Prominent decidualization following progestin treatment for endometrial hyperplasia and carcinoma as a mimic of large residual tumor: A cautionary tale

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ABSTRACT

Objective: Progestin-based therapy is common for patients with endometrial neoplasia who desire fertility preservation, but some patients ultimately require surgery. Intraoperative assessment, which can use gross lesion size, may impact the extent of surgery performed. We sought to characterize the extent to which grossly identified lesions in the setting of progestin therapy correspond to microscopic findings.

Methods: Thirteen hysterectomy specimens with progestin-treated atypical hyperplasia or endometrioid carcinoma were identified. Clinicopathologic factors were collected by chart review. Slides were assessed for the extent to which decidualized stroma (DS) comprised grossly identified lesions and comparisons were drawn with tumor size, age, and menopausal status.

Results: Mass lesions were described in 11 cases with a median of 4.5 cm (range 1–8.2) and the 2 cases without discrete masses had diffuse thickening. Two patients had only focal residual hyperplasia despite having mass lesions (7 & 2.2 cm). DS was more prominent in premenopausal patients (median 65%, range 10–90%) than in postmenopausal patients (median 18%, range 10–40%; p = 0.06). The distribution of DS throughout mass lesions was variable.

Conclusions: Large mass lesions following progestin therapy may histologically consist of DS with little to no residual neoplastic disease, such that perceived tumor size does not necessarily reflect extensive residual disease, especially in pre-menopausal patients. Intraoperative gross assessment alone may lead to unnecessary lymphadenectomy and/or oophorectomy, but this can potentially be prevented by using frozen section.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic cancer in developed countries (Siegel et al., 2019). Unlike other cancers, the incidence of EC has been increasing over time, in part due to rising levels of obesity Kim et al. (2018). EC is generally treated by hysterectomy with bilateral salpingo-oophorectomy with or without lymphadenectomy, but premenopausal women with early stage EC may prefer conservative management without surgery to maintain fertility Mutch, 2009; Mutch, 2009. Continuous progestin-based therapy, including

megestrol, medroxyprogesterone and levonorgestrel IUD, is the mainstay for those patients desiring to conceive and for those who are poor surgical candidates. Patients undergo routine surveillance of the endometrium every 3–6 months to assess for therapeutic efficacy while receiving progestin therapy and ultimately pursue hysterectomy in the setting of persistent disease or following completion of childbearing (Kesterson (2020); Buckingham et al. (2016)). Preoperatively, MRI is the best modality for detecting myometrial invasion and cervical involvement (Otero-García et al., 2019).

While comprehensive surgical staging of endometrial cancer

involves lymphadenectomy, there is no difference in recurrence following lymphadenectomy for presumed stage I disease (Frost et al., 2017). Since morbidity may exceed benefit for some patients undergoing lymphadenectomy, the "Mayo Criteria" were developed to estimate risk of lymph node metastases Practice Bulletin No, 2015. Per these criteria, patients with grade 1–2 endometrioid tumors that are 2 cm or less and with <50% myometrial invasion have sufficiently low risk for lymph node metastases to avoid systemic lymphadenectomy (Mariani et al., 2008). Full lymph node dissections can also be avoided in the setting of successful bilateral sentinel lymph node mapping, but this technique is not ubiquitous in current practice. Moreover, despite improved algorithms, sentinel lymph node mapping is unsuccessful in approximately 20% of low-grade endometrial cancers, and some surgeons pursue full lymphadenectomy in the setting of failed mapping or when there is a contraindication to mapping, such as dye allergy Tanner et al., 2017. Unlike lymphadenectomy, there is no consensus regarding oophorectomy in premenopausal women with endometrial cancers, and providers must evaluate on an individualized basis each patient's risk of extrauterine disease and potential for reduced recurrence risk against the increased risk of cardiovascular mortality, neurologic disease, and adverse effects on quality of life due to premature menopause (Rivera et al., 2009; Rivera et al., ; Atsma et al., 2006; Rocca et al., 2006; Parker et al., 2009).

Progestins result in predictable histologic changes to the endometrium that can readily be identified by surgical pathologists without the need for ancillary stains (Gunderson et al., 2014; Wheeler et al., 2007; Mentrikoski et al., 2012). Compared to pretreatment samples, samples with treatment effect show a decrease in glandular crowding and architectural complexity as well as changes in the endometrial stroma, which frequently demonstrates frank decidualization. Moreover, glands show decreased cellularity with low to absent nuclear stratification, a decrease in the nuclear-to-cytoplasmic ratio, and metaplastic features, including prominent eosinophilia. Though specific criteria for pathologic assessment have yet to be formally developed, these features guide assessment of progestin efficacy, with persistence of cytologic atypia being most predictive of residual disease on hysterectomy.

Despite the use of progestin therapy for endometrioid neoplasia, the literature describing the post-treatment pathology of these tumors is focused on microscopic descriptions (Gunderson et al., 2014; Wheeler et al., 2007; Mentrikoski et al., 2012). Given the role for intraoperative assessment in surgical decision-making, our objective was to study the gross findings of these lesions and how these findings correspond to microscopic findings and preoperative imaging. Here, we describe the gross lesions of thirteen women who underwent hysterectomy after receiving progestin therapy and the implications these findings have for routine practice.

2. Materials and methods

We obtained approval from the UW-Madison Health Sciences Institutional Review Board (IRB #2017–0765) to perform a retrospective review of charts and archived slides from women at our institution, who had undergone hysterectomy due to low-grade endometrial cancer of atypical hyperplasia after progestin treatment. Using a natural language search within our laboratory information system, we identified 13 patients treated with progestin therapy prior to hysterectomy for atypical endometrial hyperplasia (complex hyperplasia with atypia/endometrial intraepithelial neoplasia) or FIGO grade 1 endometrioid carcinoma from 2010 to 2019. Initial diagnoses were obtained from biopsy specimens from hysteroscopy and D&C for most women except for 5, 7 and 8 whose specimens were obtained by pipelle. Patient demographics obtained by chart review included ethnicity, gravidity, BMI, polycystic ovarian syndrome, clinical presentation, age at diagnosis and at surgery, duration of progestin therapy, duration between biopsy and surgery, and type of surgery. MRI imaging findings, when available, were also recorded. Patients were regarded as post-menopausal when over the age

Table 1
Detailed clinical information for patient cohort.

		Age	BMI	Initial Dx	Pre-Tx MRI	Post-Tx MRI	Tx Days	Progestin Type(s)	Indication for surgery/Pre-surgical biopsy	Gross Tumor (cm)	Worst Disease at Hyst	DS	MMR
Pre-menopausal	1	28	37	FIGO 1	2.8 cm tumor	1.4 cm thick with 8 mm focus	757	Megace, IUD	Personal decision to forgo fertility preservation/Benign	4.5	FIGO 1	90%	Intact
	2	32	29	CH	4.2 cm tumor	5.1 cm tumor	268	Megace, IUD	FIGO 1	6.2	FIGO 1	90%	Intact
	3	34	66	CAH	NA	NA	273	Megace, Provera, Norplant	CAH	2.2	CAH	70%	Not tested
	4	34	67	CH	NA	15 mm thick	62	Megace, IUD	CAH	NA	FIGO 1	25%	Not tested
	5	36	42	FIGO 1	NA	2.8 cm tumor	68	Provera	FIGO 1	7	Focal H	90%	Intact
	6	37	31	FIGO 1	NA	NA	24	Megace	FIGO 1	4.2	FIGO 1	70%	Not tested
	7	41	33	FIGO 1	NA	NA	332	Megace, Provera, IUD	FIGO 1	3.5	FIGO 1	60%	Intact
	8	42	35	CAH	NA	NA	17	Provera	CAH	NA	FIGO 1	10%	Not tested
Post-menopausal	9	51	39	FIGO 1	NA	NA	68	Megace	FIGO 1	7	FIGO 1	30%	Intact
	10	58	49	CAH	6.8 cm tumor	NA	272	Megace	FIGO 1	8.2	FIGO 1	10%	Intact
	11	58	62	FIGO 1	NA	NA	72	Provera	FIGO 1	1	FIGO 1	10%	Intact
	12	58	54	CAH	NA	NA	88	Megace	CAH	6	FIGO 1	40%	Intact
	13	59	44	CAH	NA	NA	59	Provera, IUD	CAH	2.5	FIGO 1	25%	Intact

of 50. Surveillance biopsies were performed for all pre-menopausal patients (1–8) and one post-menopausal patient (11). With the exception of Case 1, who opted for hysterectomy despite a benign surveillance biopsy, all surveillance biopsies showed persistent or worsening disease, ultimately resulting in hysterectomy (Table 1).

The size of gross lesions was recorded from review of the pathology report. Lesions were also histologically assessed using archived hematoxylin and eosin-stained slides from the hysterectomy specimens for the extent to which decidualized stroma (DS) comprised the volume of grossly identified lesions. Comparisons were made between the extent to which DS comprised lesions and age, menopausal status, and tumor size. Two cases lacking a discrete mass measurement were excluded from comparisons involving lesion size. Student's *t* test was used for statistical analysis with GraphPad Prism 8.0 Software. Errors bars represent standard errors of mean.

3. Results

We identified 13 patients who were treated with progestin therapy comprising megestrol, medroxyprogesterone, or levonorgestrel IUD and subsequently underwent hysterectomy. Demographic data and other characteristics are presented in Table 1. The median age at diagnosis was 41 years (range: 28–59) with 10 women (76.9%) having severe obesity (BMI > 35) and 5 women (38.5%) with history of PCOS. There were 8 (61.5%) premenopausal and 5 (38.5%) postmenopausal women. All 5 post-menopausal (>50 years) women received progestin therapy as a bridge to hysterectomy to control bleeding. Among the eight premenopausal women (<50 years), six patients opted for hysterectomy within three months of starting progestin therapy.

4. Characteristics of premenopausal women

Of the 8 premenopausal women (<50 years), 7 were Caucasian, 5 were nulligravid and 5 were obese with median BMI of 36 (range 29–67). All women presented with abnormal uterine bleeding except for one with amenorrhea whose hysteroscopy incidentally showed thickened endometrium with difficulty identifying normal anatomy. Five had a history of polycystic ovarian syndrome. Histologic diagnoses from biopsy were 2 with complex hyperplasia without atypia that later progressed to having atypia, 2 with complex hyperplasia with atypia, and 4 with FIGO grade 1 endometrioid carcinoma. Following diagnosis, all women were put on conservative progestin therapy that included megestrol, medroxyprogesterone and/or levonorgestrel IUD as part of the regimen. Progestin treatment lasted for a median of 168 days (range 17–757) with a median of 201 days (range 17–799) between diagnosis and hysterectomy. Of the 8 premenopausal women, 4 had oophorectomy and 3 had lymphadenectomy which occurred at the time of hysterectomy.

Six uteri were described grossly as having mass lesions, with a median mass size of 5.4 cm. Two uteri lacked discrete masses but were described as having diffuse thickening up to 4 mm and 1.8 cm. Among those with discrete mass lesions, DS comprised a between 10% and 90% (median 70%) of the gross lesion, in contrast to 10% and 25% in the two cases that were described as having thickening without a discrete mass.

5. Characteristics of postmenopausal women

Of the 5 postmenopausal women (>50 years), all were Caucasian and obese (BMI > 35) with median BMI of 51.5 (44–62). All women initially presented to clinic with abnormal uterine bleeding. Histologic diagnoses from biopsy were complex hyperplasia with atypia (n = 3) and FIGO grade 1 endometrioid carcinoma (n = 2). Following diagnosis, they used progestin therapy consisting of megestrol, medroxyprogesterone and/or levonorgestrel IUD as a bridge between diagnosis and surgery to control uterine bleeding. Progestin treatment lasted for a median of 72 days (range 59–272). All 5 postmenopausal women had oophorectomy and 2
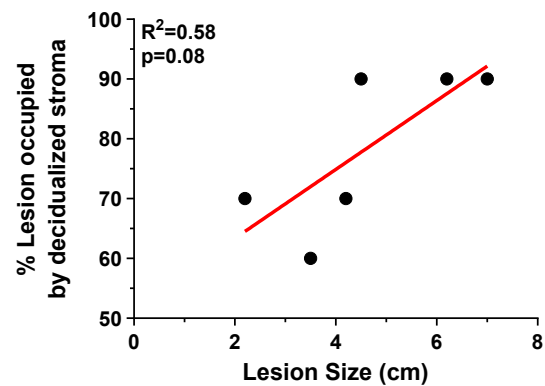

Fig. 1. Mass size of neoplastic lesion plotted against stromal decidualization for premenopausal women under age 50.
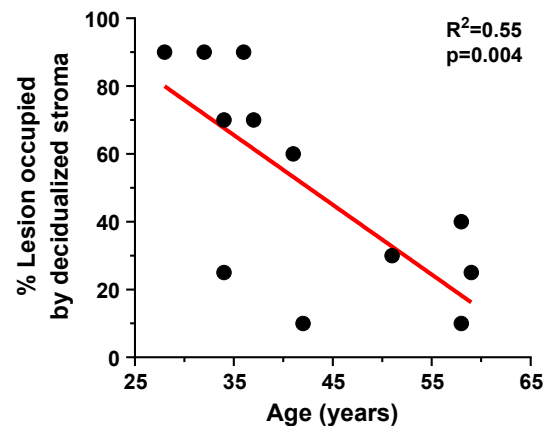

Fig. 2. Stromal decidualization plotted against age for all women.

had lymphadenectomy. The median lesion size on the hysterectomy specimen was 6 cm (range 1.0–8.2 cm) with median DS of 25% (range 10–40%) of the lesion.

6. Gross and histologic findings are often discordant in premenopausal but not in postmenopausal patients

Three lesions with 90% of volume representing DS were among the largest in the premenopausal patients, ranging from 4.5 to 7 cm in greatest dimension, suggesting a positive correlation between decidualization and lesion size. There were also two large lesions with less decidualization (7 cm with 30% and 8 cm with 10%), which occurred in patients over the age of 50, suggesting that exogenous progestin effects were less pronounced in post-menopausal women. When assessing premenopausal patients (<50 years), a positive trend for percent decidualization and lesion size emerged, with $R^2 = 0.58$ (p = 0.079) (Fig. 1). Moreover, one highly decidualized mass lesion with a size of 7 cm contained only focal residual hyperplasia without definitive atypia, despite an alarming gross appearance. Similarly, in another 2.2 cm mass, only focal atypical hyperplasia was present. Of note, when present, carcinoma was not distributed evenly throughout the mass lesions.

Finally, we noticed when assessing age in relation to DS that there was a significant negative correlation between age and the extent of decidualization (Fig. 2, R2 = 0.55. p = 0.004), suggesting that the extent of stromal decidualization by exogenous progestins is affected by the presence of endogenous hormones. There was also a modest correlation between the time on progestin therapy and the amount of DS, which was significant in premenopausal women ($R^2 = 0.259$, p = 0.038) but not in postmenopausal women ($R^2 = 0.257$, p = 0.051).
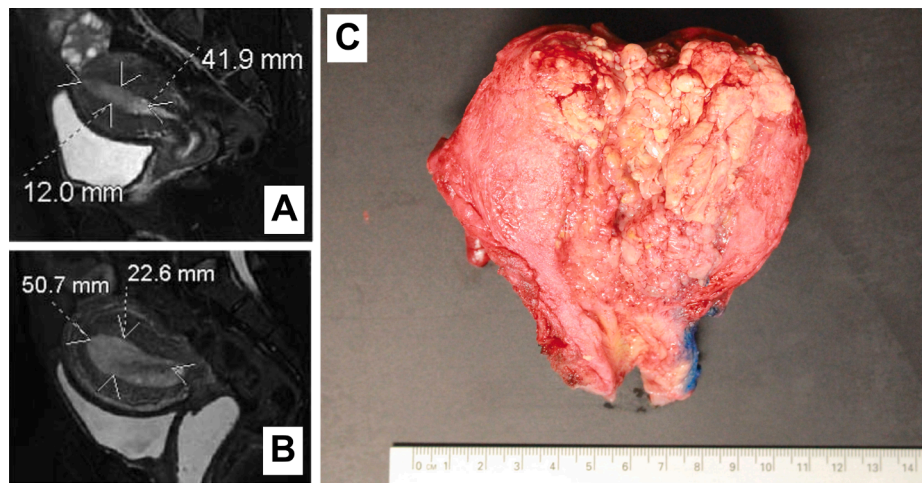
Fig. 3. (A) Pelvic MRI of mass in (C) before progestin treatment. Largest dimension is 41.9 mm. (B) Pelvic MRI of mass in (C) after treatment. Largest dimension is 50.7 mm. (C) Gross photograph of bivalved uterus showing a 6.2 cm mass lesion.
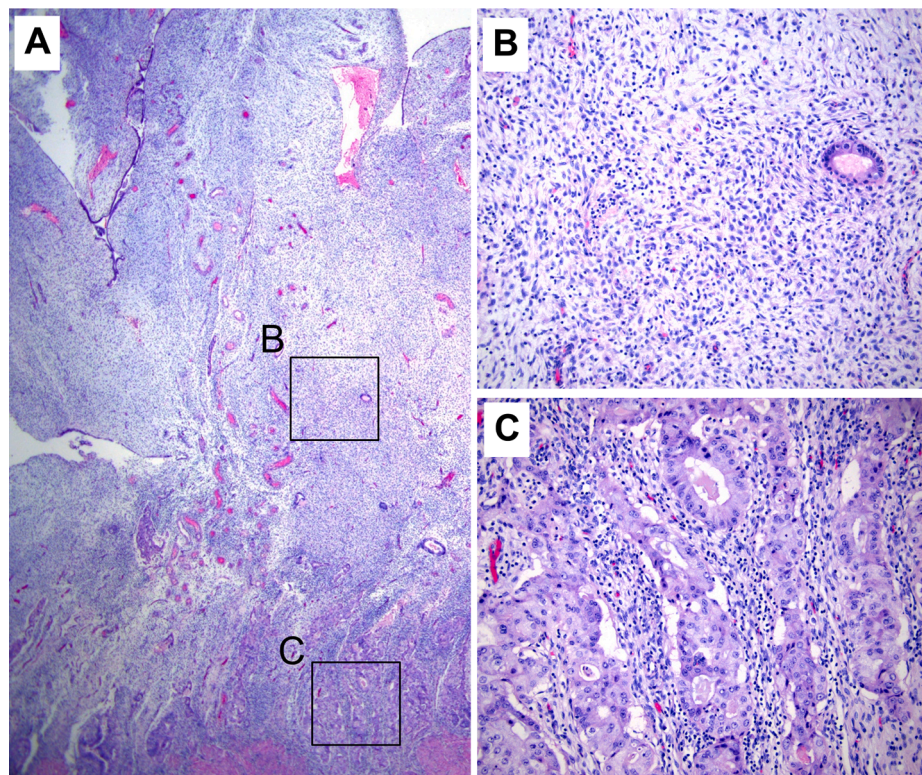
Fig. 4. (A) Scanning magnification (x20) of premenopausal patient with 6.2 cm mass. Decidualized stroma comprises the vast majority of the grossly evident mass. (B) Higher magnification (x200) of decidualized stroma and diminutive gland. (C) Higher magnification of focal endometrial carcinoma demonstrates crowded glands without intervening decidualized stroma. The focus of carcinoma comprises approximately 5% of the endometrial volume in this figure.

7. Correlation with imaging findings

MRI findings were available for a minority of patients, with both pre-treatment and post-treatment images available for only one premenopausal patient who had an original diagnosis of atypical hyperplasia (Patient 2 in Table 1). Prior to treatment, MRI demonstrated a 4.19 cm mass lesion in the endometrium. Following 7 months of treatment, repeat MRI revealed increase in this lesion to 5.07 cm (Fig. 3A, B). Following hysterectomy, the uterus grossly contained 6.2 cm mass in the endometrium (Fig. 3C), correlating well with the MRI findings. Histologically, however, while there was focal carcinoma, 90% of this lesion consisted of DS (Fig. 4A-C).

8. Discussion

Here we have shown that benign DS can comprise the vast majority of gross lesions in a subset of patients treated with progestin and that the gross appearance of the lesion in this context may not necessarily reflect the degree of treatment response. Moreover, we observed that these effects are more pronounced in premenopausal women than in postmenopausal women, raising concern that discordance between gross and histologic findings could lead to unnecessary lymphadenectomy

and/or oophorectomy, particularly in premenopausal patients for whom the decision to pursue oophorectomy is most relevant. Of note, in one case, DS produced the appearance of progressive disease by MRI during presurgical evaluation.

Intraoperative decision-making regarding lymphadenectomy and/or oophorectomy incorporates gross findings, either alone or in combination with histologic assessment. While the presence of large mass lesions is bound to be alarming, DS can be readily identified on morphologic grounds alone histologically and is therefore amenable to evaluation by frozen section for cases in which the patient desires to avoid lymphadenectomy and/or oophorectomy. By appreciating DS, it can be determined whether the tumor consists largely of tumor or if dramatic expansion of the stroma is producing a large mass lesion. The marked heterogeneity we observed in our specimens raises the possibility of a false negative due to sampling, but histologic assessment has the potential to determine whether the bulk of a lesion represents tumor or if any residual tumor remaining comprises only a small subset of the mass lesion. Multiple sections at the time of frozen evaluation will minimize the potential for false negatives.

The marked heterogeneity we observed also explains the discrepancy between surveillance biopsies and final diagnosis following hysterectomy. While it is clear that persistent disease on surveillance biopsy is predictive of residual disease at the time of hysterectomy, the absence of apparent disease does not guarantee the absence of residual disease in the uterus; even generous samples could be composed entirely of neighboring DS and leave residual carcinoma untouched in the setting of focal disease. Nonetheless, in this setting, while there may be residual tumor present, it is likely to occupy only a minority of the mass lesion. As highlighted previously, premenopausal patients had the largest lesions composed predominantly of decidualized stroma rather than neoplastic disease (Table 1).

In summary, our study demonstrates that progestin therapy may confound the gross assessment of endometrial neoplasia preoperatively and at the time of surgery, with the trend that premenopausal women are likely to exhibit exuberant mass lesions that may contain little to no residual neoplastic disease, and importantly, that may continue to generate abnormal signal on MRI. These gross findings may be deceptive and suggest a higher percentage of residual carcinoma than is present, especially in premenopausal women. In this setting, intraoperative decision-making can be supported through intraoperative frozen section. Further study in larger series are required to determine the extent to which these findings can be generalized.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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