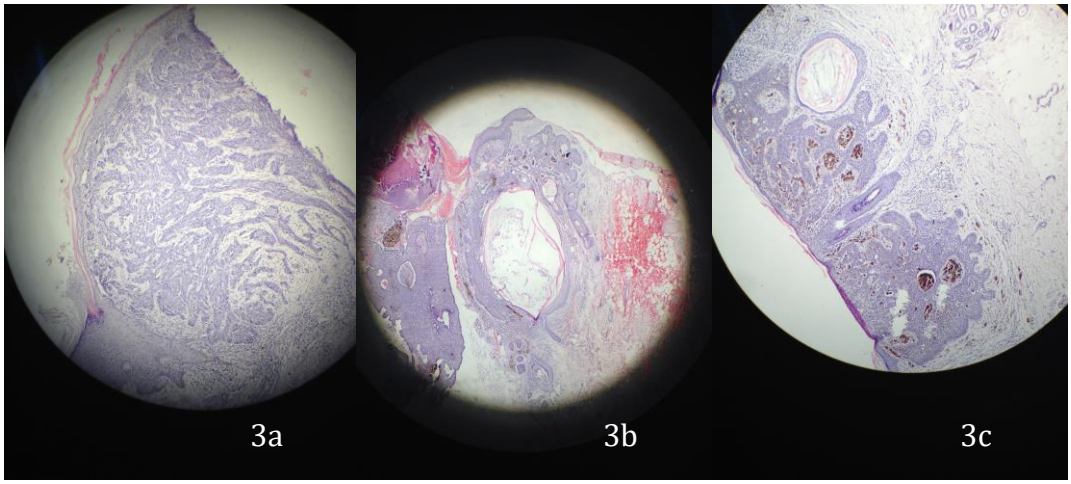

Figure 3. Histopathology of the nodular basal cell carcinoma on the left forearm (a), nodular and micronodular basal cell carcinoma on the left cheek (b)showing large and small aggregates of atypical basaloid cells with peripheral palisading occupying the dermis with mucinous stroma and focal areas of retraction artifact. Histopathology of the superficial basal cell carcinoma on the forehead (c)

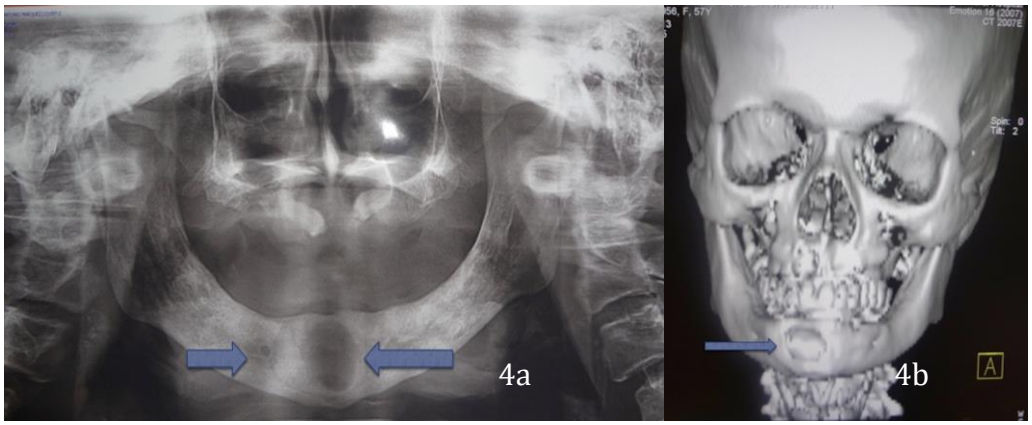

Figure 4. Panoramic radiograph (a) and NECT scan (b) showing two cystic structures in the mandible.

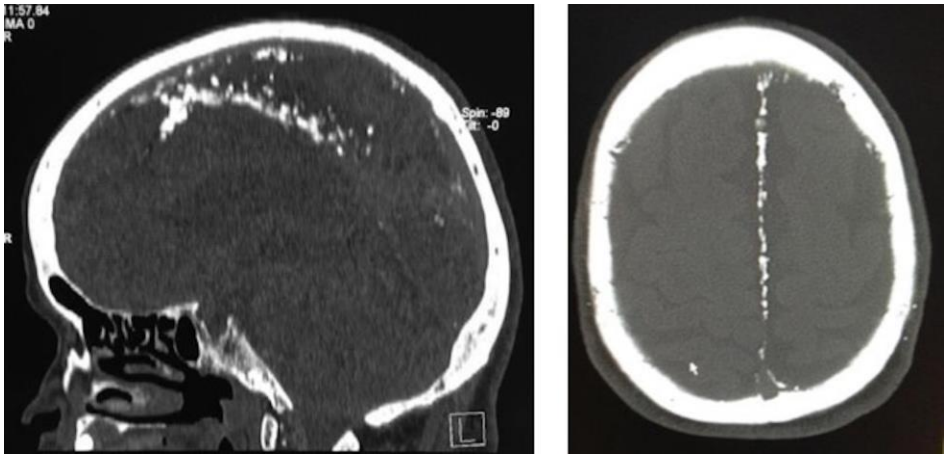

Figure 5. Sagittal and axial views of the bone window of Cranial CT showing dense intracranial calcifications along the falx cerebri and tentorium cerebelli hyperostosis of the skull and thickened cranium.

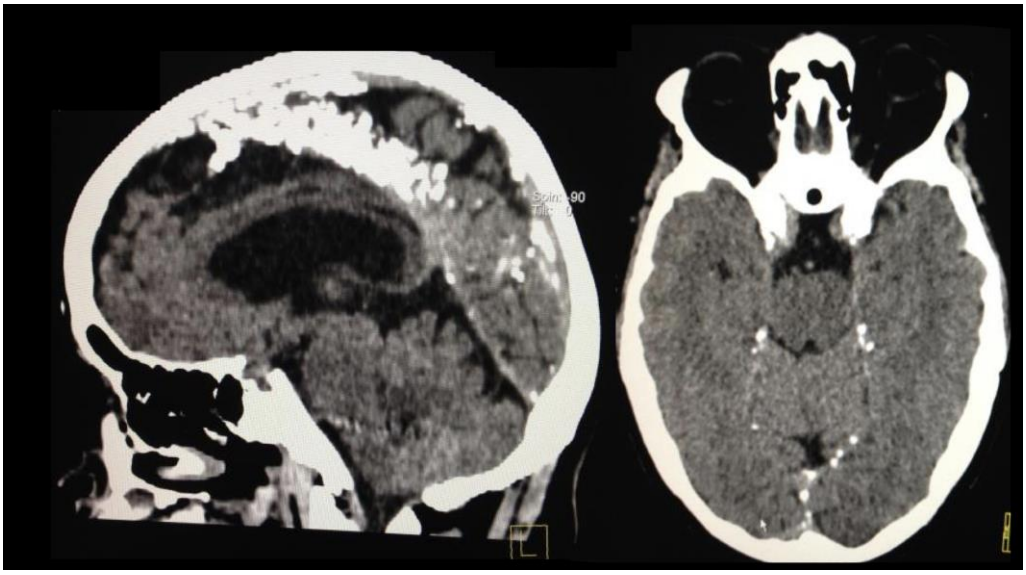

Figure 6. Sella turcica Bridging

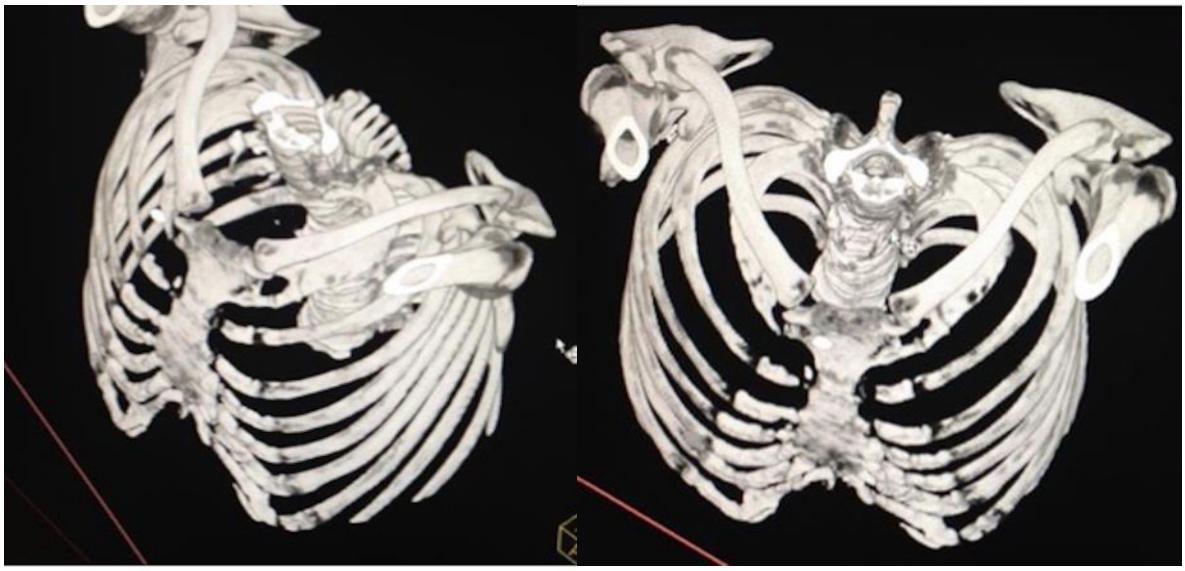

Figure 7. Chest NECT scan with reconstruction showing the bifid first set of ribs and the first set of ribs and the scapulae that are at the same level.

DISCUSSION

It has an estimated prevalence of 1 in 31,000 to 1 in 164,000 without gender predilection. [2, 3] The prevalence of basal cell nevus syndrome in the Philippines is currently unknown. Table 2 shows the reported cases of basal cell nevus syndrome in the country.

The pathogenesis of BCNS involves loss of function mutations of a tumor suppressor gene, PTCH1, located on chromosome 9q22.3. [2,3]The PTCH protein is a part of a complex along a transmembrane protein, Smoothened (SMO). The Hedgehog (HH) protein binds to the PTCH-SMO receptor complex regulating the sonic hedgehog (SHH) signaling pathway. The SHH signaling pathway is a major signal transduction pathway during embryonic development which usually shuts down after birth.Unregulated activity of SHH signaling pathway may lead to tissue overgrowth and tumor induction. Activated HH signaling caused by mutations in the tumor suppressor gene, PTCH, and/or the G-protein coupled receptor SMO promote oncogenic signaling and drives the growth of multiple basal cell carcinomas. [10]

The SUFU gene also encodes a path in the SHH signaling pathway and is found among BCNS patients without PTCH1 gene mutation. SUFU mutations were reported to be associated with milder clinical feature such as lesser BCC lesions and lack of odontogenic keratocysts but an increased risk of developing childhood medulloblastoma. [11]

Although no similar cutaneous lesions were found among the patient's first-degree relatives, she was observed to exhibit the same genetic phenotype as her father presenting with course facial features with hypertelorism. Her father died of lung carcinoma.

Disease manifestations among patients with lighter skin types may differ from the those with darker skin types. Around 70-80% of Caucasians with BCNS manifest multiple BCCs in their early twenties. A 2012 survey conducted among 157 patients with BCNS in Japan revealed a mean age of 37.4 years old.[12]The patient in this case report started to develop multiple BCCs as early as 30 years old.

Approximately 65 percent of affected persons have calcification of the falx cerebri.[3,4] Other areas of ectopic calcification include the diaphragma sellae and tentorium cerebelli which is seen in 60 to 80% and 40% of the cases, respectively.[3, 4] Palmoplantar pits are highly characteristic of BCNS, occurring in 80 percent of diagnosed cases, specifically older individuals. They are asymptomatic nonpalpable shallow depressions, which results from partial or complete absence of stratum corneum.[3] All of these major features manifested in our patient.

Other features present were macrocephaly, which is seen in 27-80% of the cases, ophthalmologic abnormalities (4.5-42%) and bifid ribs (16-26%). A study on the radiological features of 82 BCNS patients in Maryland, USA showed that 24% had dilated ventricles and 10% with cerebral atrophy.[4,5] Both findings were found in the patient.

Surveillance among affected patients includes baseline brain magnetic resonance imaging, dermatologic examination every four months or more frequently if new

lesions continue to multiply and biannual panorex until cyst free for two years. A major concern for patients with BCNS is the development of multiple BCCs, which may become invasive, penetrating underlying structures, especially if located on the face. For non-morpheaform BCCs that are not located on the canthus, nasolabial fold, perioral and post auricular areas, excision or electrodessication with curettage can be done. There is a 95% cure rate if a lesion greater than 2 cm in diameter is excised with 1.2 cm margin and a recurrence rate of 17.6%.[4]With curettage and desiccation (C&D), the highest cure rate (98%) is achieved for lesions less than 1 cm and 84% for lesions greater than 2 cm and is not recommended for large BCCs. Recurrence rate is approximately 40%. [4,5]

Superficial BCCs can be treated with topical medications. Imiquimod 5% cream can cause histologic and clinical clearance rates of 73 to 75% if applied five to seven times a week. 5-fluorouracil 4% cream treatment exhibits a 90% histologic clearance rate after 3 weeks and a 5-year recurrence rate of 21%, whichcan be reduced to 6% if curettage is performed initially. [4,5] Hence, 5-FU was the treatment option for the patient's superficial BCCs.

Other treatment options include cryosurgery, photodynamic therapy and Mohs micrographic surgery, which is superior among all the other treatment modalities with a cure rate of as high as 99% and recurrence rate of 1-5.6%. Radiation therapy can be used as an adjunct when margins are positive after excision or for extensive perineural involvement. [4]

Second generation retinoids like acitretin were found to dramatically reduce the development of premalignant and malignant degeneration of cutaneous lesion. Hence, the patient was advised to take acitretin at a dose of 20mg/day for 6 months.[13]

In general, the prognosis of basal cell nevus syndrome is excellent. Even recurrent BCCs have favorable prognosis. Periodic full body examination should be done to check for new lesions. The patient must be advised that approximately 40-50% of patients with primary carcinoma will develop one or more lesions within 5 years. [4,5]

CONCLUSION

Basal cell nevus syndrome exists among Filipinos. Because of a highly variable penetrance, various phenotypic presentations exist. Since the disease presents differently among dark-skinned individuals, early diagnosis poses a challenge among physicians. Epidemiologic and prevalence studies among Filipinos may be done to aid in the diagnosis and early management of this rare genodermatosis.

Table 2. Reported cases of Basal cell nevus syndrome [7,8,9]

Author/ year	Journal	Gender /age of diagnosis	Fitzpatrick skin type	Major criteria	Minor criteria	Chief complaint	History	Management
Magbuhat et.al. (2017)	Philippine Journal Of Otolaryngology-Head And Neck Surgery	Female/ 46 yo	V	Multiple BCCs Calcification of the falx cerebri Odontogenic keratocyst Multiple palmar pits	Vertebral anomalies (straightened cervical vertebra with spurs and sclerosis on endplates , decreased intervertebral space between C4 and C5)	Necrotic ulcer over the left orbital region	10 years prior a skin-colored, non-pruritic, non-painful papilla-like lesion appeared on her left upper eyelid that eventually became a hyperpigmented plaque and developed non healing ulcer with occasional bleeding and pustular discharge.	Wide excision of the left orbital mass with exenteration, excision of both paranasal masses and the alar mass, left total parotidectomy with facial nerve preservation, enucleation of mandibular cyst, and cervicofacial reconstruction with left orbital split thickness skin graft and left ala full thickness skin graft.
Sabido, et.al. (2013)	Journal of Philippine Dermatological society	Female/11 yo	III	Multiple BCCs before 30 yo Multiple palmar pits	Bilateral ovarian calcification	multiple discrete, skin-colored to speckled brown, pearly papules on the face, clavicular area, and upper back.	The lesions were not present at birth, and appeared a few years prior to consult with out associated pruritus, bleeding and pain	Removal of the lesions using ablative erbium:YAG laser, Imiquimod cream application every other night Photoprotection
Ledesma-Parcia et.al (2009)	Journal of Philippine Dermatological society	Female/67	V	Multiple BCCs Odontogenic keratocyst Multiple palmar pits	*	Multiple bluish black papules, plaques and tumors on the face, trunk and extremities	7 years prior to consult, the lesions started to appear on the face , trunk and anterior thighs which gradually increased in size and bled with trauma.	Excision of the large lesions Electrocautery and imiquimod cream application thrice per week on the smaller lesions Photoprotection Regular follow-up every 3 months

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