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

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ABSTRACT

Degenerative changes (myxedema, 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 progesterone/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-Estrin (Lo-E), leuprolide acetate (LA), and medroxyprogesterone (MP). Prior HT was significantly associated with increased MA and CA only in Lo-E. Hormonal effect on LM morphology varies with the particular hormone used. Certain HTs are more likely to be associated with increased degenerative and atypical changes.

BACKGROUND

Ip et al. (2007) reported convincing evidence on the association of certain DC in 147 LMs treated with Tranexamic acid (cyklokapron), an exogenous antifibrinolytic non-HT. However, the literature regarding the association of DC or atypical changes in LMs exposed to HT has been inconsistent. Most previous studies have focused on the use of gonadotropin releasing hormone agonists, particularly LA, or the synthetic progesterone analogue LN. Two classic papers by Hart (1985) and Norris (1988) provide excellent morphologic descriptions of degenerative morphology of LMs in women taking various synthetic analogues of SA progesterone or combined oral contraceptives (COC); however, prior and subsequent studies on LM and exogenous HT have a maximum of 107 total cases, and many of these studies assess degenerative or atypical changes in LMs without comparison to any control group.

MATERIALS AND METHODS

The frequency of DC, MA, and CA in LM among women on exogenous HT and those without such history was compared. The pathology database at the Yale School of Medicine between 1/1/2005 and 9/1/2011 was searched for all female patients with the diagnosis of LM; 1815 were identified. Cases associated with concurrent cancer, pregnancy or previous uterine artery embolization were excluded leaving 875 cases for the study. The medical records for the remaining patients' were examined for documentation of any prior HT, along with its duration and dosage when available. A number of different hormones, including LA, several SA progesterone compounds, and several different COCs were used by some women. Odds Ratio (OR) and Relative Risk (RR) with 95% confidence interval (CI), the Yates corrected Chi Square (X^2) statistic, and Fisher Exact test (FE) were used to investigate whether distributions of categorical variables differed in the two groups.

RESULTS

Of the 211 patients with documented hormone use, 49 (23.2%) had DC, 3 (1.4%) had MA ≥ 5/10 hpf, and 5 (2.4%) had CA. All three patients with MA ≥ 5/10 hpf were on Lo-E, and 2 of the 5 patients with CA were on Lo-E. 664 patients did not have documented hormonal use; 87 (13.1%) had DC, 1 (0.15%) had MA ≥ 5/10 hpf, and 13 (2.0%) had CA. Prior HT was significantly associated with DC in Lo-E (OR=8.29, CI=1.89-37.6; RR=4.24, CI=1.69-6.65; p=0.003 [FE]), LA (OR=5.10, CI=2.61-9.95; RR=3.32, CI=2.13-4.78; p<0.0001 [X^2]), and MP (OR=3.32, CI=1.18-9.01; RR=2.54, CI=1.15-4.54; p=0.020 [X^2]). Prior HT was significantly associated with MA (OR=332, CI=24.4-9745; RR=221, CI=22.0-5472; p<0.0001 [FE]) and CA (OR=14.3, CI=1.85-87.8; RR=11.4, CI=1.82-38.3 p=0.015 [FE]) only in Lo-E.

TABLE AND FIGURES

TABLE 1. Hormonal therapy (HT) status and patient age, tumor size, % of LMs with degenerative changes (DC), % cytologic atypia (CA), and % mitotic activity (MA) ≥ 5/10hpf

HT	Mean Age (years)	Mean Tumor Size (cm)*	DC (%)			MA ≥ 5/10 hpf (%)	CA (%)
			Any	Myxedema	Ischemia/Necrosis/ Infarction		
NONE (n=664)	50.0	8.6	13.1	11.0	8.0	0.15	2.0
ANY (n=211)	47.5	7.9	23.2	20.2	15.6	1.4	2.4
Lo-E (n= 9)	39.6*	6.6	55.6	55.6	55.6	33.3	22.2
LA (n=46)	40.8*	9.3	43.5	36.4	28.3	0	2.2
MP (n=21)	41.0*	6.9	33.3	33.3	14.3	0	0
Other** (n=135)	42.3*	7.0	12.6	10.4	8.9	0	1.5

*LM with DC only

**Other: progesterone (SA), norethindrone (SA), estrogen (SA), tamoxifen, levonorgestrel (COC), and norgestrel (COC) and unknown COC. No DC were seen with the following COC (progesterone agent listed): etonogestrol, drosperinone, norgestimate, desogestrol or noerlgestromin.

FIGURE 1. LM of patient on HT with DC (A) and associated histology (B, 10X; C, 40X)

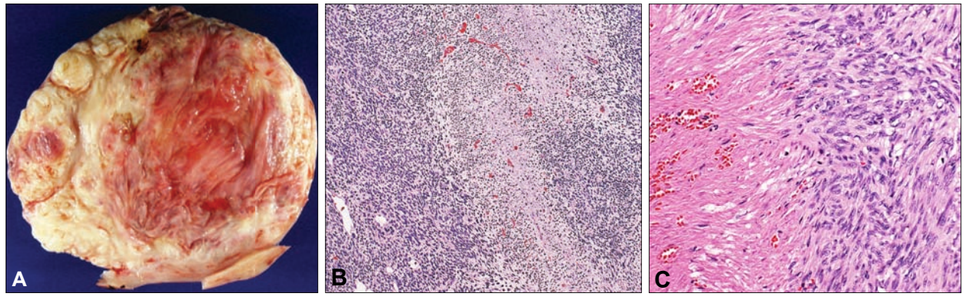
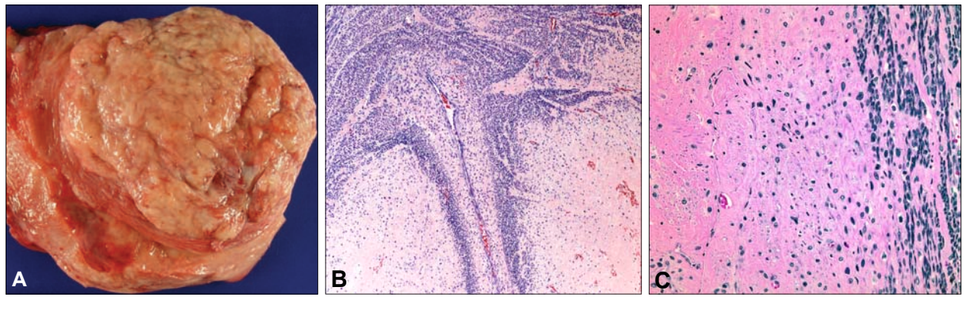


FIGURE 2. LM of patient not on HT with DC (A) and associated histology (B, 10X; C, 40X)



DISCUSSION

There is growing evidence that progesterone (Pr) can activate growth factor signaling pathways and interacts with growth factor signaling systems. While many LMs exposed to HT do not show either DC or atypical changes, and most LMs showing DC or atypical changes have not been exposed to exogenous HT, abundant DC, increased MA, and/or CA have been described in LMs associated with various HTs; these changes may pose a diagnostic dilemma for the pathologist. Most studies examining morphological features of LMs 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 LMs in both populations showed combinations of DC such as myxedema 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 DC, MA, 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.**
- **LMs in most patients on HT do not show DC or atypical changes; most LM with DC or atypical changes have not been exposed to HT.**
- **Endogenous tumor specific factors are clearly associated with morphologic changes in LMs; certain exogenous HTs may enhance or exaggerate these changes.**
- **Lo-E, LA, and MP are more likely to be associated with increased DC, including myxedema 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.**

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