Basal cell nevus syndrome in a 48-year-old male

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ABSTRACT

Introduction: Basal cell nevus syndrome is not a common disorder. It has an estimated prevalence of 1 in 57,000-164,000 persons.[1,2] It presents as a spectrum of phenotypic abnormalities that include developmental anomalies and postnatal tumors, particularly basal cell carcinomas. More than 100 clinical abnormalities have been reported in patients with basal cell nevus syndrome. The most typical features include: (1) basal cell carcinomas; (2) palmar and/or plantar pits; and (3) odontogenic cysts of the jaw. Early diagnosis of basal cell nevus syndrome is imperative to prevent developmental delay and increased risk for physical impairment.

Case report: This case involves a 48-year-old Filipino male who showed multiple well-defined hyperpigmented gray-black papules and nodules on the scalp, face, trunk, and back. Pertinent family history revealed three family members with multiple biopsy-proven basal cell carcinomas. On physical examination, the patient was noted to have frontal bossing and multiple palmar and plantar pits. Dermoscopy and skin punch biopsy of multiple sites were consistent with basal cell carcinoma, both superficial and nodular subtypes. Additional work-up included a panoramic x-ray of the jaw, which revealed a solitary odontogenic cyst on the left. A plain cranial MRI was also done, revealing thickened and hypointense falx cerebri suggestive of calcifications.

Conclusion: Based on the presence of multiple biopsy-proven basal cell carcinomas, multiple palmar and plantar pits, and the solitary odontogenic cyst, the patient was diagnosed with basal cell nevus syndrome. Other findings that aid in the diagnosis are the presence of frontal bossing and calcifications of the falx cerebri in the patient.

Key words: basal cell nevus syndrome, Gorlin-Goltz syndrome, basal cell carcinoma

INTRODUCTION

Basal cell nevus syndrome is an inherited multisystem disease associated with a germline inactivating mutation of the PTCH1 (patched) gene.[1,2] Reported cases of basal cell nevus syndrome have shown variable expressivity. Over the years, consensus has been reached requiring at least two major criteria, one major and two minor criteria, or one major criterion and genetic confirmation to make the diagnosis of basal cell nevus syndrome. The major criteria include: (1) multiple basal cell carcinomas, out of proportion to those expected from sun damage, or one in a patient <20 years old; (2) odontogenic keratocysts before age 20 years; (3) palmar and/or plantar pits; (4) lamellar calcification of the falx cerebri; (5) first-degree relative with basal cell nevus syndrome; and (6) medulloblastoma (dermoplastic) in early childhood.[3,4] The minor criteria include a range of skeletal and rib abnormalities, congenital anomalies, and/or ocular, cardiac, ovarian, or neurologic findings.

Here, we present a case of basal cell nevus syndrome in a patient with multiple biopsy-proven basal cell carcinomas, first appearing when the patient was 20 years old. The patient also presented with other common manifestations of basal cell nevus syndrome such as frontal bossing, multiple palmar and plantar pits, a solitary odontogenic cyst, and calcification of the falx cerebri. This case is being reported because the disease is not so common, with only 8 other reported cases from the 11 established Dermatology Residency-training institutions in the Philippines. This report also aims to highlight the diagnostic approach to confirm

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the diagnosis of basal cell nevus syndrome and discuss a treatment approach that balances tumor clearance with minimizing risk for disfigurement secondary to the natural course of the disease.

CASE

This is a case of a 48-year-old Filipino male presenting with multiple well-defined hyperpigmented gray-black papules and nodules on the face, scalp, nape, trunk, and back. History started 28 years prior when the patient noted a solitary hyperpigmented papule on the occipital area without associated symptoms of pain or pruritus. Patient denied any history of trauma or manipulation. No consult was done. During the interim, the patient noted a gradual increase in size of the solitary hyperpigmented papule along with the onset of new and similar lesions on the face, scalp, trunk, and back. Four months prior, the patient sought consult with a dermatologist. Multiple excision biopsies were done revealing basal cell carcinoma, both superficial and nodular subtypes. The patient was then referred to our institution for additional workup and definitive management. Review of systems revealed difficulty chewing, especially on the left, for unrecalled number of years. Past medical history was unremarkable. Family history was positive for three family members (mother and two sisters) with multiple biopsy-proven basal cell carcinomas (Figure 1). The patient is a nonsmoker, nonalcoholic beverage drinker, and previously worked as a tricycle driver with reported frequent sun exposure since 2004.

On dermatologic examination, there were multiple well-defined hyperpigmented gray-black papules and nodules on the face (Figures 2A and 2B), scalp (Figure 2C), trunk (Figure 2D), and back (Figure 2E). The patient was also noted to have frontal bossing and multiple palmar and plantar pits (Figure 3).

Dermoscopy of most lesions revealed presence of blue-gray ovoid nests, blue globules, and leaf-life areas, consistent with basal cell carcinoma as shown in Figure 4B. Dermoscopy of the ulcerated lesion on the scalp revealed blue-gray ovoid nests with multiple arborizing vessels (Figure 5B). Dermoscopy of the more superficial lesions revealed white leaf-like structures (Figure 6B) and multiple gray-brown globules and dots (Figure 7B). Histopathology of multiple sites was consistent with basal cell carcinoma, including both nodular (Figure 8) and superficial subtypes.

Additional work-up included a panoramic x-ray of the jaw (Figure 9), which revealed a solitary odontogenic cyst on the left and a plain cranial MRI (Figure 10), which revealed thickened and hypointense falx cerebri suggestive of calcifications. Karyotyping was normal 46 X, Y (Figure 11).

Based on the presence of multiple biopsy-proven basal cell carcinomas, multiple palmar and plantar pits, and the solitary odontogenic cyst, the patient was diagnosed with basal cell nevus syndrome. Other findings that aid in the diagnosis are the presence of frontal bossing and calcifications of the falx cerebri, both present in the patient.

Once the diagnosis was made, the patient was followed-up every month at the Dermatology out-patient clinic for the first six months while awaiting his schedule for Mohs Micrographic Surgery. During this time, he underwent excision of the classified low-risk tumors (i.e. those located on the trunk and back) at another institution. The patient was referred to Otorhinolaryngology - Head and Neck Surgery service where he underwent excision of the odontogenic cyst. The patient was also referred to Neurology service who cleared him of any neurologic disorder.

DISCUSSION

Basal cell nevus syndrome, also known as Gorlin-Goltz syndrome or nevoid basal cell carcinoma, is an uncommon multisystem autosomal dominant disorder with a germline mutation in the PTCH1 gene.[1,2] In spite of this condition's variable expressivity, a review of patients diagnosed with basal cell nevus syndrome revealed a classic triad of: (1) basal cell carcinomas; (2) pits of the palms and soles; and (3) cysts of the jaw.5 While genetics play a crucial role in the development of basal cell nevus syndrome, environmental exposure especially to UV radiation has also been identified to be contributory, as found in sporadic cases.

Most of the time, the diagnosis of basal cell nevus syndrome is suspected in patients with multiple hyperpigmented lesions, commonly mistaken as nevi, both in sun-exposed and non-exposed areas of the body. A high index of suspicion is necessary in order to prompt the clinician to request additional workup in order to fulfill the criteria to make the diagnosis of basal cell nevus syndrome. The patient fulfilled four major criteria involving the presence of: (1) multiple basal cell carcinomas; (2) odontogenic keratocyst with associated difficulty chewing; (3) multiple palmar and plantar pits; and (4) calcification of the falx cerebri, as seen on plain cranial MRI. In addition, the patient

fulfilled one minor criterion given his coarse facial features and presence of frontal bossing, suggestive of skeletal abnormalities consistent with the syndrome. Although the patient had a strong family history of multiple basal cell carcinomas in three first-degree relatives, the diagnosis of basal cell nevus syndrome in them could not be confirmed due to inadequate workup that would determine if they fulfill the criteria.

Among patients with basal cell nevus syndrome, the number of basal cell carcinomas may vary from several to hundreds. A total body skin examination of the patient revealed nearly 60 hyperpigmented lesions. The basal cell carcinomas typically develop in adolescence with a median age of onset of 20 years6, which is consistent with the patient. Clinically and dermoscopically, basal cell carcinomas cannot be distinguished from sporadic basal cell carcinomas. However, dermoscopic findings do vary based on histopathologic subtype. A retrospective study by Trigoni et al. of 138 basal cell carcinomas revealed dermoscopic findings more consistent with early-stage and/or superficial subtypes such as white-red structureless areas (90%), hypopigmented areas (64%), arborizing telangiectasia, blue-grey ovoid nests (50%) while features more consistent with nodular subtypes include featureless areas (94%), atypical red vessels (78%), and arborizing vessels (69%).[8,9] The utility of dermoscopy is that it aids in the identification of early nevoid basal cell lesions. Furthermore, the additional value of specific dermoscopic findings that differentiate early and/or superficial basal cell carcinomas is that it provides the opportunity of enabling tumor clearance with less invasive treatment modalities. Similarly, the histological features resemble those seen in sporadic basal cell carcinomas with findings including islands or nests of basaloid cells with peripheral palisading, surrounded by a fibromyxoid stroma with clefts at the stromal-tumor interface.10,11

In addition to basal cell carcinomas, another cutaneous finding characteristic of basal cell nevus syndrome, seen in nearly 80% of patients, is the presence of palmar and/or plantar pits.12 These asymptomatic small defects in the stratum corneum are postulated to be due to aborted attempts to generate hair follicles in the palms.12 Dermoscopic findings of the pits show red globules distributed in parallel lines inside flesh-colored, irregularly shaped, and slightly depressed lesions. Dermoscopy can aid in the identification of subclinical pits, which are otherwise not appreciated clinically.

The difficulty in making the diagnosis of basal cell nevus syndrome lies in the fact that basal cell carcinomas in patients with basal cell nevus syndrome cannot be distinguished from those in sporadic cases. Although the patient's manifestation was predominantly cutaneous, its sheer number should have prompted a clinician to suspect an underlying syndrome or genodermatoses. It is important that correct and timely diagnosis of basal cell nevus syndrome be done in order to catch possible extracutaneous involvement. Extracutaneous involvement may include developmental anomalies (i.e. cleft lip and palate), ectopic calcifications (most commonly in the falx cerebri), jaw cysts, skeletal abnormalities (i.e. frontal bossing, bifid ribs), ocular defects (i.e. cataracts, glaucoma), a myriad of benign tumors (e.g. cardiac or ovarian fibromas, meningiomas), and brain tumors (i.e. medulloblastoma).13,14 The host of possible systemic involvement in basal cell nevus syndrome, thus, warrants extensive additional workup including but not limited to magnetic resonance imaging of the brain and/or skull x-rays, panoramic x-rays of the jaw, and pelvic ultrasound in women.

The management of patients with basal cell nevus syndrome can be approached with 4 general principles,15 the mnemonic **BCNS** is proposed here for easy recall:

(1) **B**e aware of individual lesions as they arise;

(2) **C**ontinuous or frequent examination;

(3) a**N**ticipation and early treatment of small tumors;

(4) **S**un avoidance.

Targeted therapy of individual lesions is the ideal approach in the management of basal cell carcinomas. However, in basal cell nevus syndrome, by virtue of the sheer number of tumors and involvement of a potentially large surface area, the risk of physical disfigurement with targeted therapy may be neither ideal nor feasible. Dermoscopy in the identification of clinically undetectable tumors, but with features highly indicative of basal cell carcinoma, proves to be useful in the diagnosis of early and/or superficial basal cell carcinomas without histopathologic confirmation. Hence, it is proposed that dermoscopy-guided diagnosis and treatment be maximized for patients with basal cell nevus syndrome. The proposed algorithm by John and Schwartz (Figure 12) with various treatment modalities can be utilized to achieve tumor clearance and maximize patient outcomes with preservation of function, anatomical structures, and cosmesis.16

Routine follow-up among patients with basal cell nevus syndrome include: (1) dermatologic exam every

2-3 months (or more frequently if with new lesions) and a panoramic x-ray of the jaw is advised twice yearly until cyst free for 2 years; then yearly, given the high association of jaw cysts. Echocardiography is advised periodically, given the risk of development of cardiac fibroma.

Overall, basal cell nevus syndrome proves to be a challenging condition to treat given the need for frequent surveillance by a dermatologist to facilitate early diagnosis of new basal cell carcinomas.

CONCLUSION

Basal cell nevus syndrome is an important consideration when faced with a patient with multiple basal cell carcinomas. A high index of suspicion is key to prompt diagnosis. Aside from multiple skin punch biopsies, additional work-up for extra-cutaneous involvement (odontogenic, ovarian, or neurologic involvement) is necessary to clinch the diagnosis. Once confirmed, each basal cell carcinoma should be treated individually utilizing different treatment options that would primarily achieve tumor clearance followed by the preservation of function, anatomical structures, and cosmesis.

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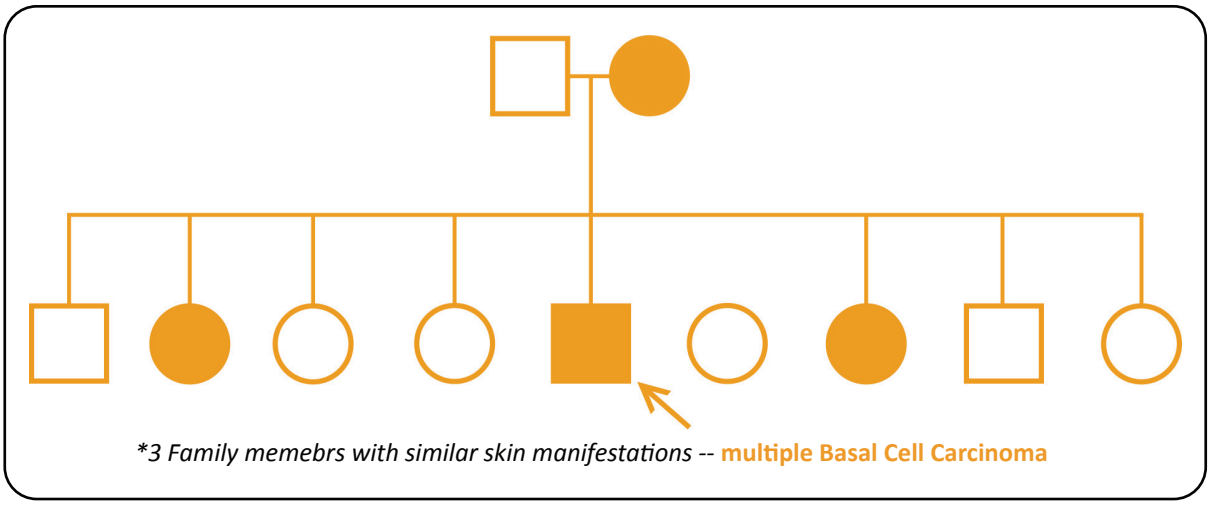

Figure 1. Pedigree chart

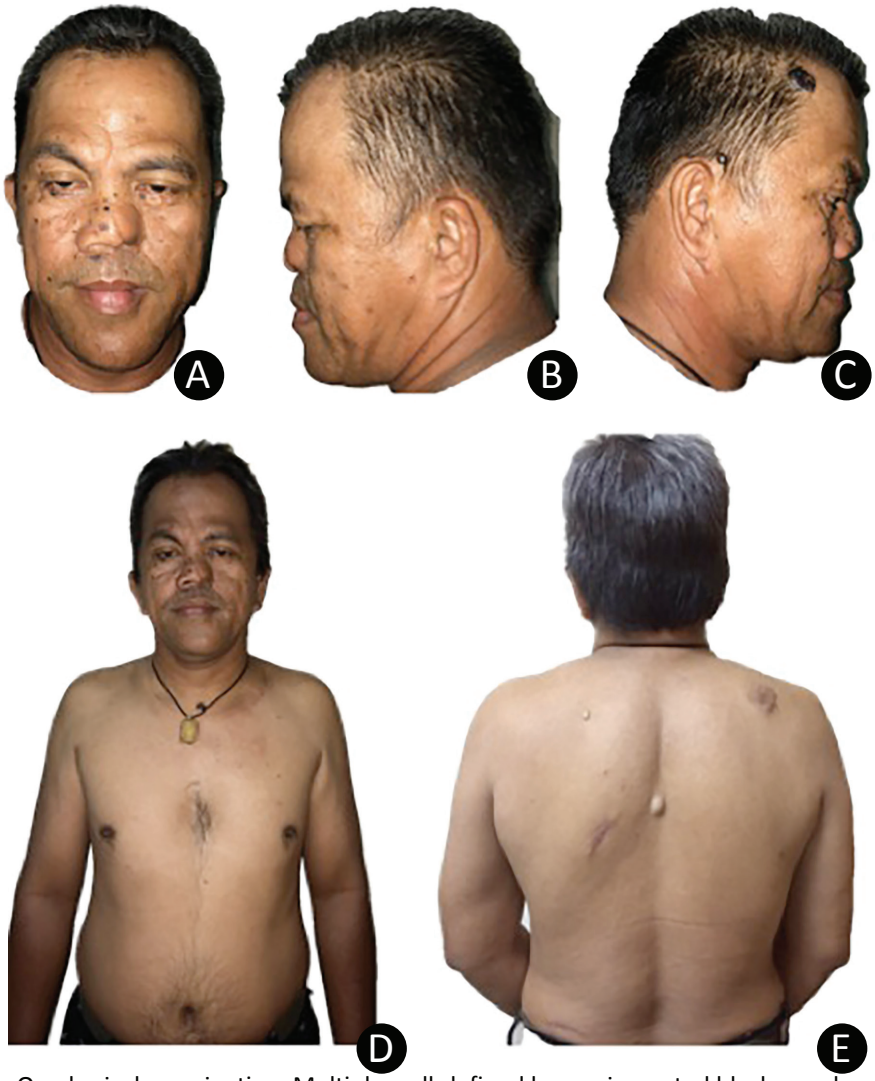

Figure 2 A-E. On physical examination. Multiple well-defined hyperpigmented black papules and nodules on the face, scalp, nape, trunk, and back.

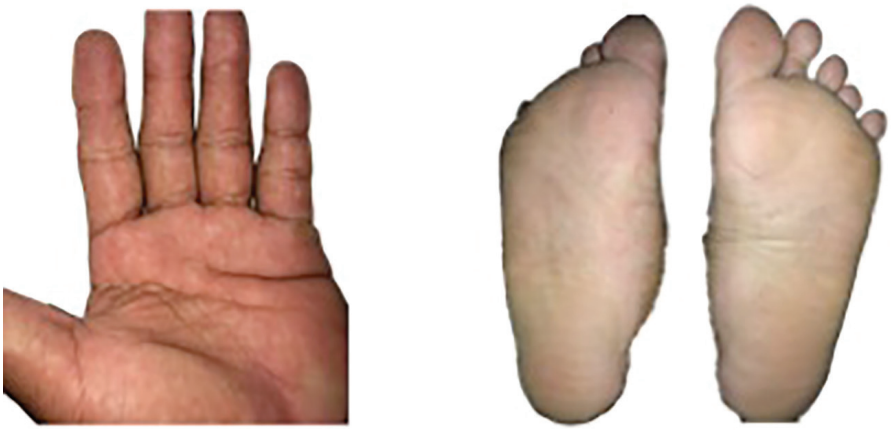

Figure 3. Palmar and plantar pits. Multiple well-defined some erythematous, some skin-colored depressed pits on bilateral palms and soles

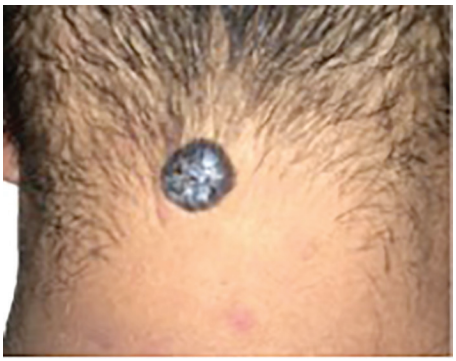

Figure 4A. Clinical image of the nape of the patient with Basal cell nevus syndrome

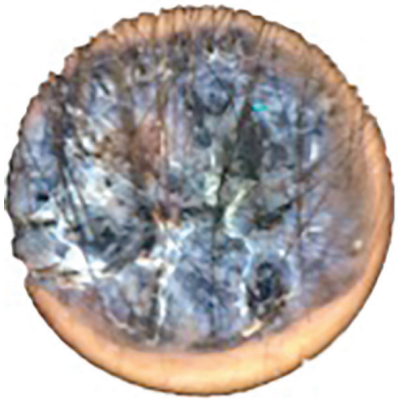

Figure 4B. Dermoscopic image of same lesion revealing blue gray ovoid nests, blue globules, and leaf-life areas.

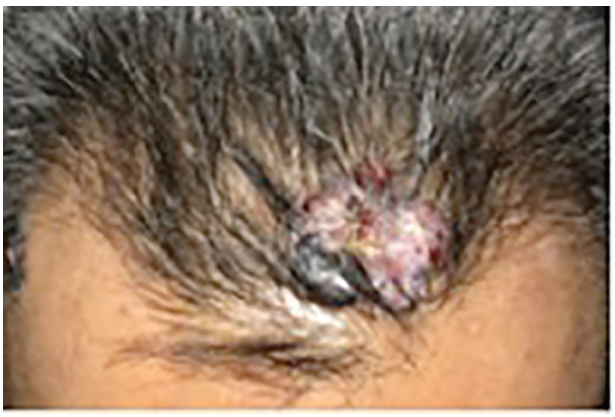

Figure 5A. Clinical image of the ulcerated lesion on the scalp

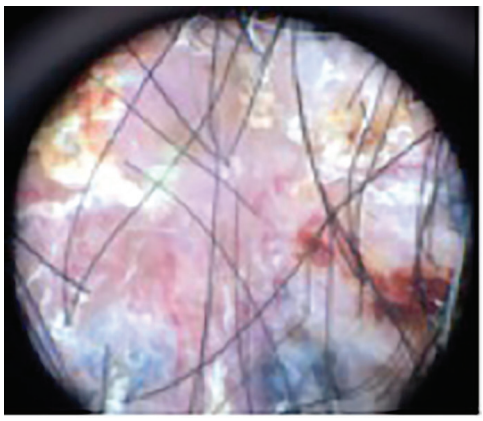

Figure 5B. Dermoscopic image of same lesion revealing blue gray ovoid nests with multiple arborizing vessels

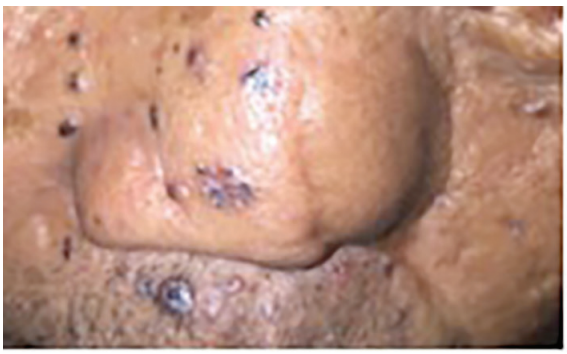

Figure 6A. Clinical image of a superficial lesion on the nose

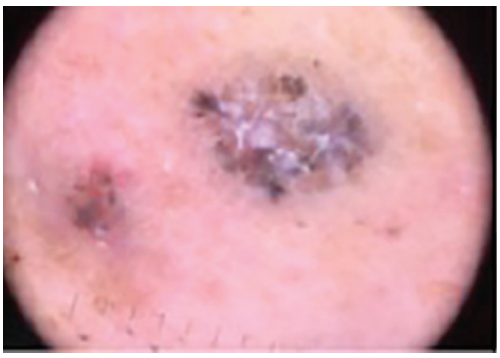

Figure 6B. Dermoscopic image of same lesion revealing white leaf-like areas

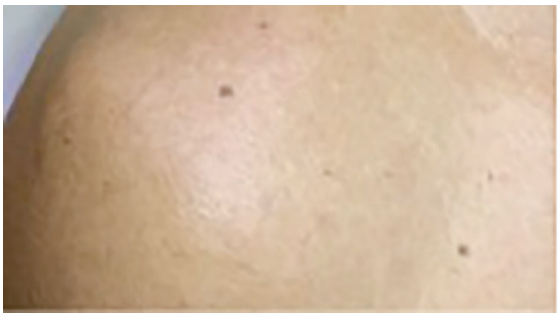

Figure 7A. Clinical image of a brown macule on the right shoulder

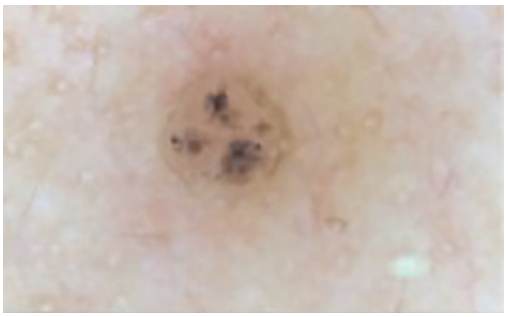

Figure 7B. Dermoscopic image of same lesion revealing multiple gray-brown globules and dots

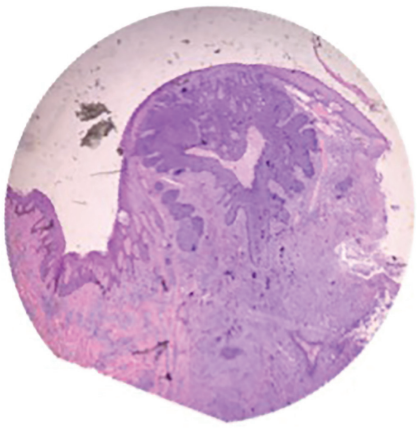

Figure 8. Sections show basketweave orthokeratosis with small nodules of basaloid cells in the dermis with clefting and mucinous stroma.

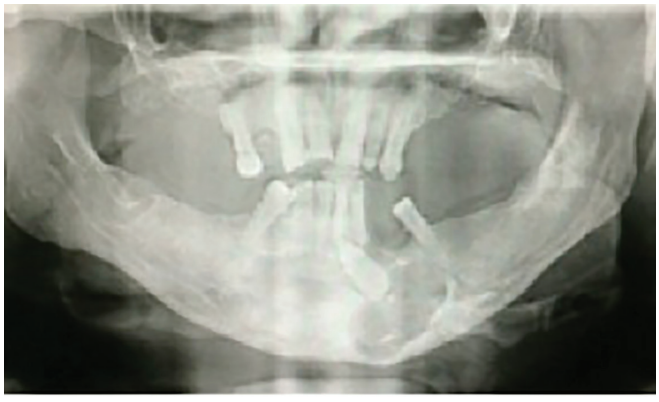

Figure 9. Panoramic x-ray of the jaw revealing a solitary well-defined mass with cystic and solid components consistent with an odontogenic cyst

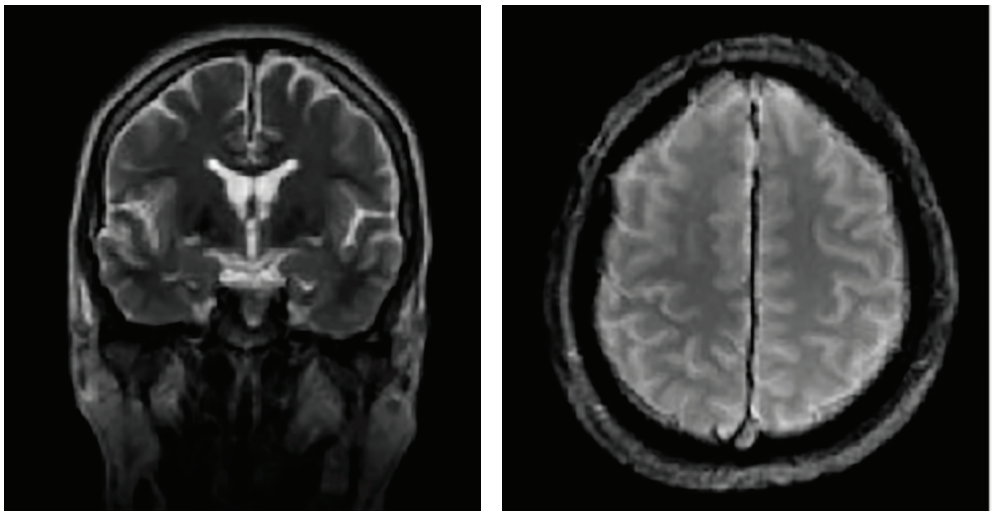

Figure 10. Plain cranial magnetic resonance imaging (MRI) with thickend and hypointense falx cerebri, indicative of calcification

Figure 11. Normal male karyotype 46 X,Y

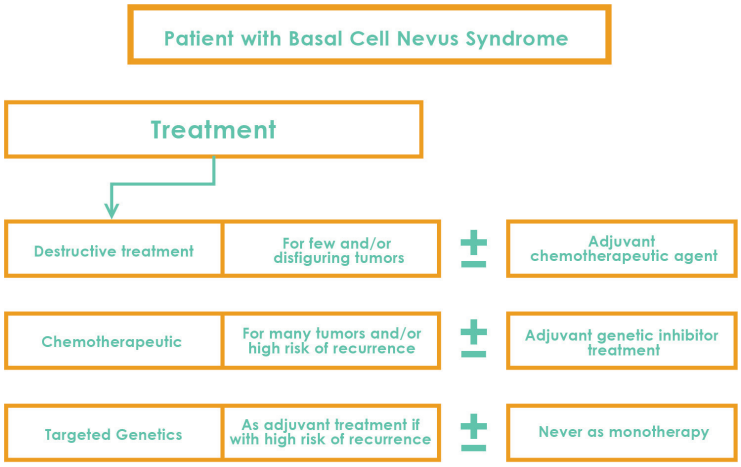

Figure 12. Treatment approach for patients with Basal cell nevus syndrome