The Clinicopathological Characteristics of Uterine Leiomyomas: A Tertiary Care Centre Experience in Saudi Arabia

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Abstract: Background: Leiomyomas are very common tumours of the female genital tract. However, large cohort studies are limited for reporting the incidence and prevalence. The aim of this study is to review the clinical and pathological pattern of leiomyoma in a tertiary care centre in Saudi Arabia. **Methods:** We retrospectively analysed the clinical and pathological data of patients diagnosed as leiomyoma in a large tertiary care centre in Saudi Arabia in the period from 2005 to 2012. **Results:** A total number of 563 patients were diagnosed as uterine leiomyoma. The age range was 22-86 years (mean 41.8 years). Leiomyomas were more common in age groups 41-50 years (40.1%) (p<0.001) followed by the age group 31-40 years (35.2%). Dysfunctional uterine bleeding was the presenting symptom in 19.2% followed by pelviabdominal mass (4.6%). In 70 % of cases, the specimen sent was delivered as myomectomy while in 30% leiomyoma was diagnosed in a hysterectomy specimen. The majority of leiomyomas were ordinary leiomyoma (97.3%) (p<0.001). Cellular leiomyoma constituted 2.7%. Hyaline degeneration was the commonest associated histological change (5.5%) followed by infarction (2.1%), and calcification (0.4%). The vast majority of leiomyomas were located intramural and multiple leiomyomas were significantly higher than single leiomyomas (p<0.001). **Discussion:** The present study is consistent with previously published data and confirms that leiomyomas are common benign neoplasms of females especially in age group of 31-50 years which may cause considerable morbidity. Further research and increase awareness on this tumour is required.
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1.Introduction

Uterine leiomyomas, also known as myomas or fibroids, originate from the smooth muscle cells of the uterus (Zaloudek *et al.,* 2011). Uterine leiomyomas are the most common benign reproductive tumour in women (Catherino *et al.* 2013), and represents about 20-40% of women in the reproductive age group in the United States (Zimmermann *et al.,* 2012). Leiomyomas vary in size from small to very large tumours and from single to multiple ones (Zaloudek *et al.,* 2011). Although these tumours are benign, they are responsible for significant morbidity in a considerable sector of females as a result of local mass effect and pressure on adjacent organs, excessive uterine bleeding, or pregnancy associated complications; infertility and repetitive abortions (Haney 2000). Leiomyomas are the most common indication for hysterectomy accounting for more than one third of surgery in the United States (Carlson *et al.,* 1993; Farquhar and Steiner, 2002). There is accumulating evidence supporting the effect of racial factor on leiomyoma. There are certain ethnic groups at increased risk for developing leiomyoma (Wei *et al.,* 2006). There is a paucity of data regarding prevalence and incidence retrieved from Population-based research (Laughlin *et al.,* 2010). Although these tumours may be associated with considerable morbidity and represent a major public health problem in Saudi Arabia, very little information is available in literature about the epidemiology, clinical manifestation and pathology of these tumours in this country. The aim of this study is to establish the clinical and pathological pattern of leiomyomas among Saudi females of western region.

2.Materials and methods

In this retrospective cross sectional study, patients diagnosed as leiomyoma at King Abdulaziz University Hospital, Jeddah, Saudi Arabia in the period from January 2005 to December 2012 were included. A computerised search in the archive of the Department of Pathology was done. Patients' data was retrieved from the archive including; age, clinical presentation and/or diagnosis, type of surgery done, histological subtype (ordinary, cellular, mitotically active, or atypical), secondary associated histological changes (infarction, calcification, degeneration, or hyaline change), classification of site within uterus (intramural, subserous, submucous, or mixed), and number of leiomyoma. The work in this study was in

accordance with the bioethical and research committee of Faculty of Medicine, King Abdulaziz University, Saudi Arabia and according to the ethical guidelines of the 1975 Declaration of Helsinki. Data was analysed in Statistical Package for the Social Sciences Program Software version 16.0 (SPSS® Inc., Chicago, IL, USA). Chi square test was used to compare the distribution of variables. A *p*-value <0.05 was considered significant and 95% confidence intervals are expressed as a 2-sided range.

3.Results

A total number of 563 patients were diagnosed as uterine leiomyoma during the study period. The age range of this group was 22-86 years (mean 41.8 years). In this study, leiomyomas were more common in age groups 41-50 years (40.1%) ($p<0.001$, CI=2.53-2.68) followed by the age group 31-40 years (35.2%). The number and percentage of cases falling in each age group is listed in table 1. The most frequent clinical presentation was fibroid ($p<0.001$, CI=7.01-9.04). Different presentations are listed in table 2. In 70 % of cases, the specimen sent was delivered as myomectomy while in only 30% leiomyoma was diagnosed in a hysterectomy specimen ($p<0.001$, CI=1.26-1.34) (Table 3). Leiomyomas were classified according to their histological subtypes; the majority of cases were ordinary leiomyoma (97.3%) and the remaining 15 patients (2.7%) were cellular leiomyomas and no other subtypes were detected (Table 4) ($p<0.001$, CI=1.01-1.04). Histological changes associated with leiomyoma were analysed and the commonest change was hyaline degeneration (5.5%) followed by infarction (2.1%) and calcification (0.4%). The remaining patients had no changes ($p<0.001$, CI=1.14-1.26) (Table 5). The vast majority of leiomyomas were located intramural ($p<0.001$, CI=1.07-1.12). The distribution of other sites is shown in table 6. Regarding the number of leiomyomas, the number of multiple leiomyomas was significantly higher than single leiomyomas ($p<0.001$, CI=1.38-1.41) (Table 7).

Table 1. Age distribution of cases

Age group	Number	Percentage
21-30	60	10.7
31-40	198	35.2
41-50	226	40.1
51-60	62	11.0
>60	17	3.0
Total	563	100.0

Table 2. Clinical Presentation and/or clinical diagnosis

	Number	Percentage
Fibroid	338	60.1
Dysfunctional uterine bleeding	108	19.2
Pelviabdominal mass	26	4.6
Pain	12	2.1
Infertility	12	2.1
Dysmenorrhoea	6	1
Pressure symptoms	3	0.5
Adenomyosis	2	0.4
Incidental clinical presentation	56	10
Total	563	100

Table 3. Surgery done

	Number	Percentage
Myomectomy	394	70
Hysterectomy	169	30
Total	563	100

Table 4. Histological subtype

	Number	Percentage
ordinary	548	97.3
Cellular	15	2.7
Total	563	100

Table 5. Secondary histological changes

	Number	Percentage
Hyaline Degeneration	31	5.5
Infarction	12	2.1
Calcification	2	0.4
No Changes	518	92
Total	563	100

Table 6. Uterine Site distribution

Site	Number	Percentage
Intramural leiomyoma	492	87.4
Subserosal leiomyoma	27	4.8
Submucosal leiomyoma	11	2
Mixed sites	33	5.8
Total	563	100

Table 7. Number of leiomyoma

	Number	Percentage
Single	233	41.4
Multiple	330	58.6
Total	563	100

4.Discussion

Uterine leiomyomas are benign smooth muscle neoplasm originating from the muscle layer of uterus (Zaloudek *et al.,* 2011). Knowledge of leiomyoma

prevalence worldwide could provide clues to the importance of diet, environmental factors, and ethnicity (Flake *et al.,* 2003). The exact prevalence figures are not available mostly because of limited population-based researches and variability of clinical presentation (Ofori *et al.,* 2012). Also data are difficult to compare due to differences in the study population and screening methods (Zimmermann *et al.,* 2012). Despite their common occurrence, data with regard to the aetiology and pathogenesis of leiomyomas are scanty when compared to other neoplasms, most likely due to their benign nature and low mortality rate. Although the aetiology and pathogenesis of leiomyoma is understudied and not clear, several aetiological risk factors such as genetic, racial, environmental and hormonal factors are identified and investigated by researchers and published in recent literature (Flake *et al.,* 2003; Parker, 2007). Translocation t(12:14) and deletion of 7q are common karyotypic abnormalities (Levy *et al.,* 2013).

An increase with age in the prevalence of fibroids during the reproductive years has been demonstrated by several epidemiological studies (Ross *et al.,* 1986; Wilcox *et al.,* 1994; Marshall *et al.,* 1997). The current study shows that leiomyomas are most common in the age group of 41 to 50 years old followed by age group 31-40 years old. The frequency decreased by increasing age to be only 3 % in women above 60 years old. The above findings is in concurrence with figures reported worldwide which show that leiomyomas are common in the age groups of 30-40 and 41-50 years and least common in the age group of 60s (Baird *et al.,* 2003; Divakar, 2008; Ofori *et al.,* 2012; He *et al.,* 2013). However, another survey showed that the mean age ranged between 33.5 and 36.1 years across several countries (Zimmermann *et al.,* 2012). Leiomyomas occurring at a much younger age group is probably related to family history and racial differences (Kjerulff *et al.,* 1996). Our data showed a higher mean age of incidence than in that study which can be explained by the fact that the diagnoses in our cases was done on surgical specimen of post-operative patients while the majority of patients reported in the above study were diagnosed before any surgical intervention. It is clear that in good number of cases, the time between the initial diagnosis and surgical intervention may take several years depending on the presenting symptoms and the trial of medical therapy.

Although leiomyomas are considered benign neoplasms, these tumours are responsible for significant morbidity in women and 20-50 % of patients with leiomyomas present with symptoms such as excessive uterine bleeding, pelvic pain, pressure effects on surrounding organs such as bladder and infertility (Buttram, 1986). On the other hand, the majority of women with uterine leiomyoma are asymptomatic; consequently get less clinical attention and fibroid tumours often remain undiagnosed (Corson, 1995; Schwartz *et al.,* 2000; Okolo, 2008; Ofori *et al.,* 2012). In the present study, only two percent of cases were asymptomatic and discovered in association with other diseases. The clinical symptoms and management strategy are directly related to the type, location and size of leiomyoma (Buttram, 1986). Our study showed that the most common clinical presentation of was dysfunctional uterine bleeding followed by pelviabdominal mass. In 60.1% of cases the clinical diagnosis of leiomyoma was evident to clinicians before surgery based on clinical examinations including the detection of pelviabdominal mass, enlarged uterine size or prolapsed fibroid. However the majority of cases were diagnosed based on radiological examinations including ultrasound, CT scan and pelvic MRI. It has been reported that uterine myomas are associated with infertility in 5–10% of cases when other causes are excluded (Buttram and Reiter, 1981; Wallach and Vu, 1995). Our finding is substantially lower (2.1%) than previous report. This may be related to the age of diagnosis as the age in our series is higher.

According to their location, leiomyomas are classified as sub mucosal (projecting into the endometrial canal) intramural (within the substance of the myometrium), or subserosal (beneath the serosa) (Nucci and Quade, 2011). Submucosal leiomyomas are the least submucosal leiomyomas of uterine leiomyomas representing 5% (Garcia and Tureck, 1984). The results of the study also indicated that 63 out of 143 (44 %) of the fibroids were intramural with only 5.60% been submucosal. Fibroids are muscular in origin which therefore follows that they may be more intramural leiomyoma's compared to the rest (Ofori *et al.,* 2012). Our data showed that the vast majority of leiomyomas were located intramural, followed by mixed locations, subserosal with a minor fraction located submucosal.

Our study showed that multiple uterine leiomyomas were diagnosed in a higher frequency than single leiomyomas. This finding has not been reported in most prevalence based studies regarding uterine leiomyoma. The multiplicity may be related to racial or genetic elements and has to be extensively investigated.

Leiomyomas are classified morphologically histopathologically into types; ordinary leiomyoma, atypical leiomyoma, cellular leiomyoma, myxoid leiomyoma, epithelioid leiomyoma and mitotically active leiomyoma. This histopathological classification usually reflect the morphological features but provide little prognostic information or

clinical guidance for postoperative management (Kempson and Hendrickson, 2000; Ip *et al.,* 2010). The present study showed that 97.3 % out of all cases are ordinary leiomyomas and only 2.7 % were labelled as cellular leiomyomas. No other histopathological subtypes were identified in the present study. This finding concurs with other previous data which indicate that the commonest histopathological type is ordinary leiomyoma and that subtypes other than ordinary are rare (Rammeh-Rommani *et al.,* 2005). Pathologists reviewing cases of leiomyomas should take great care not to confuse the benign leiomyomas of other than ordinary subtypes such as cellular, atypical and mitotically active leiomyomas with leiomyosarcomas (Prayson and Hart, 1995).

Secondary histological changes are associated with leiomyoma. As leiomyoma enlarges, blood supply decreases and results in degeneration. These changes are not associated with outcome or progress of the disease (Prayson and Hart, 1995; Rein *et al.,* 1995). Hyalinising degeneration is common in leiomyomas and is not helpful in predicting the malignant potential of a smooth muscle tumour. Necrosis secondary to ulceration in submucous leiomyomas features acute inflammatory cells and a peripheral reparative process, whereas ghost outlines of nuclei are usually inconspicuous or absent. This must be distinguished from the coagulative tumour cell necrosis that is present in many leiomyosarcomas. Apoplectic leiomyomas are characterized by areas of haemorrhage, but necrosis is absent (Kempson and Hendrickson, 2000). Red degeneration is a subtype of haemorrhagic infarction of leiomyomas that often occurs during pregnancy (Phelan, 1995). In the present study, secondary histological changes were generally very low. The highest frequency was for hyaline change which is consistent to that reported above.

The primary treatment of symptomatic leiomyomas has traditionally been hysterectomy especially for women who completed their childbearing while myomectomy especially the laparoscopic one is performed for women who wish to preserve their uterus (Reiter *et al.,* 1992; Friedman and Haas, 1993; Reich, 1995; Rein *et al.,* 1995; Duhan, 2011). In the current study, 30% of cases were operated for hysterectomies and in 70% myomectomies were performed. Hysterectomy has been the most common treatment modality for symptomatic fibroids in the past. Based on data from 1990 to 1997, the presence of uterine fibroids formed the main indication for hysterectomy in the United States (Farquhar and Steiner, 2002). The difference between our finding and international figures may be explained by the high fertility rate in Saudi Arabia and the tendency of Saudi women to preserve their uteri. A differential diagnosis of leiomyomas includes adenomyosis and differentiating adenomyosis from leiomyomas has clinical importance as adenomyosis requires hysterectomy (Mark *et al.,* 1987; Leibsohn *et al.,* 1990; Scoutt *et al.,* 1994). In the current study, two cases were clinically diagnosed as adenomyosis and the pathological findings in post hysterectomy specimens showed leiomyoma rather than adenomyosis.

Conclusion

The current study presents a series of leiomyomas with findings consistent with previously published data and confirms that leiomyoma are common benign neoplasm in females especially in age group of 31-50 years and may cause considerable morbidity. Further research investigating the genetic and molecular changes in leiomyomas will be needed for better understanding the aetiopathogenesis and to help design better therapeutic strategies in future.

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