Mitotically Active Leiomyoma: A Word of Caution

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Leiomyomas occur at various anatomical sites. While gastrointestinal leiomyomas are relatively uncommon, the female genital tract leiomyomas are one of the most common benign tumors. It is important to rule out the possibility of leiomyosarcoma whenever examining leiomyomas. At times this may be quite taxing as the nuclear atypia may be minimal. Not only many sections have to be submitted but also each section has to be carefully scrutinized for mitotic counts. Even slightly increased mitotic counts have been associated with malignancy. On the other hand, there are occasionally tumors which despite having very high mitotic counts are benign. These tumors are clinically distinct and if proper attention is given diagnosis of malignancy in such cases can be avoided. We describe here a case of vaginal leiomyoma with high mitotic counts in which correct diagnosis was achieved with patience and proper consultation.

Key words: Leiomyoma; mitotically active leiomyoma; mitotic counts.

Introduction

Leiomyomas are the common smooth muscle tumors of female genital tract. Usually their diagnosis poses no problem. On the other hand leiomyosarcomas are highly malignant tumors. Distinction between the two poses no problem if the leiomyosarcoma shows significant dysplasia, however at times it may become a serious problem to differentiate between a leiomyoma and well-differentiated leiomyosarcoma. Under such circumstances the mitotic count per 10 high power fields is considered by many as the most important criterion of distinction. However, mitotic count in uterine smooth muscle tumors has been criticized because of its apparent lack of standardization and reproducibility. Occasionally despite high mitotic counts a leiomyoma may turn out to be a benign tumor. This possibility of “Mitotically active leiomyoma” must be kept in mind in order to avoid unnecessary radical surgery. We encountered such a case and after some initial reservations reached to the correct conclusion. We here describe the case, discuss the difficulties in arriving diagnosis and the role of mitotic counts in smooth muscle tumors.

Case Report

A 28 year old Saudi lady, 29 weeks pregnant (G4P3), was admitted as a case of antepartum hemorrhage. Vaginal examination revealed a ‘granulation polyp’; biopsy was taken and patient was advised bed rest. She again came back after about 10 days with history of more bleeding. At this time a thorough examination revealed a 4 cm submucosal polyp. The polyp was excised and sent for surgical pathology examination. The report revealed a vaginal submucosal smooth muscle tumor showing focal areas of ulceration and granulation tissue. However, aside and apart from these areas the tumor showed edema, hemorrhage and most importantly a high mitotic count. Disregarding the endothelial cells and fibroblasts and concentrating on the smooth muscle cells the mitotic count was over 10/10 HPF. In some focal areas the count reached over 20/10HPF In terms of rapid occurrence and ‘angry looks’ of the tumor, malignancy was a serious consideration. Considering that the patient was in the final stage of pregnancy, it became important to decide whether to continue pregnancy and to wait and see or not. The other
Leiomyomas are the common smooth muscle tumors of female genital tract.1 Usually their diagnosis poses no problem. Clinically apparent lesions are less common in parous than nulliparous women and premenopausal than postmenopausal women.1 25% of women are in reproductive age group.2 These tumors occur subserosally, intramurally and submucosally and produce symptoms referable to their size and location. Although rare but smooth muscle tumors of ovary (both benign and malignant) are also on the record. Many variations of the basic theme exist including red degeneration, apoplectic leiomyoma, hydroid degeneration, leiomyoma with lymphoid infiltration, cellular leiomyoma, atypical or symplasmic leiomyoma, leiomylipoma, palisaded leiomyoma, benign leiomyoblastoma, diffuse leiomyomatosis, intravenous leiomyomatosis and parasitic leiomyoma. Smooth muscle tumors of vulva and vagina show enlargement during pregnancy, however, only vaginal tumors have shown high mitotic activity.

Leiomyosarcomas are highly malignant tumors. Distinction between the two poses no problem if the leiomyosarcoma shows significant degree of dysplasia. However at times it may become a serious problem to differentiate between a leiomyoma and well-differentiated leiomyosarcoma. Under such circumstances the mitotic count per 10 high power field is considered by many as the most important criterion of distinction. The importance of mitotic activity in assessing malignant potential has been widely accepted since the retrospective follow up study by Taylor and Norris in 1966 reestablished the value of mitosis counts in distinguishing histologically cellular and atypical benign leiomyomas from leiomyosarcomas.3 Subsequently, several other studies corroborated the diagnostic value of mitosis counts and provided additional data on the levels of mitotic activity found in clinically benign and malignant tumors.4, 5, 6 From these studies, new recommendations were established for the diagnosis of uterine leiomyosarcoma and a category of "uncertain malignant potential" was added for borderline cases.7 The most popularly used guidelines for diagnosis of uterine smooth muscle tumors have been stated as follows: (1) tumors with fewer than 5 mitotic figures (MF) per 10 high power fields (HPF) are classified as leiomyomas, regardless of the degree of cellularity or the presence of cytologic atypism; (2) tumors with 5 or more MFs/10 HPFs are classified as leiomyosarcomas whenever they also contain cytologically atypical neoplastic cells; (3) tumors with at least 5 but fewer than 10 MFs/10 HPFs are classified as smooth muscle tumors of uncertain malignant potential (S.T.U.M.P) if they are devoid of cytologic atypia; and (4) tumors of 10 or more MFs/10 HPFs are diagnosed as leiomyosarcomas regardless of whether they contain cytologically atypical cells.8 Although the degree of mitotic activity has proved to be an important criterion for malignancy, it is not the only one.4, 9 In 1978 Hart and Billman4 indicated that they had not seen biologically malignant uterine smooth muscle tumors that did not have ominous histologic features of hypercellularity and nuclear atypia in addition to high mitotic activity.

The cause of increased mitotic activity in benign leiomyomas is uncertain. Hormonal stimulation either exogenously or endogenously, may be associated with many morphologic changes. During pregnancy hypertrophy of myometrial smooth muscle cells is common, as is infarction of leiomyomas. Apoplectic leiomyomas with multi-focal hemorrhagic hypercellular zones containing mildly increased mitotic activity have developed in patients taking oral contraceptive hormones, usually combined estrogen/progestin preparations, and in association with pregnancy.10, 11 Tiltman has reported that...
patients using a progestin-only preparation had significantly higher mitotic activity in fibromyomas than did patients using a combined estrogen/progestin oral contraceptive or those who never used any exogenous hormone. In Tillman’s study mitotic counts up till 39 MFs/HPFs were found, however focal areas contained up till 8 MFs/HPFs. None of these myomas showed significant pleomorphism and pursued a benign clinical course. The role of endogenous ovarian hormones in stimulating mitotic activity has been assessed by Kawaguchi and his colleagues. They found high mitotic counts in leiomyomas removed during secretory phase of menstrual cycle than during proliferative and menstrual phases. The mean mitotic count during secretory phase was 12.7/100 HPFs. The relative lack of mitotically active leiomyomas during old age may be related to cessation of ovulation and absence of secretion of progesterone after menopause. Increases mitotic activity may also be related to anatomic location of leiomyomas. It has been observed that pedunculated submucosal myomas are subjected to greater traumatic stimuli and are associated with increased mitotic activity. It is important to emphasize that MFs noted in endothelial cells and fibroblasts of granulation tissue must not be included while performing mitotic counts of ulcerated and infarcted tumors. There has been some criticism regarding interobserver variations while performing mitotic counts. Different methods of counting yield different results. The highest count in a single set of 10 HPFs (method A) produces higher estimates of mitotic activity than does the use of average number of MFs in 10 HPFs (method B). Theoretically delay in fixation can lead to decrease in mitotic count presumably because of the inability to identify pyknotic MFs. However, relatively short delays in fixation that usually occur in modern surgical pathology laboratories can rarely cause this problem.

Silverberg has challenged the emphasis on mitotic activity alone. According to him several other factors have equal or even greater importance while determining the malignant potential of a smooth muscle tumor. These include menopausal status, race, gross appearance of the tumor, extension, invasive tumor margins, cytologic atypia and vascular invasion. So if a patient is premenopausal, tumor grossly resembles leiomyoma and the histologic features are not otherwise disturbing except for a high mitotic count (sometimes in excess of 10 MFs/10HPFs), the preferred diagnosis is mitotically active leiomyoma and the treatment of choice is myomectomy in a young patient if she wishes to preserve her fertility. On the other hand mitotically active smooth muscle tumors that show marked cytologic atypia, necrosis and have invasive margins should be considered malignant regardless of the age of the patient even if the mitotic count is < 10 /10 HPFs. Only rarely such a patient would be young.

Mitotically active leiomyomas as defined by Bell, Kempson and Hendrickson are smooth muscle tumors having more than 5 and less than 20 mitotic figures/10HPFs, show no atypia (or no more than mild atypia), and no coagulative tumor necrosis. The same is true if more than 20 MFs/10HPFs are found, but in this group the experience is little since very few cases have been reported in this category. These mitotically active leiomyomas behave in a benign fashion and they should be labeled as “leiomyomas” regardless of their mitotic activity. These resemble

<table>
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<tr>
<th>Maximum MF/10HPF</th>
<th>Atypia</th>
<th>Diagnosis</th>
<th>Metastatic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Any degree</td>
<td>Leiomyoma</td>
<td>Very low</td>
</tr>
<tr>
<td>5-9</td>
<td>None</td>
<td>Leiomyoma with high mitotic activity</td>
<td>Very low</td>
</tr>
<tr>
<td>5-9</td>
<td>Grade 1*</td>
<td>Smooth muscle tumor of uncertain malignant potential</td>
<td>Low</td>
</tr>
<tr>
<td>5-9</td>
<td>Grade 2 or 3*</td>
<td>Leiomyosarcoma</td>
<td>Moderate</td>
</tr>
<tr>
<td>10 or more</td>
<td>Grade 1*</td>
<td>Leiomyosarcoma</td>
<td>High</td>
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typical leiomyomas both macroscopically and microscopically therefore the older designation of these tumors, “tumors of uncertain malignant potential” should be abandoned. As mentioned before patients with mitotically active leiomyomas are relatively young (mean age=39 years) as compared to patients with leiomyosarcoma (mean age = 43-57 years).

Mitotically active smooth muscle tumors that otherwise resemble typical leiomyomas are clinically benign. Mitotic counts up till 4MF/10 HPFs sometimes occur in leiomyomas and rarely upto 10-25 MFs/10HPFs have been identified as was the case here. A diagnosis of leiomyosarcoma is not justified for such mitotically active leiomyomas unless unequivocal cytological atypia is also present. Leiomyosarcomas are usually hypercellular and are also accompanied by necrosis. Like benign cellular and pleomorphic leiomyomas, mitotically active leiomyomas are relatively small (usually<10 cm in greatest dimension) and are grossly unremarkable. They are usually found in women of reproductive age group and appear to be associated with secretory phase of menstrual cycle, with exogenous hormonal stimulation and of course pregnancy as in this case. Such tumors should not be placed in the category of “uncertain malignant potential” nor should these be diagnosed as low-grade leiomyosarcomas. Myomectomy appears to be a reasonable treatment for such patients.

References

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