Hormonal Therapy and Associated Degenerative Changes, Cytologic Atypia, and Mitotic Activity in Uterine Leiomyomas
A Clinicopathologic Study of 875 Cases

Bradley M. Turner MD, MPH and Fattaneh A. Tavassoli, MD
Department of Pathology, Yale School of Medicine, New Haven, CT, USA

ABSTRACT
Degenerative changes (myxema, ischemia/necrosis/infarction), increased mitotic activity (MA), and/or cytologic atypia (CA) have been observed in uterine smooth muscle tumors in association with oral contraceptive (OC) use. We compared the presence of these changes in leiomyomas (LMs) with and without an associated history of hormonal therapy (HT). A total of 875 cases, including 733 hysterectomies and 142 myomectomies, were eligible for the study. Of the 211 cases on HT, 49 (23.2%) had degenerative changes (DC) compared to 87 of the 664 (13.1%) cases that were not on HT within 3 months of surgery. HTs included combination progestrone/estrogen (102), single agent (SA) progesterone (17), estrogen (29), leuprolide acetate (46) and Tamoxifen (17). Prior HT was significantly associated with DC only in Lo-E (Et-Lo = 4.24, CI=1.69-6.65; p=0.003 [FE]).

RESULTS

<table>
<thead>
<tr>
<th>HT</th>
<th>Mean Age (years)</th>
<th>Mean Tumor Size (cm)</th>
<th>DC (%)</th>
<th>MA ≥ 5/10 hpf (%)</th>
<th>CA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE (n=664)</td>
<td>50.0</td>
<td>8.6</td>
<td>13.1</td>
<td>11.0</td>
<td>8.0</td>
</tr>
<tr>
<td>ANY (n=211)</td>
<td>47.5</td>
<td>7.9</td>
<td>23.2</td>
<td>20.2</td>
<td>15.6</td>
</tr>
<tr>
<td>Lo-E (n=9)</td>
<td>39.8*</td>
<td>6.6</td>
<td>55.6</td>
<td>55.6</td>
<td>55.6</td>
</tr>
<tr>
<td>LA (n=48)</td>
<td>40.8*</td>
<td>9.3</td>
<td>43.5</td>
<td>36.4</td>
<td>28.3</td>
</tr>
<tr>
<td>MP (n=21)</td>
<td>41.0*</td>
<td>6.9</td>
<td>33.3</td>
<td>33.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Other** (n=135)</td>
<td>42.3*</td>
<td>7.0</td>
<td>12.6</td>
<td>10.4</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*Lo-E is also more likely to be associated with increased MA.
**Other: progesterone (SA), norethindrone (SA), estrogen (SA), tamoxifen, leuprolide acetate, and unknown COC. No DC were seen with the following HTs: estrogen (102), single agent (SA) progesterone (17), estrogen (29), leuprolide acetate (46) and Tamoxifen (17).

TABLE AND FIGURES

FIGURE 1. LM of patient on HT with DC (A) and associated histology (B). (18K, C, 40X)

FIGURE 2. LM of patient not on HT with DC (A) and associated histology (B). (18K, C, 40X)

REFERENCES

DISCUSSION
There is growing evidence that progesterone (Pr) can activate growth factor signaling pathways and interacts with growth factor signaling systems. While many LMss exposed to HT do not show either DC or atypical changes, and most LMss showing DC or atypical changes have not been exposed to exogenous HT, abundant DC, increased MA, and/or CA have been described in LMss associated with various HTs; these changes may pose a diagnostic dilemma for the pathologist. Most studies examining morphological features of LMss in women on HT have been observational studies of case series without comparison to any control group. Our study examines a large population of women with LM on HT against a large control population. Many LMss in both populations showed combinations of DC such as myxema and/or ischemia/necrosis/infarction, some with increased CA and/or MA; overall, a higher proportion of women on HT showed these morphologic alterations. Among the various hormones, our preliminary data suggests that Lo-E, LA, and MP are more likely to be associated with varieties of DC, and that Lo-E is more likely to be associated with MA and CA. It is important for the pathologist to consider hormone effect in smooth muscle tumors with MA, DC, and/or CA to avoid over diagnosis of uterine smooth muscle tumors as either a sarcoma or a tumor of uncertain malignant potential.

CONCLUSIONS
- Hormonal effect on LM morphology varies with the particular hormone used.
- LMss in most patients on HT do not show DC or atypical changes; most LMss with DC or atypical changes have not been exposed to HT.
- Endogenous tumor specific factors are clearly associated with morphologic changes in LMss; certain exogenous HTs may enhance or exaggerate these changes.
- Lo-E, LA, and MP are more likely to be associated with increased DC, including myxema and/or ischemia/necrosis/infarction, compared to untreated controls in this population.
- Lo-E is also more likely to be associated with increased MA ≥ 5/10 hpf, and CA. Other HTs did not show a significant association with MA ≥ 5/10 hpf or CA in this population.
- Pathologists should inquire about a history of HT in patients with LM that display such changes to avoid over diagnosis of uterine smooth muscle tumors as sarcomas or of unknown malignant potential, particularly when patients are younger than 40 years of age.