Case Report

Ovarian leiomyoma and the relevance of the size of ovarian mass to clinical management

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ABSTRACT

This article describes a 45 year old woman with a 13cm right ovarian leiomyoma (OL) coexisting with multiple uterine fibroids. Ovarian leiomyoma is rare, there are only few reports from Africa but it is likely that the incidence from Africa is under-reported. There was no associated abdominal pain in spite of the size of the mass and multiple adhesions from a previous myomectomy done 12 years prior to this presentation. We discuss the relevance of the size of an ovarian mass to clinical management and the other factors guiding the choice of the appropriate management options in patients with ovarian masses, such as the age of the patient, the clinical symptoms, the risk of malignancy, the desire for future fertility and the proximity to menopause. The clinical (including ultrasonographic features), histopathologic, immunohistochemical and molecular features of the disease are also discussed.

Key words: Adnexal masses; ovarian leiomyoma; size of ovarian mass; ultrasonography.

Introduction

Ovarian leiomyoma (OL) is a rare benign tumor accounting for 0.5%–1% of all benign ovarian tumors.[1] Most primary adnexal leiomyomas occur in women age 20–65 years with approximately 15% of cases occurring in postmenopausal women.[2]

We present a 45-year-old premenopausal woman with a medium-sized OL coexisting with multiple uterine leiomyomas. There are only few reports of OL from Africa such as the one from Nigeria by Okoye IJ, Okezie OO in 2000 (http://dx.doi.org/10.4314/wajr.v7i1.34175), and from Tanzania by Lema *et al.* in 2013. The ovarian mass in the index patient was missed during ultrasonography and we hope that this report would create awareness about this rare disease among sonographers, primary care physicians, gynecologists, and histopathologists.

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We present clinicopathologic findings in this patient, review the existing literature, and discuss the appropriate diagnostic work-up with a focus on the relevance of the size of anovarian mass to clinical management, and other considerations guiding the choice of appropriate management.

Case Report

A 45-year-old Para 1 woman presented at a private medical center in Lagos, Nigeria, in May 2016 with heavy menstrual bleeding and an abdominal mass. There was no abdominal pain or discomfort. She had a myomectomy in 2004 on account of symptomatic uterine fibroids. She also had a caesarean delivery in 2005, for her only confinement. She

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was desirous of further pregnancies and had been trying to conceive.

On examination, she was found to be overweight (body mass index of 28.80 kg/m^2) and mildly pale (hemoglobin of 11.4 g/dL). The abdomen was distended and the uterus was 28-week sized with multiple fibroids palpable par abdomen. Transvaginal ultrasound scan confirmed a large uterus with multiple fibroids. There was no documentation of a mass in the ovary in the patient's ultrasound scan report.

A diagnosis of symptomatic uterine fibroids was made; myomectomy was done and the uterus conserved in consideration of her desire for future conception. A right ovarian mass was found at surgery, along with multiple pelvic adhesions, and a 26-week-sized uterus with multiple fibroids of different sizes at subserosal, intramural, and submucosal locations. The right ovary contained a solid tumor measuring 13 cm × 10 cm × 6 cm. The right ovarian mass was excised. The left ovary was normal in size and appearance.

Grossly, there were 30 greyish-white firm nodules altogether weighing 800 g and ranging in size between 1 × 0.5 × 0.5 cm and 7 × 6 × 3 cm. There was a 700-g right ovarian mass with an intact capsule which measured 13.0 × 9.0 × 5.0 cm. Cut sections through all the nodules and the right ovarian mass showed a greyish-white whorled appearance [Figure 1]. Microscopic examination of the ovarian mass showed a well-circumscribed benign mesenchymal neoplasm surrounded by a rim of normal ovarian tissue stroma [Figure 2]. The tumor was composed of whorls and interlacing fascicles of uniform spindle-shaped cells with blunt-ended cigar-shaped nuclei. There was no evidence of nuclear atypia or pleomorphism. Mitosis was not observed. Immunohistochemical staining showed strong and diffuse positive staining for smooth muscle actin and desmin. The tumor was completely negative for Inhibin. Ki-67 was less than 1%. These histologic and immunohistochemical features are consistent with those of an OL.

Discussion

The first case of OL was described by Sangalli *et al.* in 1862. Since then, less than 100 cases of this rare tumor have been reported.[3,4] The majority of the cases in scientific literature exist as independent reports, along with a few case series including the ones by Fallahzadeh *et al*.[5] of 5 cases in 1972, Doss *et al.*[6] of 19 cases in 1999, and Koo *et al.*[7] of 9 cases in 2011.

OL is rare, with only a few reports from Africa. This disease may be under-reported among Africans, more likely due to a failure to publish cases than to difficulties with recognition of this entity with clearly defined histopathologic features. The counterpart of this tumor in the uterus is diagnosed often by an average Nigerian pathologist. Uterine leiomyoma is the most common benign tumor of the female genital tract seen in Nigeria.[8] Uterine leiomyoma is known to be more common in blacks than in whites, and the lifetime risk of fibroids in a woman over the age of 45 years is more than 60%.[9] Some cases of OL among Africans may not be fit for publication because a definitive diagnosis was not obtained due to lack of access to immunohistochemistry and failure to exclude the differential diagnoses.

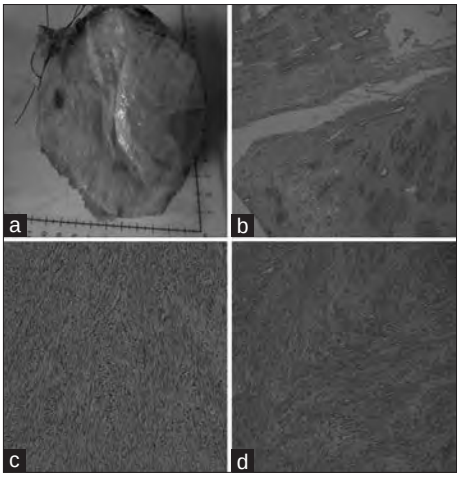

Figure 1: (a) The gross appearance of the ovarian mass with cut-surfaces showing a greyish-white whorled appearance. (b) Ovarian leiomyoma (bottom right) surrounded by ovarian stroma (top left) (H&E x40). (C) Histologic section showing sheets of uniform spindle-shaped cells with blunt-ended cigar-shaped nuclei (H&E x100). (d) Interlacing fascicles of smooth muscle cells (H & E x 100)

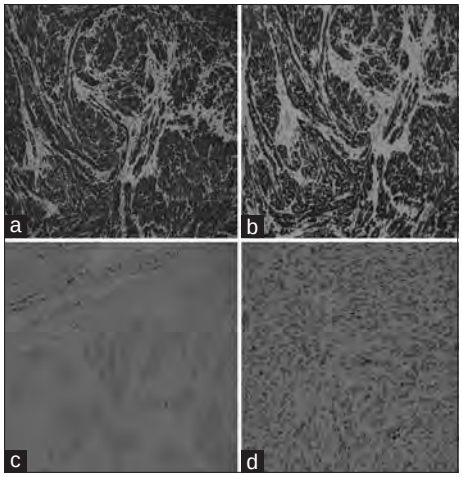

Figure 2: (a) Smooth muscle cells of ovarian leiomyoma showing diffuse and strong positive staining with SMA (x100). (b) Smooth muscle cells of ovarian leiomyoma showing diffuse and strong positive staining with Desmin (x100). (c) Smooth muscle cells of ovarian leiomyoma showing completely negative staining with Inhibin, ositive staining in the adjacent ovarian stroma (top left corner) (x40). (d) Positive staining with Ki-67 in less than 1% of tumour cells (x200)

OL appears to be most commonly reported from Eurasia, with five reports from India (Gunasekaran *et al.*, 2015;[10] Sasikala *et al.*, 2014; Agrawal *et al.*, 2013,[11] Jena *et al*., 2013; and Ramalakshmi *et al*., 2009); four from Turkey (Kelekci *et al*., 2015; Taskin *et al.*, 2014; Guzel *et al.*, 2014; and Cavkaytar *et al.*, 2010); and two each from South Korea (Koo *et al.*, 2011 and Kim *et al.*, 2000), Japan (Ichigo *et al.*, 2015 and Kozawa *et al.*, 2013), and Iran (Rajabi *et al.* 2014 and Safaei *et al.*, 2011). Koo *et al.* found nine cases in a period of 17 years in South Korea.[7] There is also a paucity of reports from Europe and North America which could be as a result of a lack of interest of researchers and/or journals in this rare but well-described entity.

OLs can be primary, secondary, or parasitic in origin. Primary OLs are defined as lesions that originate from ovarian tissues, including the intraovarian blood vessels, smooth muscle fibers, or similar tissues within the ovarian stroma and tunica albuginea.[7] Secondary involvement of the ovaries can occur from intravenous leiomyomatosis or from leiomyomatosis peritonealis disseminata.[12] Parasitic OLs are extraovarian in origin, often originating from a pedunculated uterine leiomyoma that becomes pinched off and secondarily attached to the ovary.[7,11,13] The incidence of primary ovarian leiomyomas is particularly low.[7]

OL may originate from smooth muscle fibers which may be found in the ovarian stroma, in the ovarian hilar blood vessels, smooth muscles, in mature cystic teratomas, and in the walls of mucinous cystic tumors.[1] Other possible origins for an OL include cells in the ovarian ligament, multipotential cells in the ovarian stroma, undifferentiated germ cells, cortical smooth muscle metaplasia, or smooth muscle metaplasia of endometriotic stroma.[1]

OLs are usually unilateral, with no predilection for the left or the right side.[11] Bilateral cases appear to be more common in patients younger than 35 years.[1,11] The first case of bilateral OL was reported in a 21-year-old by Kandalaft *et al.* in 1992. Several previous reports state that no case of bilateral OL had ever been seen in a patient older than 35 years (Usta *et al.*, 2006; Wei *et al.*, 2008; Tomas *et al.*, 2009; van Esch *et al.*, 2011; Lema *et al.*, 2013; Zhao *et al.*, 2014). In 2011 however, a case of bilateral disease was reported from the Netherlands in a 37-year-old woman.[2] The index patient had a right ovarian mass, while the left ovary was completely free of masses.

Along with the ovarian mass, the index patient had multiple fibroid nodules in the uterus. Doss reported that 78% of the 19 cases described in their series had OLs coexisting with uterine leiomyomas.[6] The hormone estrogen has been implicated in the growth and development of both ovarian and uterine leiomyomas.[4,11] Hormonal dependency of these tumors is evidenced by the increased incidence in the reproductive age with reduced incidence before puberty, after menopause, and in males; the increase in size during pregnancy; and their postpartum regression.[12]

The first case of OL in a patient who was yet to attain menarche was reported in 2014 by Blue *et al*. Far more cases have been described in postmenopausal women, with up to 15% of cases occurring in postmenopausal women.[2] Three of the four cases in postmenopausal women that we reviewed for this article occurred in women in their late 40s to early 50s who were likely in their early menopause years.[14-16] Two of the nine patients studied by Koo *et al*. were postmenopausal women, in their 50s, and also likely to have been in the early menopause years. The fourth case occurred in a 76-year-old woman.[17] We suggest the possibility that this fourth patient may have been on hormone replacement therapy.

Up to 70% of patients with uterine leiomyomas carry somatic mutations in the mediator complex subunit 12 (MED12) exon 2 which have been implicated in tumorigenesis.[18] Since OLs also originate from smooth muscle cells, it is hypothesized that similar mutations could be present in OLs. Kämpjärvi *et al*. studied 42 cases of extrauterine leiomyomas and found that none showed somatic MED12 mutations.[18]

Rarely, multiple OLs may occur in patients with Gorlin syndrome (GS).[19,20] Ovarian fibroma, a far more common manifestation of GS than OL, is found in 12%–25% of patients with GS, and it is a minor criterion for the diagnosis of GS.[19] GS, otherwise known as nevoid basal cell carcinoma syndrome, is an autosomal dominant disorder resulting from a mutation in *PTCH1* gene on chromosome 9q22.[19] It is associated with various congenital anomalies and development of tumors including basal cell carcinomas and keratocystic odontogenic tumors.[19]

The index patient presented with menorrhagia, likely due to the associated uterine fibroids. There was no history of associated abdominal pain or discomfort at presentation. The ovarian mass was discovered incidentally at surgery, and she had no symptoms suggestive of an OL. OL is usually asymptomatic, and it is often discovered as an incidental finding during routine physical examination, at surgery or at autopsy.[1] In symptomatic cases, clinical features that have been described include abdominal pain, a palpable mass, hydronephrosis, elevated CA-125 levels, hydrothorax, and ascites.[1,2]

Abdominal pain is the most common presenting symptom among patients with ovarian masses.[21] Acute or chronic

pain accounts for more than 10% of referrals to gynecologists and 40% of gynecologic diagnostic laparoscopies.[22] Ovarian masses cause abdominal pain due to their mass effect on adjacent tissue, by inciting the formation of fibrous adhesions, especially after surgery, and from the presence of endometrial tissue (endometriosis).[23] The fact that ovarian masses can cause pain directly from their mass effect on adjacent tissue suggests that the larger an ovarian mass is, the more likely it is to be associated with clinical symptoms. In the case reported by van Esch *et al.*, the complaints of abdominal discomfort disappeared shortly after resection of the ovarian masses.[2]

After extensive literature search, we found only one case of OL larger than 10 cm in diameter (19 cm) that was not associated with lower abdominal pain and occurring in a 76-year-old woman. Daoust *et al.* demonstrated a linear decrease with age of scores for visceral pain among persons in the 18–44, 45–64, 65–74, and >75 year age groups, but the differences identified were not found to be statistically significant.[24]

All the other cases documented in scientific literature with diameter greater than 10 cm were associated with lower abdominal pain or discomfort, often chronic and lasting for periods ranging from 1 month to 2 years before presentation (Sasikala *et al.*, 2014; Rajabi *et al.*, 2014; Agrawal *et al.*, 2013; Kozawa *et al.*, 2013; Jena *et al.*, 2013; Safaei *et al.*, 2011;[16] Cavkaytar *et al*., 2010; Tomas *et al.*, 2009; Ramalashkmi *et al.*, 2009). Pain was chronic in most cases, but rarely it could be intermittent or acute if it arises from an endometriotic cyst or is associated with complications.[1,15]

In spite of the size of 13-cm diameter ovarian mass in the index patient, and the multiple adhesions from a previous myomectomy done 12 years earlier, there was no associated lower abdominal pain or discomfort, and there was no tenderness elicited on physical examination.

A wide range of tumor sizes have been reported for OL.[4] Several articles report that OLs are usually small, they measure only a few millimeters in diameter, and they are often no larger than 3 cm diameter.[1,2,11] However, there have been several recent reports of masses with diameter greater than 10 cm (as listed above). The largest mass documented in literature measures 25 cm in widest diameter.[11]

A small OL may also present with symptoms, especially if it becomes associated with complications. Guzel *et al.* described a patient with a 6-cm diameter OL who presented on account of acute pain due to torsion.[25] Other causes of acute pain from an ovarian mass include rupture of an ovarian cyst, hemorrhage into a cyst, acute pelvic infections, malignancy, and non-gynecological causes.[26] Taskin *et al.* described a 4-cm diameter OL with lower abdominal pain, in the absence of complications, the absence of fibrous adhesions, and without being associated with uterine leiomyoma.[13]

The main goal in the evaluation of an adnexal mass is to differentiate between benign conditions and more serious diseases such as ovarian cancer.[27] Ovarian cancer is the most frequent cause of death from gynecological malignancies in the Western world.[27,28] The preferred imaging modality for the initial evaluation of an adnexal mass is ultrasonography.[26,29,30] This is because it is the least invasive and the most cost-effective method that is available.[29] The relative echogenicity of leiomyomas depends on the ratio of fibrous tissue to smooth muscle, the extent of degeneration, and the presence of dystrophic calcification.[29] A computerized tomography (CT) scan can be useful even though leiomyomas are indistinguishable from healthy myometrium unless they calcify or become necrotic.[29] Magnetic resonance imaging (MRI) can define the anatomy of the uterus and ovaries, but the availability of this method and its high cost are serious limitations.[29]

Ultrasound findings in OL are similar to those for uterine leiomyoma.[22] Two-dimensional ultrasound is readily available in most cosmopolitan cities across Nigeria. New advances, such as three-dimensional (3D) sonography, 3D vascular assessment, and contrast imaging, show promise for augmenting diagnostic accuracy.[22]

On MRI, OLs show intermediate signal intensity on T1-weighted images and low signal intensity on T2-weighted images.[12] Ovarian fibroma is the most important entity to consider in the differential diagnosis.[12] The early contrast enhancement of leiomyomas may aid in their differentiation from other fibrous ovarian tumors such as fibromas or fibrothecomas, which usually demonstrate delayed weak enhancement.[12] There are rare reports of extensive cystic degeneration in ovarian vascular leiomyomas, a feature that causes them to closely resemble cystic tumors such as cystadenomas.[12]

During initial evaluation with ultrasonography, the size of the adnexal mass is determined. Aside of suggesting the likelihood of finding associated clinical symptoms or complications in an ovarian mass, the size of an ovarian mass plays a crucial role in suggesting the risk of malignancy and in predicting the likelihood of success of laparoscopic surgery.[26]

In 2009, Givens *et al.*, in a consensus paper released on behalf of the American Academy of Family Physicians (AAFP),

recommended that prepubescent girls and postmenopausal women with an adnexal mass should be referred to a gynecologist or gynecologic oncologist for further treatment, and that all women, regardless of menopausal status, should be referred if they have evidence of metastatic disease, ascites, a complex mass, an adnexal mass greater than 10 cm, or any mass that persists longer than 12 weeks.[27] Prior to the paper by Givens *et al.*, the cut-off size of uterine adnexal tumors for surgical intervention in the early detection of cancer had not yet been well-determined.[28] In 2016, a new consensus paper showed that the AAFP had reviewed the cut-off size for referral for surgical intervention to 6 cm.[30]

Al-Shukri studied 57 women with adnexal masses who had surgical intervention on account of acute symptoms and found that the size of the mass seemed to contribute significantly toward the success of laparoscopic surgery.[26] Conversion of surgical approach from laparoscopy to laparotomy became necessary in >50% of the patients studied due to the size of the tumor being more than 10 cm, a suspicion of malignant disease, and the patient being clinically unstable.[26]

The definitive diagnosis of an OL requires a demonstration of the smooth muscle nature of the tumor by histology and immunohistochemistry.[11,12] On histology, OLs must be distinguished from cellular fibromas and stromal sclerosing tumors of the ovary.[13] The index case showed positivity with SMA and desmin, and was negative with Inhibin; immunohistochemical features were consistent with leiomyoma of the ovary. Ki-67, a marker of proliferative index, was low. OL must be differentiated from leiomyosarcoma using features such as mitotic activity, the presence of necrosis, and cytological atypia.[1,10]

The chosen approach for treatment of an ovarian mass should be individualized depending on factors such as the age of the patient, type and severity of clinical symptoms, risk of malignancy, desire for future fertility, and proximity to menopause.[29] Ovarian-preserving surgery should be offered to adolescent girls and reproductive age women, while hysterectomy with removal of the adnexa is appropriate for perimenopausal and postmenopausal women.[26] Preservation of ovarian function is even more of an important consideration in cases with bilateral disease, and oocyte cryopreservation may be considered in these cases.[20]

Accurate diagnosis of benign disease in the preoperative period is critical to ensuring that ovarian-preserving surgery can be offered to young patients.[7] van Esch *et al.* suggest that frozen sections be obtained for diagnosis from the ovarian mass during an initial elective diagnostic procedure to prevent the need for a second laparoscopic surgery or for laparotomy.[2] There are several considerations that help the surgeon to choose between laparoscopy and laparotomy including the size of the mass and the risk of malignancy.[2,26] Surgery may be offered by laparoscopic approach during pregnancy if the OL is symptomatic and/or associated with rapid growth.[4]

Conclusion

We have described the case of a medium-sized OL coexisting with uterine leiomyoma. OL may be under-reported from Africa. There was no associated pain in spite of the size (13 mm) and multiple adhesions from a previous myomectomy. The occurrence of abdominal pain appears to be proportional to the size of an ovarian mass and its ability to exert a mass effect on adjacent tissues. The determination of the size of an ovarian mass at ultrasonography is useful for predicting the occurrence of associated symptoms, complications, the risk of malignancy, and the success of laparoscopic surgery. The chosen approach for treatment of an ovarian mass should be individualized depending on the age of the patient, type and severity of clinical symptoms, risk of malignancy, desire for future fertility, and proximity to menopause.

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Conflicts of interest
There are no conflicts of interest.

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