

Case Report**Bilateral ovarian fibroma associated with Gorlin syndrome***Shahnaz Aram*, Noushin Afshar Moghaddam*****Abstract**

Gorlin syndrome (GS), also known as nevoid basal cell carcinoma syndrome (NBCCS), is a rare inherited multisystem disorder. This paper presents a 22-years-old Iranian woman with this syndrome whose past history was multiple keratocysts of maxillary bone. She was referred to gynecology clinic with the chief complaint of irregular menses and vaginal spotting. On examination, frontal bossing and hypertelorism were detected. Physical examination of genitalia disclosed bilateral adnexal masses. Pelvic ultrasound showed two solid, echogenous and calcified masses measuring 100*50*10 & 60*50*45 mm in the left and right ovaries, respectively. The patient underwent right oophorectomy and ovarian mass resection with preservation of intact ovarian tissue on the left side. On frozen and permanent histological sections, bilateral and calcified ovarian fibromas were diagnosed. Surprisingly, during the last follow-up one year after the surgery, we found that our patient was expecting a baby. It can be concluded that in the presence of bilateral and calcified ovarian fibromas, the possibility of GS should be considered. Accurate diagnosis is only possible with close attention to the familial and past medical history and physical examination. In these patients, careful follow up for detecting malignancies and other complications is highly recommended.

KEY WORDS: Gorlin syndrome, ovarian fibroma, multiple keratocysts.

JRMS 2008; 14(1): 57-61

Gorlin syndrome (GS) -also known as nevoid basal cell carcinoma syndrome (NBCCS)- is a rare inherited multisystem disorder due to germline mutations in the human homolog of the patched (PTCH) gene.¹ The approximate prevalence is reported as 1 case per 57000 to 164000 population.²⁻⁴ The syndrome is characterized by specific developmental malformations in association with a predisposition to neoplasia. These malformations include odontogenic keratocysts of the jaw, palmar and plantar pits, ectopic intracranial calcification, and craniofacial anomalies including macrocephaly, frontal bossing and hypertelorism. A predisposition to neoplasia exists and in particular multiple basal cell carcinomas are seen at younger ages. Ovarian fibromas, often calcified and bilateral, develop in 15 to 25 percent of women with Gorlin syndrome.⁵⁻⁷ Recently, we faced a case with this

syndrome following evaluation of bilateral ovarian masses.

Case report

A 22 years-old Iranian female was referred to gynecology clinic of Alzahra Hospital because of irregular menses and vaginal spotting in March 2007. She had an operation on maxillary bone with the diagnosis of multiple keratocysts in the same centre ten years ago (figure 1). Her father had a history of multiple basal cell carcinomas of the skin. On physical examination, facial dysmorphism in the form of frontal bossing and hypertelorism were detected. Physical examination of genitalia disclosed bilateral adnexal masses. Pelvic ultrasound and CT scan showed two solid, calcified masses measuring 100*50*10 and 60*50*45 mm in the left and right ovaries, respectively (figure 2).

*Gynecology and Obstetrics Department, Faculty of Medicine, Isfahan University of Medical Sciences, Iran.

** Pathology Department, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence to: Noushin Afshar moghaddam MD, Pathology Department, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan ,Iran. E-mail: afsharmoghaddam@med.mui.ac.ir

According to high clinical suspicion of malignancy, laparotomy was planned. The right ovary had been totally replaced by the mass, so it was completely resected. However, since the patient was nulliparous, only mass resection was performed on the left side with preservation of intact ovarian tissue. The specimens were sent for intraoperative consultation by frozen section. In contrast to clinical suspicion of malignancy, bilateral fibroma was reported and surgery was terminated because of the benignity of the lesion.

In permanent histological sections, spindle stromal cell proliferation was seen, arranged in a storiform pattern (figure 3) with massive calcification (figure 4) and devoid of mitotic activity. Immunohistochemical staining revealed a positive reaction for vimentin and negative immunostaining for keratin and EMA. According to pathological findings, the diagnosis of bilateral-calcified ovarian fibroma was made. Finally, Gorlin syndrome appeared to be the most probable diagnosis for the patient.



Figure 1. Radiograph of multiple odontogenic keratocysts around upper incisors as lytic lesions.



Figure 2. Calcified ovarian masses are marked in CT-scan.

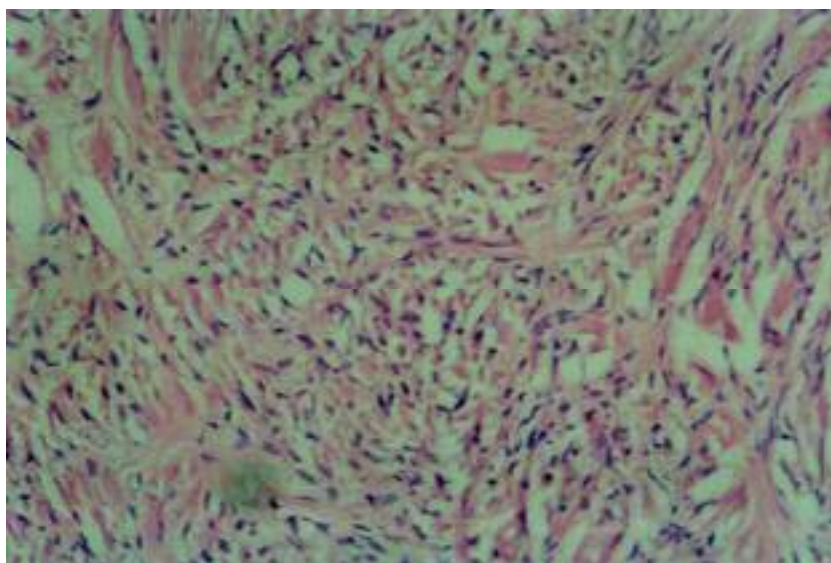


Figure 3. Microscopic appearance of fibroma showing benign spindle cells (Hematoxylin and Eosin staining*400).

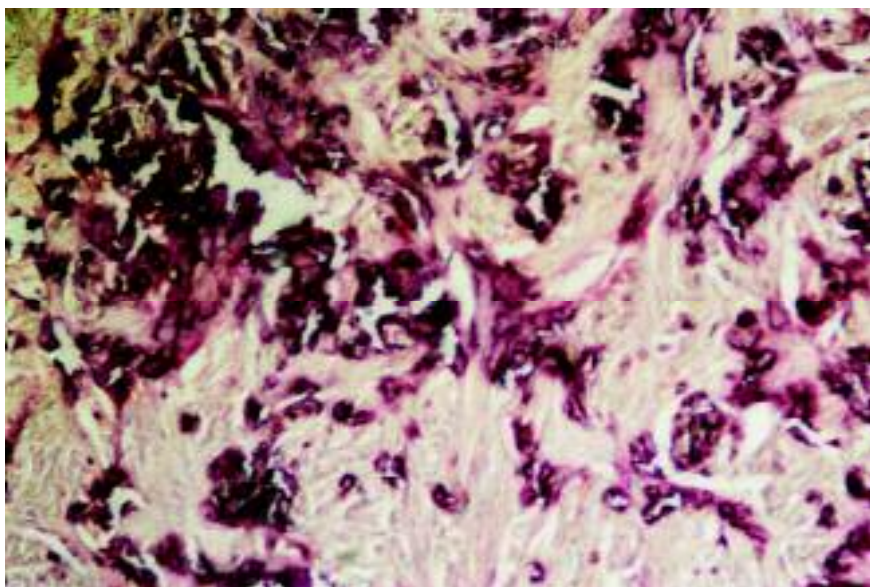


Figure 4. Microscopic appearance of fibroma showing calcified foci (Hematoxylin and Eosin staining*100).

Discussion

Gorlin syndrome (GS) is an inherited multisystem disorder with variable manifestations. There seems to be no phenotype-genotype correlation between a specific point for gene mutation and major clinical features.⁸ Because of variable manifestations and the multi-system nature of the syndrome, patients with GS present at a variety of ages with considerable variability in their clinical features. Many undergo a wide variety of surgical treatments for

BCC over many years. The combination of disease process and effects of surgeries causes many patients to acquire disfigured features which can result in both functional and visual problems.^{5,9} More than 100 clinical abnormalities have been described in GS.² The major manifestations include multiple basal cell carcinomas, odontogenic keratocysts, palmar and plantar pits, ectopic intracranial calcification and positive family history of GS. The minor criteria follow: craniofacial dysmorphism

(i.e. macrocephaly, frontal bossing and hypertelorism), early onset of medulloblastoma, cardiac or ovarian fibroma, lymphatic mesenteric cysts and congenital malformations. GS diagnosis is confirmed by two major or one major plus two minor criteria.¹⁰⁻¹³ Ovarian fibroma, often calcified, bilateral and multinodular, will develop in 15-20% of women with GS. Howell and colleagues have reported bilateral ovarian fibromas in an 8 year-old American girl of African descent. According to their report, the preservation of normal ovarian tissue was recommended despite the acknowledged risk of recurrence.¹⁴ Springate JE reported an eight year-old girl whose initial complaint was acute abdominal pain secondary to torsion of an ovarian fibroma.⁹ Smith LM demonstrated complex karyotypic abnormality of a large unilateral ovarian fibroma in a 12 year-old female associated with Gorlin syndrome.¹⁵ Basal cell carcinoma usually appears after puberty although it can be seen as early as in the second year of life. They are numerous and can develop on both sun-exposed and unexposed skin.⁹ About 70% of patients with GS have odontogenic keratocysts of jaw. In our patient, these lesions were noted 10 years ago. They mostly appear in the first decade of life and may cause jaw pain, swelling, tooth loss and pathologic fractures.⁹ They

are neoplastic rather than developmental in origin and lined with keratinized epithelium. Keratocytes are divided into solitary and multiple types. The multiple type is a component of GS.^{1,16} In our case, GS was diagnosed considering one major criterion (odontogenic keratocysts) and 2 minor ones (bilateral ovarian fibromas, facial dysmorphism in the form of frontal bossing and hypertelorism). It is very important to distinguish fibroma both grossly and microscopically from thecoma, Brenner and Krukenberg tumors. Fibromas are solid, firm and uniformly white while thecomas have a yellow color in the cutting surface, an important feature in the differential diagnosis with fibroma. Brenner and Krukenberg tumors were excluded by negative immunoreactivity for keratin and EMA.¹⁷ Other ovarian tumors including fibrosarcoma are rarely reported and could be differentiated from fibroma with the help of their high cellularity and mitotic index.¹⁸ In conclusion, bilateral and calcified ovarian fibroma is suggestive of the possibility of GS. The accurate diagnosis is possible with close attention to familial and past medical histories and physical examination findings. In these patients, careful follow up for detecting malignancies and other complications is highly recommended.

Conflict of interest

Authors have no conflicts of interest.

Authors' Contributions

ShA was the surgeon of the patient. She gathered patient data and history, carried out articles review.

NAM was the pathologist that diagnosed patient's tumor, prepared the manuscript and coordinated the study. All authors have read and approved the content of the manuscript.

References

1. Rosai J. Mandible and maxilla. In: Rosai J, editor. Rosai and Ackerman's surgical pathology. St. Louis: Mosby, 2004: 279-304.
2. Genevieve D, Walter E, Gorry P, Jacquemont ML, Dupic L, Layet V et al. Gorlin syndrome presenting as prenatal chylothorax in a girl. *Prenat Diagn* 2005; 25(11):997-9.
3. Barankin B, Alanen K. Nevoid basal cell carcinoma syndrome. *Emedicine Up to Date*: December 2006.
4. Berg D. Nevoid basal cell carcinoma syndrome. *Emedicine Up to Date*: January 25 2007.
5. Taylor SF, Cook AE, Leatherbarrow B. Review of patients with basal cell nevus syndrome. *Ophthal Plast Reconstr Surg* 2006; 22(4):256-9.

6. Bitar GJ, Herman CK, Dahman MI, Hoard MA. Basal cell nevus syndrome: guidelines for early detection. *Am Fam Physician* 2002; 65(12):2501-4.
7. 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(3):299-308.
8. Bale AE. Variable expressivity of patched mutations in flies and humans. *Am J Hum Genet* 1997; 60(1):10-2.
9. Springate JE. The nevoid basal cell carcinoma syndrome. *J Pediatr Surg* 1986; 21(10):908-10.
10. Kirova GI, Stratiev A. A case of nevoid basal cell cutaneous syndrome - radiological, CT and MRI findings. *J BUON* 2004; 9(2):209-13.
11. Ogunsalu C, Daisley H, Kamta A, Kanhai D, Mankee M, Maharaj A. Odontogenic keratocyst in Jamaica: a review of five new cases and five instances of recurrence together with comparative analyses of four treatment modalities. *West Indian Med J* 2007; 56(1):90-5.
12. Rupprecht M, Mensing CH, Barvencik F, Ittrich H, Heiland M, Rueger JM, et al. Skeletal and dermatological manifestations of the nevoid Basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Results of 8 patients in 12 years. *Rofo* 2007; 179(6):618-26.
13. Evans DG, Ladusans EJ, Rimmer S, Burnell LD, Thakker N, Farndon PA. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet* 1993; 30(6):460-4.
14. Howell CG, Jr, Rogers DA, Gable DS, Falls GD. Bilateral ovarian fibromas in children. *J Pediatr Surg* 1990; 25(6):690-1.
15. Smith LM, Hu P, Meyer LJ, Coffin CM. Complex karyotypic abnormality in ovarian fibroma associated with Gorlin syndrome. *Am J Med Genet* 2002; 112(1):61-4.
16. Agaram NP, Collins BM, Barnes L, Lomago D, Aldeeb D, Swalsky P, et al. Molecular analysis to demonstrate that odontogenic keratocysts are neoplastic. *Arch Pathol Lab Med* 2004; 128(3):313-7.
17. Rosai J. Female reproductive system. In: Rosai J, editor. *Rosai and Ackerman's surgical pathology*. St. Louis: Mosby, 2004: 1694-709.
18. Kraemer BB, Silva EG, Sneige N. Fibrosarcoma of ovary. A new component in the nevoid basal-cell carcinoma syndrome. *Am J Surg Pathol* 1984; 8(3):231-6.