Primary Bilateral Multiple Ovarian Leiomyomata in a Patient with Gorlin-Goltz Syndrome: Would Intraoperative Frozen Section Have Prevented Surgical Menopause?

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ABSTRACT

Benign ovarian tumours are a diagnostic criterion for Gorlin-Goltz syndrome (GGS), especially when bilateral. We report this rare case of bilateral multiple ovarian fibroids that posed a diagnostic dilemma in a patient with Gorlin-Goltz syndrome. She is a 31-year-old nullipara, primarily infertile, referred with a 13-year history of lower abdominal swelling, a 22-week size pelvic mass, which was hard and slightly mobile, with no ascites. Tumour markers were normal. Abdominopelvic CT revealed multiple small bowel calcifications likely metastatic. Intraoperative findings were those of bilateral huge, extremely hard, craggy, multi-lobulated ovarian tumour measuring 28cmx12cm on the right and 20cmx10cm on the left. No grossly normal ovarian tissue identified. The appearance and consistency of the tumour raised a suspicion for malignancy. As there was no facility for intraoperative frozen section and patient was not consented for hysterectomy, bilateral salpingo-oophorectomy was done following second and third opinions. Histology revealed bilateral ovarian leiomyomata. During follow up, she was discovered to have major and minor criteria for Gorlin-Goltz syndrome. Patient is currently on hormone replacement therapy for menopausal symptoms and regular with follow up.

Keywords: Frozen Section, Gorlin Goltz Syndrome, Odontogenic Keratocyst, Ovarian Leiomyoma, Surgical Menopause

INTRODUCTION

Patients presenting with a newly discovered ovarian mass often undergo diagnostic laparoscopy / laparotomy without a definitive preoperative diagnosis because of low sensitivity and specificity of imaging studies and serum markers, and lack of accessible sites for a tissue biopsy or cytology sampling. Intraoperative frozen section evaluation plays a critical role in guiding the type and extent of surgery in such cases, especially in young patients where fertility preservation is paramount. If surgery and histology confirms primary ovarian fibroids, it is important to check for other features

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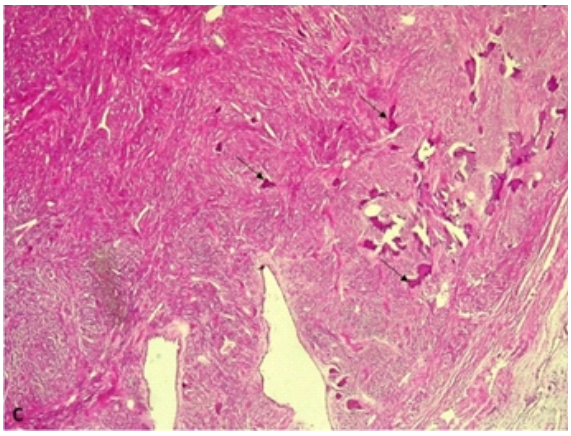

Figure 1: showing bony trabecular, maxillary antral lining and minor salivary gland.

of Gorlin-Goltz syndrome which, though rare, could have been missed easily due to low index of suspicion. We report this rare case of bilateral multiple primary ovarian leiomyomata that posed a diagnostic dilemma in a patient later discovered to have Gorlin-Goltz syndrome. We did not find a previously reported similar case in Nigerian literature and as such wish to raise the index of suspicion by this publication

CASE REPORT

A 31-year-old married nullipara, university graduate, primarily infertile, was referred with a 13-year history of slowly growing lower abdominal swelling. Menses was regular with normal flow and there was no weight loss or previous blood transfusions. She was also being managed for vaginismus since coitarche four years ago with kegel's exercise and graduated vaginal dilatation.

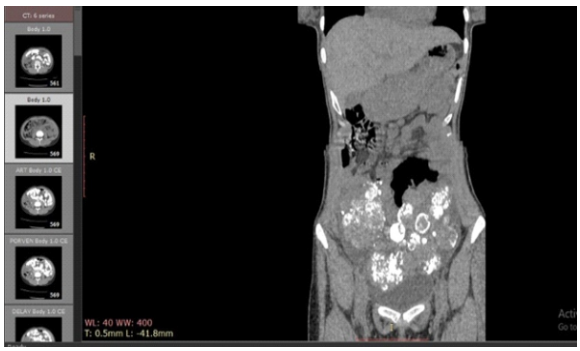

Figure 2: CT image showing multiple "small bowel calcifications" likely metastatic

She also had a past history of odontogenic keratocyst (OKC) removed the previous year at the maxillofacial surgery unit of our hospital; where she presented with a 2 month's history of left facial swelling. Enucleation of the lesion was done and histology revealed a cystic lesion lined by stratified

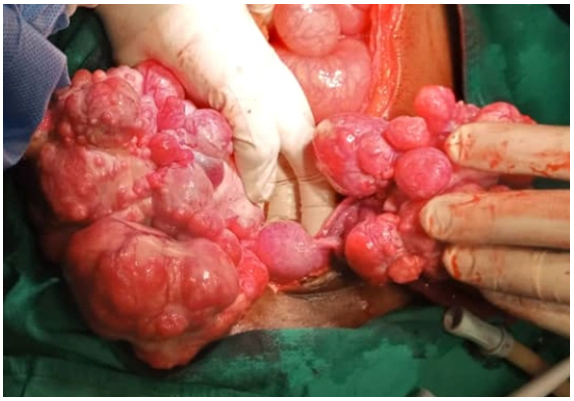

Figure 3: intra-operative picture showing bilateral ovarian tumours and a normal uterus

squamous epithelium of varying thickness characterized by prominent pallisaded basal layer with reverse polarity in areas and a corrugated parakeratotic surface layer. Other areas showed bony trabecular, maxillary antral lining and minor salivary gland which is in keeping with the histological features of odontogenic keratocyst.

On examination, she was underweight, had obvious bilateral proptosis (since birth) but no goiter. Pulse rate was 76 beats per minute and blood pressure was 110/60mmHg. There was a 22-week size non tender pelvic mass, which was hard, had irregular surface and slightly mobile. There was no clinically demonstrable ascites. Pelvic examination was declined by patient. Clinical impression was that of multiple uterine fibroids to rule out benign ovarian lesion.

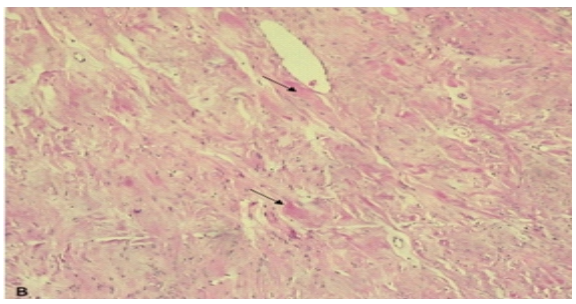

Figure 4: interlacing fascicles of smooth muscle bundles - leiomyoma

Ultrasound scan revealed a normal uterus with huge calcified pelvic masses of undetermined origin. Tumour markers (Cancer Antigen-125, Carcinoembryonic antigen, Alpha Feto-Protein, Lactate Dehydrogenase and beta Human Chorionic Gonadotrophin) were all within normal limits. Thyroid function test was ordered because of the eye signs but was normal. Abdominopelvic Computerized Tomography scan revealed multiple small bowel calcifications likely metastatic

This necessitated inviting the general surgeons. She was scheduled for exploratory laparotomy after obtaining informed consent. Intraoperative findings were those of bilateral huge, extremely hard, craggy, multi-lobulated ovarian tumours measuring 28x12cm on the right and 20x10cm on the left

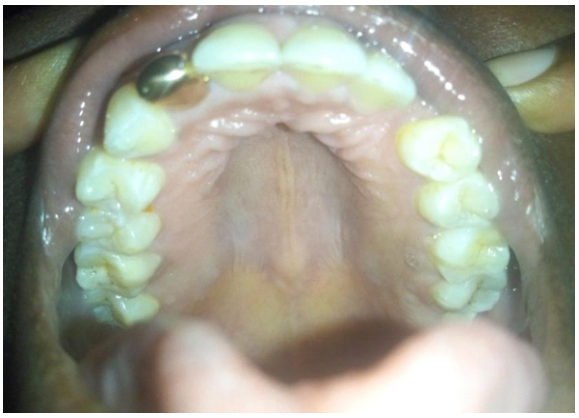

Figure 5: high arched palate

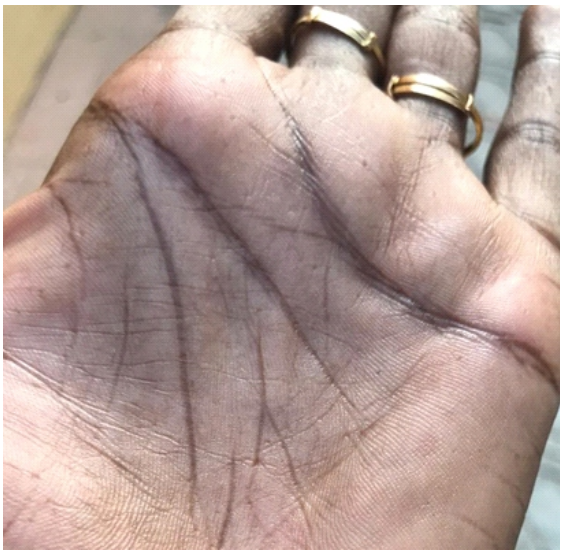

Figure 6: palmer pits and numerous nevi on the face, neck, trunk, legs and thigh.

Figure 7: nevi Her Chest X-ray reviewed showed splayed ribs

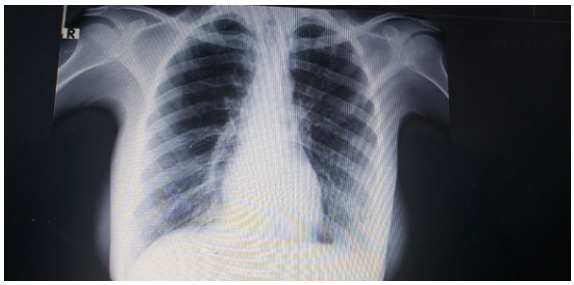

Figure 8: Splayed ribs, prominent on the right

No grossly normal ovarian tissue identified hence it was not feasible to conserve any. The uterus was normal in size with no fibroid seedlings palpable. The appearance and consistency of the tumour raised a suspicion for malignancy. As there was no facility for intraoperative frozen section, no grossly normal ovarian tissue and patient was previously not consented to hysterectomy, bilateral salpingo-oophorectomy was done following second and third opinions of Professors of Gynaecology in our hospital. Other pelvic organs, bowel and peritoneal surfaces, liver and diaphragm were normal. Histology of the surgical specimen revealed a lesion composed of interlacing fascicles of smooth muscle bundles, elongated cells with euchromatic nuclei and moderate amphophilic cytoplasm, fibro-collagenous stroma and areas of dystrophic

calcifications.
The conclusion of bilateral ovarian leiomyomata was made. Patient is currently on hormone replacement therapy (HRT) using conjugated estrogen – Premarin – and levonorgestrel releasing intrauterine system for bothersome symptoms caused by surgical menopause. She is also on alendronic acid, vitamins and water-based vaginal lubricants.

During clinic follow up after reviewing existing literature on bilateral ovarian fibroids, a more thorough examination was carried out and patient was discovered to have other features fulfilling the diagnostic criteria for Gorlin-Goltz syndrome. These included low pitched voice, high arched brows, frontal and biparietal bossing, high arched palate.

Prior to the enucleation of the maxillary lesion, she had an extra oral radiograph, the occipitomental view of the jaw revealed an expansile unilocular lesion with a tooth like structure in the maxilla which was in keeping with an odontogenic cyst. She didn't have a skull X-ray or orthopantomogram.

In our patient, the diagnosis of Gorlin-Goltz syndrome was established by the presence of three major criteria (histologically proven OKCs of the jaws, palmar and plantar pits and splayed ribs) and some minor criteria (bossing, ocular hypertelorism, low pitched voice, widespread nevi, proptosis, and ovarian fibroids).
Her diagnosis was explained to her, and the need for regular follow up for the nevi. Her option of using donor eggs for invitro fertilization and embryo transfer was also explained. Being Muslim, she declined this option and may consider adoption in future. She currently has no complaints after being followed up for 3 years.

DISCUSSION

Primary ovarian leiomyoma (POL) is a very rare benign tumor, first described in 1862 by Sangalli et al. Since then, barely a hundred cases have been reported, mostly from Euroasia. [1] and mostly unilateral. A few bilateral cases have been reported, first was reported in the English literature in 1992 by Kandalaft et al. Most bilateral cases occurred in patients between the ages of 16 and 25 [2][3] or generally less than 35 [1] Our patient's symptoms dated back to this age. Usually, primary ovarian leiomyoma presents as a small mass, about 3cm in size, with unilateral predominance and no predilection for the left or right ovary. [2] Patients with primary ovarian leiomyomas do not have concomitant uterine fibroids just like in our index patient. Bilateral cases, as seen in this patient, are rare, and only a few have been reported. [2][3] POL has also been reported in pregnancy [4]

The pathogenesis of ovarian leiomyoma remains uncertain. It is thought to originate from the walls of blood vessels in the ovarian hilus or from the smooth muscle fibers near the attachment of the ovarian ligament. [4] Other probable sites of origin include multipotent cells in the ovarian stroma or undifferentiated germ cells in the ovarian stroma. [5] Endometriotic cysts which may trigger metaplasia of the surrounding stroma into the smooth muscle cells may also result in the development of POL. [5] Additionally, the metaplasia of the smooth muscles present in mature cystic teratomas or mucinous cystic tumour may explain the pathogenesis in some cases. [5]

Other authors suggest the role of estrogens as stimulating factors for the development of POL since most tumors appear in nulliparous patients just like uterine fibroids. Ovarian leiomyomata are concomitantly seen with uterine leiomyomas (78%), which suggests an identical hormonal stimulation. [6] Bilateral POL, as seen in this case, may be associated with Gorlin- Goltz syndrome (GGS), [7] especially since the patient had a previous history of odontogenic keratocyst removed. Ovarian tumours associated with GGS are most often bilateral (75%), calcified, and nodular, often overlapping medially. In fact, the first patient reported by Gorlin also had pelvic calcifications!!! [8] This was the exact characteristic of the tumour the index patient had.
A number of such cases have been erroneously diagnosed as calcified uterine leiomyomas. Those ovarian fibromas not associated with the syndrome are unilateral and calcified only 10% of the time. Within the limits of our literature search, Gorlin-Goltz syndrome presenting with bilateral POL has not been reported in Nigeria. The first case of GGS was reported by Daramola in a Nigerian boy in 1980. [9]
Gorlin-Goltz syndrome (which is also known as nevoid basal cell carcinoma (BCC) Syndrome, Gorlin syndrome, Basal cell nevus syndrome, Fifth phacomatosis, Multiple basilioma syndrome,

Hereditary cutaneomandibular polyoncosis and the most complex one "Jaw-cyst-basal-cell-nevus, bifid rib syndrome") [10] is an infrequent multisystemic disease that is characterized by a predisposition to neoplasms and other developmental abnormalities. [10] Its prevalence is 1/57,000 – 1/256,000 with no gender predilection. [11] It is a hereditary condition inherited in an autosomal dominant fashion with strong penetrance and extremely variable expressivity, which is characterized by multiple odontogenic keratocysts (OKC) and basal cell carcinomas (BCC), skeletal, dental, ophthalmic, and neurological abnormalities, intracranial ectopic calcifications of the falx cerebri, and facial dysmorphism. Pathogenesis of the syndrome is attributed to abnormalities in the long arm of chromosome 9 (q22.3-q31) and loss or mutations of human Patched 1 gene (PTCH1 gene). [12] Diagnosis is based upon established major and minor clinical and radiological criteria and ideally confirmed by deoxyribonucleic acid (DNA) analysis which was not done in this patient. It was reported by Jarish and White in 1894. Robert J. Gorlin and Robort W. Goltz described the distinct syndrome, consisting of multiple nevoid BCCs, jaw cysts, and bifid ribs. [13] Early diagnosis is essential as it may progress to aggressive basal cell carcinomas and neoplasias. Gorlin-Goltz syndrome has rarely been reported in the black race.

The most important criteria to make a diagnosis for this syndrome are the presence of pigmented basocellular carcinomas, OKC, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri. [14] Our patient had three of these and the calcification of the falx was not ascertained as she didn't have skull X-ray. Together with these major features, more than 100 minor features have been described, with other minor criteria still being proposed. [10]

The more relevant minor criteria are: cardiac or ovarian fibroma, macroencephaly, splayed (bifid) ribs, kyphoscoliosis, cleft palate, medulloblastoma, alterations in the sella turcica, mandibular prognathia, lateral displacement of the inner canthus, frontal and biparietal bossing, imperfect segmentation of the cervical vertebrae, linfomesenteric cysts that tend to calcify, meningiomas, fibrosarcoma, rhabdomyosarcoma, short fourth metacarpal, ocular hypertelorism, congenital blindness, high arched eyebrows and palate, narrow sloping shoulders, immobile thumbs, low pitch voice in women, renal anomalies, and hypogonadism in men. In certain occasions, a tall height and even similar characteristics to acromegaly have been associated with the syndrome. [14] Deformities of the skull often result in the appearance of hypertelorism and proptosis.

Evans et al. [15] first established major and minor criteria for the diagnosis of the syndrome and later were modified by Kimonis [16] et al. in 2004. The presence of two major and one minor or one major and three minor criteria are necessary to establish diagnosis. [15][16] Our patient had three major and six minor criteria identified within the limits of our examination and investigations

Major criteria

- Multiple basal cell carcinomas or one occurring under the age of 20 years.
- Histologically proven OKCs of the jaws.
- Palmar or plantar pits (three or more).
- Bilamellar calcifications of the falx cerebri.
- Bifid, fused, or markedly splayed ribs.
- First degree relative with nevoid basal cell carcinoma syndrome.

Minor criteria

- Macrocephaly (adjusted for height).
- Congenital malformation: Cleft lip or cleft palate, frontal bossing, coarse face moderate or severe hypertelorism.
- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
- Radiological abnormalities: Bulging of sella turcica, vertebral anomalies such as hemi vertebrae, fusion or elongation of vertebral bodies, modeling defects of the hands and feet, or flame-shaped hands or feet.

- Ovarian fibroma.
- Medulloblastoma.

Immunohistochemical analysis (IHC) with smooth muscle specific staining (SMA and h-Caldesmon) is helpful to rule out differential diagnoses of POL. Immunohistochemical (IHC) analysis is essential in a number of cases to establish the diagnosis of POL. Leiomyomas show diffuse positivity for desmin whereas fibromatous tumours are characteristically negative or only focally positive. In the index patient, diagnosis was quite apparent on microscopic examination and hence IHC analysis was not done.

It is also important to distinguish between primary ovarian leiomyomas and parasitic leiomyomas. In this patient, the uterus had no palpable fibroid seedling and the gross appearance were multiple fibroids in each ovary hence ruling out a case of parasitic fibroids

The common surgical approach of ovarian leiomyomas in middle-aged to elderly patients is by hysterectomy and bilateral salpingo-oophorectomy (BSO). [3] For symptomatic and large bulky masses, complete resection is recommended. For bilateral ovarian leiomyomas, bilateral oophorectomy is often required as was done in this patient. However, this patient was nulliparous and there was no grossly normal ovarian tissue seen even on histology. If a frozen section was done and had revealed fibroids, some authorities believe that probably a right sided salpingo-oophorectomy and left debulking could have been done to preserve some ovarian function; while others would have still preferred to do a BSO and place her on HRT as was done in this patient. Some authors have recommended frozen section [3] because intraoperative frozen section diagnosis appears to be an accurate technique for the histopathologic diagnosis of ovarian tumors. However, limitations in use of frozen section must be recognized such as large specimens, especially mucinous subtype. Regular re-evaluation or consultation concerning disagreements between frozen section diagnosis and final permanent paraffin diagnosis should be conducted by both surgeons and pathologists as part of quality assurance to determine the most appropriate intraoperative management for patients with ovarian tumors. [17]

Another study describing the accuracy of intraoperative frozen section revealed that review of discrepant cases showed that major pathological causes of under-diagnosis were misinterpretation and sampling errors. Univariate analysis showed that presence of bilateral tumour and positive peritoneal cytology were associated with under-diagnosis. They concluded that, despite significant risk of under-diagnosis, FS analysis is an accurate method for intraoperative diagnosis of borderline ovarian tumours. [18]

A quite similar presentation of a young infertile women with POL and GGS was recently reported in India [10] This patient had enucleation of the mass with preservation of ovarian function. This was not feasible in our patient due to huge size, and grossly absent normal ovarian tissue. (figures 2) Other authors also report that ovarian conservation is possible if grossly normal tissue is found, usually in smaller tumours [7][19] with return of normal menses afterwards. Although data about the fertility potential of females with GGS is scant, there are several reasons why fertility may be compromised in them. Because GGS is associated with several cancers that present at a young age, many patients have already received gonadotoxic cancer therapies and have reduced ovarian reserve. Surgical resection, particularly if extensive, may also compromise fertility potential by reducing the amount of viable ovarian tissue. Resection may result in adhesive disease and tubal obstruction. [7] None of these was the case in our patient. The cause of her primary infertility was likely due to the vaginismus that completely prevented penetrative sexual intercourse.

Currently available fertility preservation options that may be offered to appropriate patients include ovarian stimulation with embryo or oocyte banking, or ovarian tissue cryopreservation. Alternatively, ovarian tissue could be banked at the time of resection. These options are not feasible for this patient who didn't have any grossly ovarian tissue.

Patients should also be informed that donor egg, donor embryo, or adoption are options if future infertility occurs related to a decrease in ovarian reserve or surgical menopause like in our patient. Although life expectancy seems to be normal in patients with GGS, patients should be informed about the potential for future malignancy and treatment-related morbidity. [7] In particular, basal cell carcinomas may be aggressive, invade locally, and metastasize. [8]

Rarely, the ovarian tumor in GGS may be virilizing [20] or renin-secreting. [21] they could be ovarian fibroids, fibromas, fibrosarcomas [22] primary ovarian leiomyosarcomas [23] or even rhabdomyosarcomas [24]

This case draws attention to the need to search for GGS in women presenting to the gynaecology clinic with bilateral ovarian neoplasms, or to the MFU with odontogenic keratocysts. It also emphasizes the need for intraoperative frozen section which might have made the option of leaving some tumour behind feasible and surgical menopause prevented.

CONCLUSION

Bilateral POL still remains a rare, likely under-reported finding. Its association with GGS may be commoner than it is reported in blacks. Patients with GGS may present with complex gynecologic needs as seen in this patient (infertility, vaginismus, bilateral POL) as such meticulous gynecologic evaluation, careful surgical management, long term follow up, and counseling on options for future fertility should be offered to all patients. Probably, the availability of intraoperative frozen section might have changed the surgical management in this patient.

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Statement of Ethics: Health Research Ethics Committee approval was not required but written informed consent was obtained from the patient for publication of this case report and its accompanying images on the condition that no identifiers or facial pictures will be used, and the publication will be shared with the patient.

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