Gorlin Syndrome in a 48-year-old Filipino Woman: A Case Report*

April Janel R. Geraldez, MD[1]
Daisy King-Ismael, MD, FPDS[2]

ABSTRACT

INTRODUCTION: Gorlin syndrome is a rare autosomal dominant disorder characterized by a wide range of developmental abnormalities and a predisposition to neoplasms. The estimated prevalence is 1/57,000[1] to 1/256,000[2]. Main clinical manifestations include multiple basal cell carcinomas, odontogenic keratocysts, skeletal abnormalities, ovarian fibromas and other disorders.

CASE: A 48 year old woman presented with multiple brown-black to skin-colored pearly macules, papules and nodules over the scalp, face, neck, trunk, upper and lower extremities. Histological examination at 2 sites revealed basal cell carcinoma. This was accompanied by findings of odontogenic keratocysts, palmar pits, posterior falx calcification, exotropia and multiple myoma uteri. Electrodessication with curettage of superficial basal cell carcinomas (< 1 cm.) was combined with wide excision of nodular basal cell carcinomas on the left temporal area (followed by rotational scalp flap reconstruction), right lateral breast, left inframammary area, right and left anterior thigh.

CONCLUSION: Gorlin syndrome is a hereditary condition affecting various organ systems. Management requires a multidisciplinary approach and regular medical surveillance is required.

**From the University of Sto. Tomas Hospital Department of Dermatology*
[1] Resident Graduate, University of Sto. Tomas Hospital Department of Dermatology
[2] Consultant, University of Sto. Tomas Hospital Department of Dermatology

INTRODUCTION

Gorlin syndrome, also known as Gorlin-Goltz syndrome, nevoid basal cell carcinoma syndrome (NBCCS) and basal cell nevus syndrome (BCNS), is a rare autosomal dominant condition with complete penetrance and variable expressibility. This syndrome is characterized by multiple basal cell carcinomas (BCCs), odontogenic keratocysts, palmar or plantar pits, ectopic calcification including calcification of the falx cerebri, skeletal abnormalities and neoplasms.

This disorder was found to arise from mutations in the tumor suppressor PTCH1 gene. Although commonly inherited, it may also arise de novo. The estimated prevalence is estimated at 1/57,000[1] to 1/256,000[2]. Although it may affect any ethnic group, most documented cases are Caucasians.[2,3] In the Philippines there have only been two cases reported. [4,5]

Diagnosis is based on the spectrum of clinical findings. The objective of the present study is to report a case of a 48-year-old Filipino woman with clinical findings consistent with Gorlin Syndrome.

CASE REPORT

A 48-year-old Filipino woman from Laguna presented with multiple brown to black and skin-colored pearly macules, papules, plaques and nodules on the scalp, face, neck, trunk and extremities that were noted to increase in number in size in the past 12 years. This was accompanied by intermittent pruritus and bleeding upon manipulation.

Review of systems revealed prolonged and excessive menstrual bleeding with intermittent tooth pain. There was no weight loss, anorexia, jaw swelling, bleeding gums or seizures. Patient has a history of prolonged sun exposure for 7 years working as a door-to-door saleslady. No similar lesions were noted in other family members.

Physical examination revealed exotropia (FIGURE 1). No teeth abnormalities, jaw masses and skeletal deformities were noted. Examination of the skin revealed brown to black and skin-colored pearly macules, papules, plaques and nodules measuring 0.2 x 0.2 cm to 1.5cm x 1.5cm on the scalp, face, neck, trunk, back, upper and lower extremities (FIGURES 2-5). Numerous tiny pits were noted on both palms (FIGURE 6). No plantar pits were observed.

On dermoscopy of lesions, arborizing telangiectasias and blue-grey ovoid nests were noted.

A 3-mm skin punch biopsy was done at two (2) sites: a macule on the sternal area (FIGURE 7-A, 7-B), and a nodule on the left temporal region (FIGURE 8-A, 8-B). Histopathology of both specimens showed islands of basaloid cells containing dense melanin pigments, some showing hyperchromatic nuclei. The specimens were signed out as superficial BCC and nodular BCC, respectively.

Transvaginal ultrasound revealed multiple uterine myomas (FIGURE 9). Digital panorex x-ray done revealed the presence of odontogenic keratocysts (FIGURE 10). Cranial MRI revealed posterior falx calcification (FIGURE 11). Investigative findings were consistent with our clinical diagnosis of Gorlin syndrome.

The patient was admitted for removal of all skin lesions. Patient underwent electrodessication and curettage of superficial basal cell carcinomas measuring less than 1 cm on the scalp, face, chest, trunk and extremities with wide excision of multiple basal cell carcinomas on the right lateral breast, left infra-mammary area, right and left anterior thigh and left temporal area followed by rotational scalp flap reconstruction.

On follow-up after 1 week, lesions were noted to be healing well. At 3 and 6 months, no new lesions or recurrence of lesions were noted.

DISCUSSION

Gorlin syndrome is a rare autosomal dominant condition with complete penetrance and variable expressibility. Although commonly inherited, 35-50% of cases represent de novo mutations.[6] In 1960, Gorlin and Goltz defined a condition comprising a triad of multiple basal cell nevi, keratocysts of the jaw and bifid ribs characterizing the this syndrome.[7] The estimated prevalence is estimated at 1/57,000[1] to 1/256,000[2]. There is no sexual and racial predilection.[8,9]

The mutation in Gorlin syndrome involves the PTCH gene located on chromosome 9q22.3[1] that acts as a tumor suppressor in the hedgehog signaling pathway which regulates the production of growth promoting transcription factors.[10]

This syndrome is characterized by multiple basal cell carcinomas, odontogenic keratocysts, palmar or plantar pits, ectopic calcification including calcification of the falx cerebri, skeletal abnormalities and neoplasms such as uterine fibromas. Anomalies in Gorlin syndrome are summarized in Table 1.[3] Diagnostic criteria are summarized in Table 2.[8,9]

Table 1. Anomalies in nevoid basal cell carcinoma syndrome[3]

Skeletal anomalies	palatine ridges
Bifid ribs	Odontogenic keratocysts
Splayed/fused ribs	Malocclusion(s) (maxillary hypoplasia
Cervical ribs	and
Absent/rudimentary ribs	mandibular hyperplasia, cleft palate)
Scoliosis	Dental ectopic position
Hemivertebrae	Impacted teeth and/or agenesis
Flame-shaped lucencies hand/feet	
Polydactyly	*Skin anomalies*
Syndactyly	Basal Cell Carcinoma
Shortened 4th metacarpal	Palmar and/or plantar pits
Craniofacial anomalies	*Sexual anomalies*
Frontal bossing	Uterine and ovarian fibromas
Brachycephaly	Calcified ovarian cysts
Macrocephaly	Supernumerary nipple
'Coarse face'	Hypogonadism and cryptorchidism
Calcification of falces	
Tentorium cerebellum calcification	
Bridged sella turcica	*Ophthalmic anomalies*
	Congenital amaurosis
Neurological anomalies	Exotropia
Agenesis/disgenesis of corpus callosum	Hypertelorism
Congenital hydrocephalus	Ptosis
Mental retardation	Internal strabismus
Medulloblastoma	Glaucoma
Meningioma	Coloboma
Schizoid personality	Blindness
Oropharyngeal anomalies	*Cardiac anomalies*
Cleft lip and/or palate	Cardiac fibroma
High-arched palate or prominent	

Table 2. The diagnostic criteria of nevoid basal cell carcinoma syndrome[8,9]

The diagnosis of NBCCS requires the presence of two major, or one major and two minor criteria:

Major criteria:

1. Multiple (>2) basal cell carcinomas (BCC) or one BCC < age of 20 years
2. Histologically-proven odontogenic keratocysts of the jaw
3. Three or more palmar or plantar pits
4. Bilamellar calcification of the falx cerebri
5. Bifid, fused or markedly splayed ribs
6. First degree relative with NBCCS
7. PTC gene mutation

Minor criteria:

1. Proven macrocephaly, after adjustment for height
2. One of several orofacial congenital malformations: cleft lip or palate, frontal bossing, 'coarse face', moderate or severe hypertelorism
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modelling defects of the hands and feet, or flame shaped lucencies or the hands or feet
5. Ovarian fibroma
6. Medulloblastoma

The presence of multiple basal cell carcinomas, odontogenic keratocysts, palmar pits and calcification of falx cerebri in association with exotropia and uterine myomas described in the case presented earlier fulfilled the diagnostic criteria of Gorlin syndrome.

The most frequent skin manifestation of Gorlin syndrome are multiple basal cell carcinomas (BCCs). BCCs are seen more frequently in Caucasians compared to African Americans which probably reflect the protective action of melanin from UV light.[9] It has been demonstrated that UV radiation increased BCC development in mice with PTCH gene mutation.[10] This finding is especially important as early avoidance and sun protection can prevent the appearance of basal cell carcinomas in patients with this syndrome. Lesions usually appear between puberty and 35 years of age, ranging in number from one to thousands and principally affecting the epithelium of the chest and cervicofacial regions.[11] Most are located superficially in the epidermis for years before they begin invading the dermis. Signs of local invasion and

evidence of aggressiveness include increase in size and the development of ulceration, bleeding, and crusting.[3] Aside from chest and cervicofacial areas, patient also had multiple lesions involving the lower back and both upper and lower extremities.

Histopathology of nevoid BCC cannot be differentiated from sporadic BCC and about 30% of patients would present with two or more types of BCC patterns (superficial, morphea-like, solid, cystic, adenoid fibroepithelial).[12] In our patient, histopathology done at two sites revealed findings consistent with basal cell carcinoma. Intraoperative tissue sections revealed scalp nodule to be a mixed nodular and adenoid cystic type while lesions on the body were of the superficial type.

Odontogenic keratocysts (OKCs), which form from cells of the dental lamina, occur in 75% or the cases.[3] OKCs have a very aggressive nature. In patients with Gorlin syndrome, there is continued development of new and recurring cysts until the age of 30 after which it tends to decrease.[13] Most are asymptomatic but can manifest as jaw swelling, toothache or impacted teeth when enlarged. Most common sites are the mandible in the molar-ramus region (44%) followed by the incisor-canine (15%) and molar tuberosity (13%) regions.[13] Our patient presented with intermittent tooth pain. Digital panorex of the jaw revealed presence of odontogenic keratocysts. Patient was advised surgery, however, patient decided to defer the procedure to a later date due to financial constraints.

Palmar and plantar pits appear in 87% of patients with Gorlin syndrome.[9] They are asymptomatic, increase in number with age and are more commonly found on the palms (77%) than the soles (50%).[14] This may explain why our patient had palmar pits in the absence of plantar lesions.

Falx calcification is the most frequent radiologic sign of Gorlin syndrome, appearing in 37-80%[3]. Although usually asymptomatic, this may be of value in confirming the diagnosis.

Ovarian cysts and fibromas are found in 25-50% of affected women and are usually bilateral.[13] Pathologies in the ovary and uterus other than ovarian fibromas have also been documented in patients with Gorlin syndrome.[9] The ultrasonographic findings of multiple uterine myomas/ fibroids in our patient may also be attributed to the defect in tumor suppressor activity in patients with this syndrome. No ovarian abnormality was noted in our patient.

Patients affected with Gorlin syndrome must be evaluated and managed by a multidisciplinary team. Children and siblings must be clinically evaluated for evidence of the syndrome. The approach to adult patients with suspected or known Gorlin syndrome are as follows: Baseline cranial MRI and digital panorex of the jaw, dermatological examination every 4 months and prenatal counseling.[9] Management depends on the specific abnormalities present. Our patient was advised total abdominal hysterectomy and bilateral salpingo-oophorectomy to address symptomatic uterine fibroids and surgical removal of odontogenic keratocysts but patient decided to defer both procedures due to financial constraints.

There are no existing guidelines for the treatment of BCCs in patients with Gorlin syndrome. Frequent examination, counseling about avoidance of sun exposure and removal of small tumors are of particular importance. The type, location, size and aggressiveness of the lesions need to be assessed. The treatment recommendations must ideally have high cure rates, maximum preservation of surrounding tissue, acceptable cosmetic result and short healing time with minimal side effects.

Standard surgical excision with wide margins is a highly effective and common treatment option for BCCs. The 5–year cure rate is more than 99%.[15] Curettage with or without electrodessication is also widely used in the management of low –risk, non-aggressive, superficial BCCs- the type commonly seen in patients with Gorlin syndrome.[16] Cure rates of 95% or higher are possible for well-defined primary lesions.[17]

Non-invasive treatment methods include 5-FU, imiquimod and photodynamic therapy. 5-Fluorouracil 5% cream may be used for small, superficial BCCs in low-risk areas. It interferes with DNA synthesis by inhibiting thymidylate synthetase and inhibits cell proliferation. Cure rates of 91% were achieved after 3-4 weeks of treatment. Imiquimod 5%

cream, an immune response modifier, has been approved for the treatment of non-facial superficial BCC. Histologic clearance rates of 82% were achieved after 5 day application per week for 6 weeks.[19] Photodynamic therapy involves application of a tumor-localizing photosensitizing agent and light to cause selective destruction of malignant tissue. Local control rates of 56.3% at 12 months have been achieved.[20]

Patient underwent electrodessication and curettage of multiple superficial basal cell carcinomas measuring less than 1 cm on the scalp, face, chest, trunk and extremities with wide excision of multiple basal cell carcinomas on the right lateral breast, left infra-mammary area, right and left anterior thigh and left temporal area followed by rotational scalp flap reconstruction. Choice of treatment was based on the superior cure rates and cost-effectiveness compared to the other modalities.

Prognosis depends on the malignant progression of the patient's lesions. Lifetime monitoring is warranted to identify appearance of new and recurrent lesions. However, life expectancy as found to be no different from that of the general population.[2]

SUMMARY

We present a case of a 48-year-old woman with multiple skin-colored and pigmented macules, papules and nodules over the scalp, face, neck, trunk, upper and lower extremities that were histologically confirmed to be basal cell carcinomas. Additional findings were odontogenic keratocysts on digital panorex xray, palmar pits, exotropia, posterior falx calcification on cranial MRI and multiple uterine myomas on ultrasound. The spectrum of findings is consistent with Gorlin syndrome. Electrodessication with curretage of superficial basal cell carcinomas were combined with wide excision of nodules and plaques. In patients with Gorlin syndrome, a multidisciplinary approach involving experts from different specialties is important to appropriately evaluate and manage the different manifestations of the disease. As lesions can be recurrent, regular follow-up and medical surveillance is required. As each child has a 50% chance of inheriting this condition, genetic counseling is also mandatory.[5]

REFERENCES

1. Farndon PA, Del Maestro RG, Evans DG, Kilpatrick MW: Location of gene for Gorlin Syndrome. Lancet 1992, 339:581-582.

2. Lo Muzio L, Nocini PF, Savoia A, Consolo U, Procaccini M, Zelante L, et al. Nevoid basal cell carcinoma syndrome. Clinical findings in 37 Italian affected individuals. Clin Genet 1999;55:34 –40.

3. M. Manfredi, P. Vescovi, M. Bonanini, S. Porter: Nevoid basal cell carcinoma syndrome: a review of the literature. Int. J. Oral Maxillofac. Surg. 2004; 33: 117–124.

4. Sabido, W, Jamora MJ, Encarnacion L. Multiple basal cell carcinomas in an 11-year-old Filipino-American girl with basal cell nevus syndrome. J Phil Derm Society 2013 May; 22 (2):44-47

5. Ledesma-Pacia AG, King-Ismael D, Reyes-Cacas TM, Tan ED. Basal cell carcinoma arising from a palmar pit in a Filipino with nevoid basal cell carcinoma syndrome. J Phil Derm Society 2009 Nov; 18 (2):27-31.

6. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Dermatol Clin 1995: 13: 113– 125.

7. Gorlin RJ, Goltz RW: Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 1960; 262:908e12

8. Evans DG Farndon PA, Burnell LD, Gattamaneni HR, Birch JM. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer 1991: 64: 959–961.

9. Kimonis, VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997: 69: 299–308.

10. Smith V ,Walton S. treatment of facial basal cell carcinoma: A review. Journal of skin cancer. 2011:1-7.

11. Hilgert R, Fonseca LA, Felipe FF. Gorlin's Syndrome: report of family involve- ment. Revista de Cirurgia e Traumatologia Buco-maxilo-facial Camaragibe 2010;10:39–44.

12. Gorlin RJ: Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med 2004, 6:530-539.

13. Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis 2008;3:32.

14. Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine (Baltimore) 1987;66:98–113.

15. Rubin A, Chen E, Ratner D. Basal Cell Carcinoma. N Engl J Med 2005, 353:2262-2269.

16. Mitropoulos P, Norman R. Nevoid Basal Cell Carcinoma (Gorlin Syndrome): Updated review of minimally invasive treatments. Cutis. 2008; 81:53-60.

17. Silverman MK, Koff AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basalmcell carcinoma: Curettage and Electrodessication. J Dermatol Surg Oncol 1991: 17:720-726.

18. Miller BH, Shavin JS, Cognetta A, Taylor RJ, Salashe S, Korey A et al. Nonsurgical treatment of basal cell carcinoma with intralesional 5-Flurouracil/epinephrine injectable gel. L Am Acad Dermatol. Jan 1997; 36(1):72-7.

19. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from the two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatolo. 2004;50:722-733.

20. Loncaster J, Swindell R, Slevin F, Sheridan L, Allan D et al. Efficacy of Photodynamic therapy as a treatment of Gorlin syndrome-related basal cell carcinomas.Clinical Oncology 2009;21:502-508.

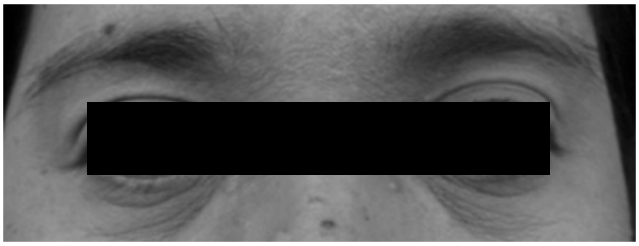

FIGURE 1. Exotropia

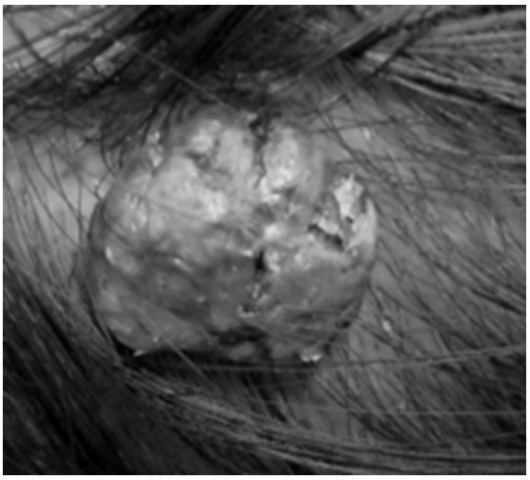

FIGURE 2. Nodule on left temproparietal scalp

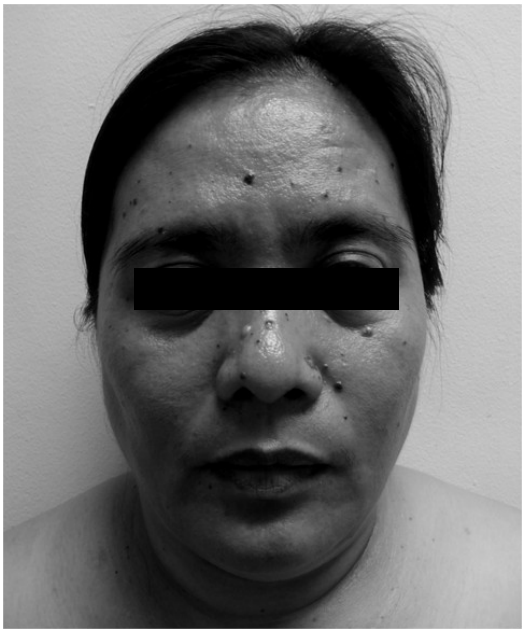

FIGURE 3. Face

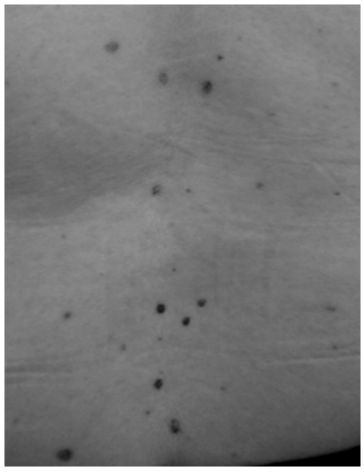

FIGURE 4. Lower Back

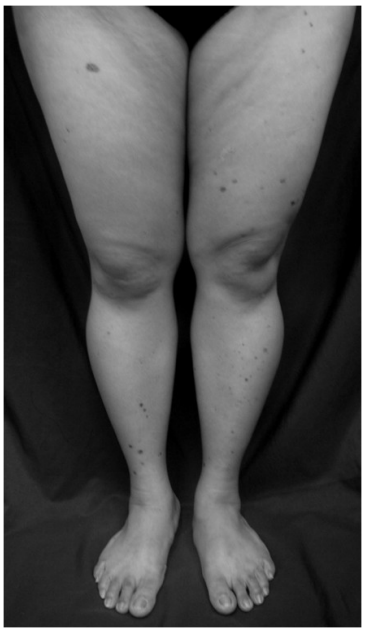

FIGURE 5. Lower extremities

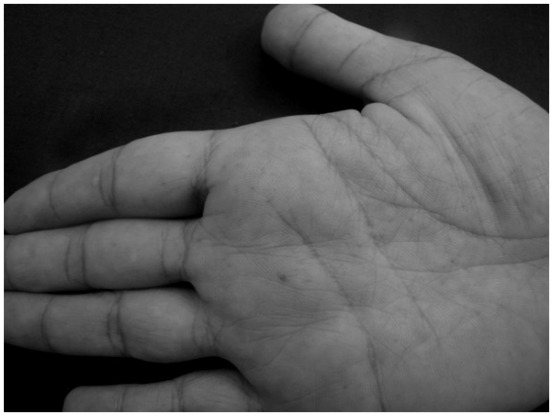

FIGURE 6. Palmar pits

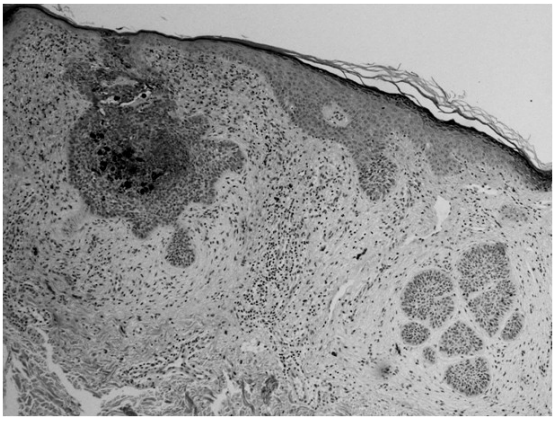

FIGURE 7-A

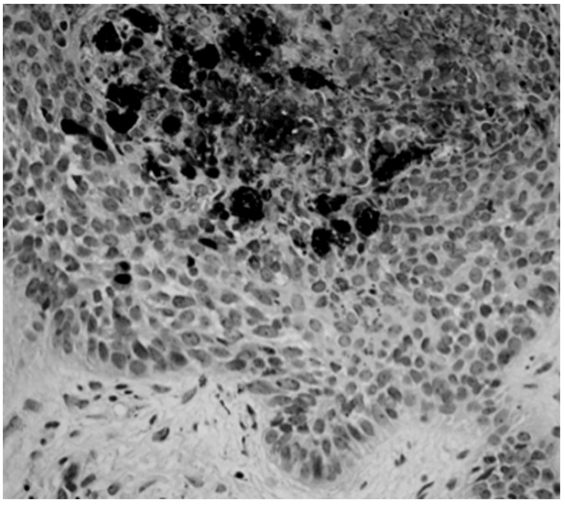

FIGURE 7-B

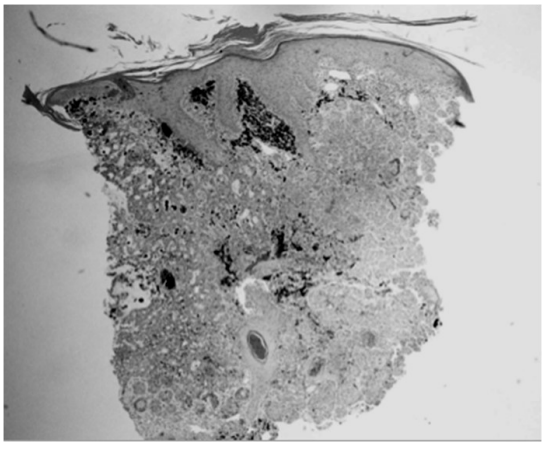

FIGURE 8-A

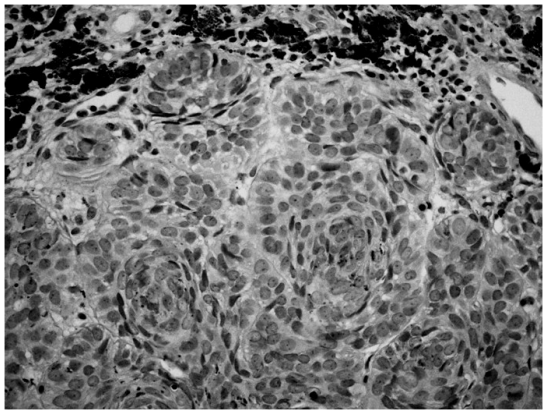

FIGURE 8-B

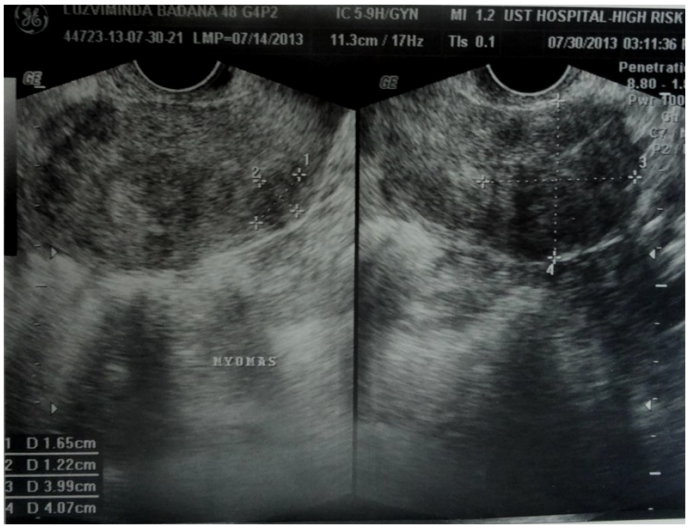

FIGURE 9. Uterine myomas

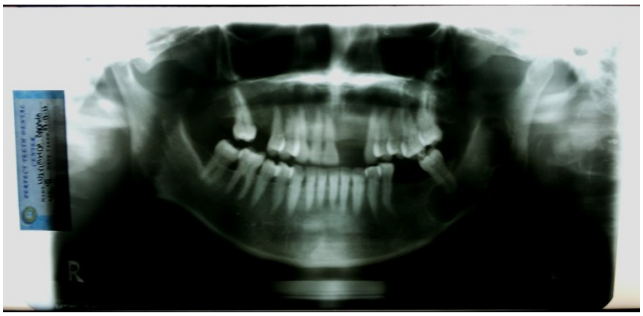

FIGURE 10. Odontogenic Keratocyst, body of the mandible Left

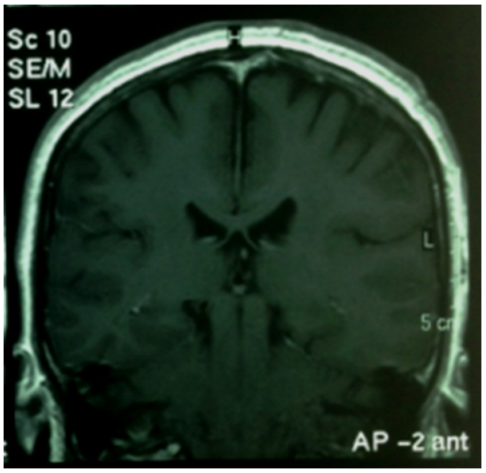

FIGURE 11. Posterior falx calcification