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Correlation between steroid receptor expression and response to progestational therapy in patients with atypical endometrial hyperplasia or cancer

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ABSTRACT

Background: Conservative management of atypical endometrial hyperplasia (AEH) or endometrial cancer (EMCA) often relies on the treatment of synthetic progestins, which show varied success and response rates. We evaluate the correlation between steroid receptor expression and response to progestin therapy in patients with AEH and EMCA.

Methods: Retrospective cohort study collected data for patients with AEH or EMCA who had an endometrial sample after receiving conservative therapy utilizing either Megestrol acetate or Levonorgestrel Intrauterine device (IUD). Immunohistochemistry (IHC) was performed on pre- and post- treatment biopsy samples to assess androgen receptor (AR), estrogen receptor (ER), and progesterone receptor (PR) expression. IHC scores (1–12) were calculated based on staining intensity and percentage of positive cells.

Results and analysis: We identified 15 patients with AEH and EMCA between 2015 and 2023 with the majority of African American ethnicity (53 %). Fourteen patients (93 %) received Megestrol acetate, and 1 patient received Levonorgestrel IUD alone. Three patients ultimately underwent hysterectomy. Seven (46.6 %) endometrial samples had strong positivity for AR, PR and ER expression on pre-treatment biopsies, and only 3 (20 %) of them maintained strong positivity for the 3 receptors in the post-treatment. Patients who successfully responded to the treatment demonstrated a significantly greater decrease in IHC scores after the treatment compared to those who did not respond ($p = 0.009$).

Conclusion: Steroid receptor expression could be used as a possible biomarker for response to progestin therapy in patients undergoing conservative management for AEH and EMCA.

1. Background

Endometrial cancer (EMCA) is the sixth most commonly cancer worldwide and the fourth most common cancer affecting women in the United States. In 2020, 417,000 individuals were diagnosed with EMCA across the world, and in 2023 an estimated 66,200 women will be diagnosed with EMCA in the United States (Sung et al., 2021). While EMCA is predominantly a disease affecting post-menopausal women, 25 % of women diagnosed with EMCA will be premenopausal and 5 % will be under the age of 40 (Biler et al., 2017). ESGO guidelines recommend standard surgery including total hysterectomy, bilateral salpingo-oophorectomy (TAH/BSO) in stage 1 EMCA with the option for ovarian preservation for premenopausal women less than 45 with low grade endometrioid histology confined to the uterus (<50 % invasion) (Concin et al., 2021). There are options of hormonal therapy for patients with atypical endometrial hyperplasia (AEH) or G1 EMCA wishing

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fertility preservation or medically unfit patients if offered (Concin et al., 2021). Successful treatment of AEH, a premalignant endometrial lesion, and early-stage cancers in women desiring fertility or elderly, morbidly-obese, patients with multiple medical comorbidities where the risk of surgery could outweigh the likely benefit. using synthetic progestins such as medroxyprogesterone acetate (MPA), Megestrol Acetate (Megace) or the Levonorgestrel intrauterine device (LNG IUD) has been well described (Akhavan, 2021; Chandra, 2016).

Recently, a randomized control trial of LNG IUD for AEH and stage 1EMCA reported 6-month complete response rates of 82 % and 43 % for AEH and early stage EMCA respectively (Janda et al., 2021). Although reports have shown that conservative management of AEH and early-stage EMCA is often successful, the reasons for response or lack of response are unclear. Various biomarkers have been evaluated for correlation with response to progestin therapy including estrogen receptor (ER), progesterone receptor (PR), phosphatase and tensin homolog (PTEN), Nuclear factor erythroid 2-related factor 2 (Nrf2), human epididymis protein 4 (HE4), paired box gene 2 (PAX2), and proliferating cell nuclear antigen (PCNA) among others (Wang, 2021; Behrouzi, 2020; Chen, 2020; Travaglino et al., 2019). Studies have demonstrated conflicting results about biomarkers such as PTEN, which has shown inconsistent reliability (Chen, 2020; Raffone, 2019), and Nrf2 which exhibited a strong correlation with progestin resistance (Wang, 2016). Additionally, PR has been identified as a predictive biomarker for therapeutic response (Yamazawa, 2007). Megestrol Acetate (Megace ^{R}) is a 17-hydroxy progestin used in the treatment of AEH, advanced or recurrent EMCA and metastatic breast and prostate cancer. Overall response rates of up to 35 % to Megestrol acetate have been reported in patients with recurrent or advanced EMCA (Rauh-Hain and Del Carmen, 2010). In addition to its progestational activity, in-vivo experiments have demonstrated strong androgenic and glucocorticoid activity (Sung, 2015; Ghatge, 2005), explaining its efficacy in prostate cancer (La Vecchia, 2022). Similarly, data has also revealed androgen receptor (AR) binding activity for other progestins including Levonorgestrel (Shamseddin, 2021).

To our knowledge few studies have assessed the glandular expression of the steroid receptors specifically AR in AEH or EMCA as a biomarker for response to progesterone therapy. Given the heterogenous and inconclusive results of the biomarkers that have been examined, research into steroid receptor expression could have both prognostic and therapeutic implications. We hypothesize that glandular expression of the steroid receptors, specifically AR correlates with response to progestin therapy in patients undergoing conservative therapy of AEH or EMCA.

2. Method

We reviewed the data of all the AEH and EMCA patients treated at Karamanos Cancer Institute/ Wayne State University from January 2015 to the present (# IRB-22-05-4609). We included patients aged $\geq$ 18 who underwent conservative therapy for AEH or EMCA utilizing either Megestrol acetate or LNG IUD. We excluded patients with Lynch syndrome, those who had a prior hormonal therapy or patients without an evaluable pre-therapy endometrial biopsy sample. Clinicopathological parameters of the patients were collected, including age at pretreatment biopsy, race, histology, BMI at diagnosis, type, dose and duration of progesterone therapy, smoking history, previous medical history, type of surgery, FIGO disease stage, tumor size, date of last follow- up, and pregnancy status. Immunohistochemistry (IHC) for AR, PR and ER was performed on pre- and post-treatment biopsy samples. The results were independently scored by two gynecology pathologists. The IHC assessment was performed according to the manufacturer's antibody manual which typically includes positive and negative controls to validate the staining procedure. Glandular and stromal IHC staining was assessed based on intensity of intranuclear staining: (no staining (0), weak (1), moderate (2), and strong (3)). Percentage of positive cells was scored: (1–10 % (1 +), 11–50 % (2 +), 51–80 % (3 +) and > 80 % (4 +)). The final immunohistochemical score was calculated as described by Remmele et al. by multiplying the staining intensity by the percentage of positive cells (Remmele et al., 1986). Overall Scores were classified as: (1–4: low immuno reactivity, 5–8: moderate immunoreactivity, 9–12: high immunoreactivity). Response to the treatment was defined as regression of endometrial histology (AEH or EMCA) to benign endometrium and non-response was defined as either no evidence of disease regression or a worsening of the patient pathology. The expression of pre- and post-treatment steroid receptors were correlated with the response to progestin therapy. Univariate and multivariate logistic regression analyses and Pearson correlation coefficient were utilized for statistical analysis.

3. Results

Fifteen patients met our inclusion criteria during the study period, and fourteen of them are currently alive. The median age at diagnosis is 36 (range;25–68), and median BMI at diagnosis is 41.7 (range; 27–65). The majority of the patients are of African American (AA) ethnicity (53 %), the remaining are white, Asian and unknown (26 %, 6 % and 13 % respectively). None of the patients had a previous medical history of other malignancy or smoking. Nine patients were diagnosed with EMCA (60 %) and 6 with AEH (40 %). Fourteen (93 %) patients received Megestrol acetate; either alone (10 patients) or along with Levonorgestrel IUD (4), and one patient received Levonorgestrel IUD alone. The median length of treatment was 12 months (range, 3–25). Three patients ultimately underwent TAH-BSO due to persistent disease with the final pathology documenting AEH for 2 patients and grade 2, stage 2 EMCA for 1 patient. Complete response was seen in nine patients, and six had no response (Table 1). Fig. 1 shows representative examples of IHC staining in pre and post treatment biopsies of patients who had a complete response to therapy.

On evaluation of pre-treatment biopsy, 7 (46.6 %) patients had strong positive expression for all three receptors (AR, ER and PR) but

Table 1
Patients Demographics.

Characteristics	N=15 (%)
Age at pretreatment biopsy (median)	36 (25-68)
BMI (median)	41.7 (27-65)
Race	
African American (AA)	8 (53%)
White	4 (27%)
Asian	1 (7%)
Unknown	2 (13%)
Previous history of Smoking	
Yes	0 (0 %)
No	15 (100%)
Previous history of cancer	
Yes	0 (0 %)
No	15 (100%)
Current status	
Alive	1 (7%)
Dead	14 (93%)
Pre-treatment Diagnosis	
Endometrial cancer	9 (60%)
FIGO grade 1	8 (89%)
FIGO grade 2	1 (11%)
Atypical endometrial hyperplasia	6 (40%)
Treatment	
Megestrol acetate	14 (93%)
Megestrol acetate alone	10 (71%)
Megestrol acetate + Levonorgestrel IUD	4 (29%)
Mirena IUD	1 (7%)
Responders	9 (60%)
Non-responders	6 (40%)
Surgery	
Yes - TAH-BSO	3 (20%)
No	12 (80%)
Follow up period, years (median)	5 (0.5-8).

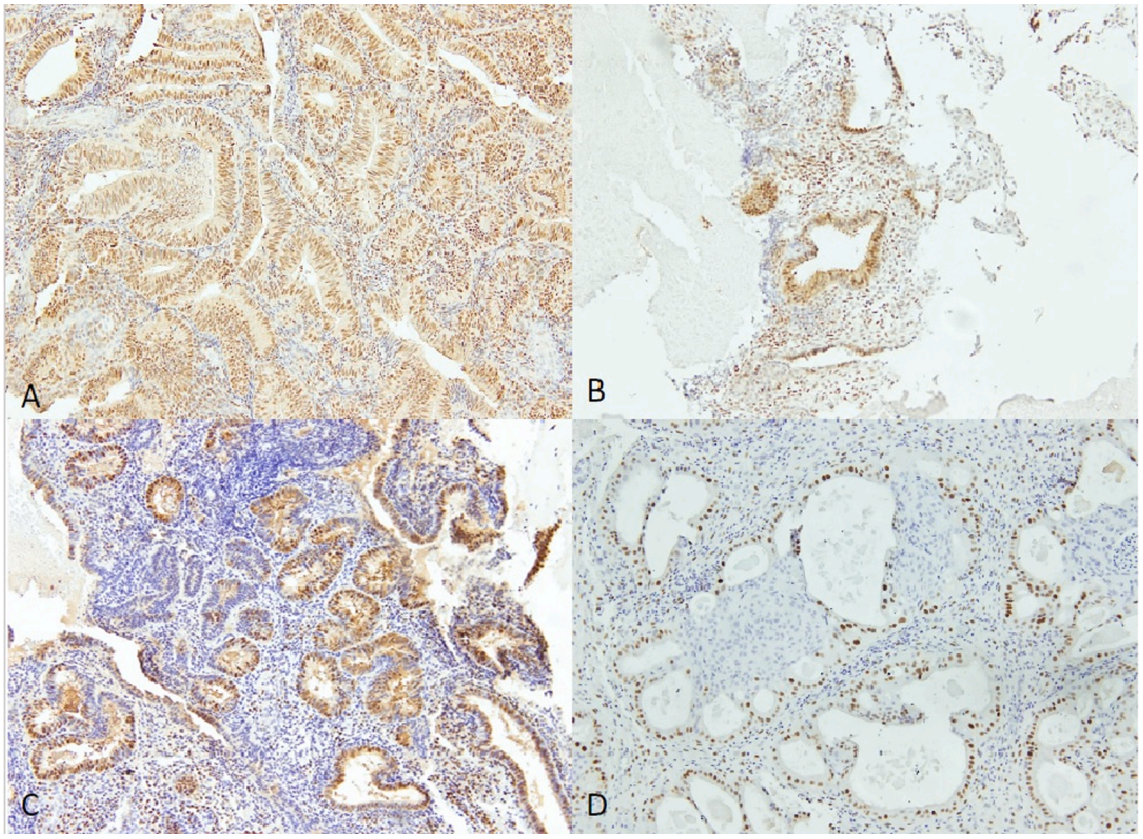

Fig. 1. EMCA and AEH biopsies with IHC stain at 100X power. (A) EMCA sample, AR expression in pre-progesterone treatment, (B) EMCA sample, AR expression in post-progesterone treatment. (C) EMCA sample, PR expression in pre-progesterone treatment, (D) EMCA sample, PR expression in post-progesterone treatment.

after receiving the progesterone treatment, only 3 (20 %) of them maintained strong positivity for the 3 receptors. Evaluating AR staining alone, 11 (73 %) pre-treatment biopsies had high scores, with 2 (18 %) of them changed to moderate and 4 (36 %) to low score after the treatment. Regarding PR staining, 10 patients (66 %) had a high score with 4 (40 %) of them changed to low score after receiving the treatment. For ER staining, all (100 %) patients had high intensity pre-treatment biopsy with only 3 (20 %) of them changed to moderate and low intensity post-treatment (Fig. 2).

To correlate receptor expression with response to therapy, pre and post treatment biopsy samples were compared between the responders and non-responders. Patients who responded to the treatment demonstrated a significantly greater decrease in AR score alone (mean −6.11 vs. −0.50; p = 0.009), PR score alone (mean −5.44 vs. −0.50; p = 0.007), and combined AR + PR + ER scores (mean −12.11 vs. −1.5; p = 0.001) after the treatment when compared to those who did not respond. The ER score did not show a significant decrease (mean −0.56 vs. −1.50; p = 0.603) (Table 2).

Then, we evaluated the correlation between race and changes in receptor expression. AA patients demonstrated a significantly greater decrease in AR scores after the treatment compared to non-AA patients (mean −2.33 vs. −7.4; p = 0.041). No change in ER or PR expression was noted between the 2 groups.

Finally, we evaluate the relation between BMI and smoking to

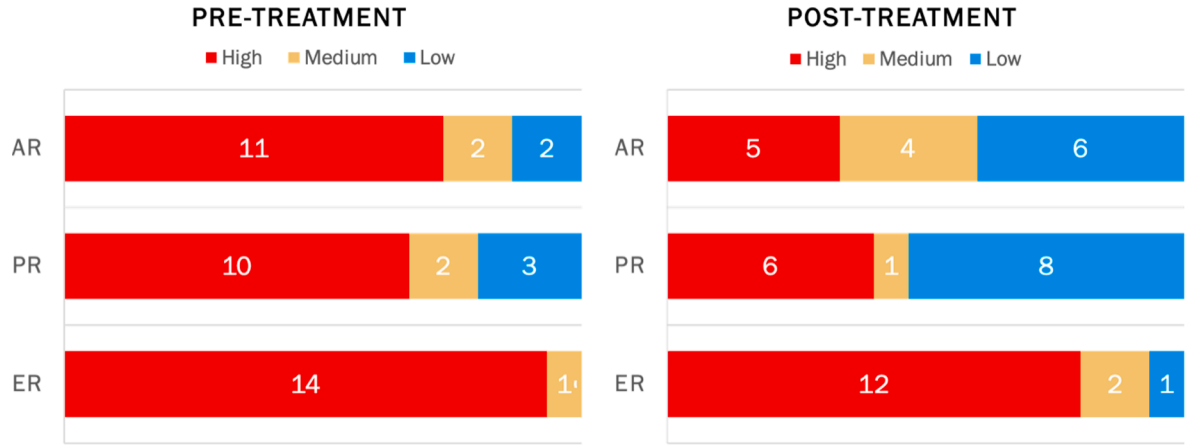

Fig. 2. Changes in overall-score levels for hormone receptors markers before and after progestin therapy. Receptor expression before (left) and after (right) the treatment. high score (red), medium score (yellow), low score (blue).

Table 2
Unpaired *t*-test for difference in scores post-treatment to pre-treatment.

		N	Mean IHC score in pre-treatment	Mean IHC score in post-treatment	Difference (post-pre)		p
					Mean	SE	
AR	**Responder**	9	11.5	5.4	−6.11	1.25	*0.009*
	Non-responder	6	9.8	9.3	−0.5	0.45	
PR	**Responder**	9	10.2	4.7	−5.44	1.29	*0.007*
	Non-responder	6	6.1	6.6	0.5	0.32	
ER	**Responder**	9	11.5	11	−0.56	0.7	0.603
	Non-responder	6	12	10.5	−1.5	0.95	
AR + PR + ER	**Responder**	9	33.2	21.1	−12.11	1.06	*0.001*
	Non-responder	6	27.9	26.4	−1.5	1.12	

changes in receptors scores. BMI and smoking were not correlated with receptor expression changes (Table 3).

4. Discussion

Conservative management of AEH and EMCA either due to fertility preservation or medical comorbidities has become increasingly prevalent in the practice of gynecologic oncologists. The optimization of patient outcomes when treated with progestin therapy lies heavily on our understanding of the molecular markers associated with treatment response. While there are several biomarkers which have been evaluated for their differing effects on the progression or indication of increased risk for cancer, their role in predicting treatment response to hormonal therapy has been limited. While the vast majority of patients will respond to progestational therapy, questions such as when to stop unsuccessful therapy or how to counsel patients about their chance for successful resolution remain. Data in prostate and breast cancer have suggested a correlation between AR expression and successful treatment of metastatic prostate (La Vecchia, 2022) and breast cancer (Ghatge, 2005) with Megestrol acetate. We thus asked whether steroid receptor expression either individually or in aggregate in the endometrium predicted a positive response to progestational therapy in patients with AEH or EMCA (Westin et al., 2021).

There is a large discrepancy in the reported efficacy of hormonal therapy in the treatment of EMCA and AEH. Synthetic progestins have been used to treat various endometrial pathologies including AEH and early-stage EMCA. Also, multiple factors including dose, histology and route of delivery can play a role in the response rate to progestin therapy. Piatek et al, reported a higher response rate with higher progesterone dose comparing to lower doses 73.3 % vs. 55.6 %, respectively (Piatek et al., 2021). While Zhang et al and Westin et al, reported a discrepancy based on the diagnosis, EMCA vs. AEH (79.47 % Vs. 88.74 %) (Zhang et al., 2017), and (66.7 % vs 90.6 %) (Westin et al., 2021) respectively. Systematic reviews and *meta*-analyses have compared the therapeutic effect of LNG IUD vs. oral progestin with varying degrees of response (Baker et al., 2012 Apr; Yuk et al., 2017 May; Abu Hashim et al., 2015; Gallos et al., 2010) This wide variety of approaches and responses has prevented a lack of definitive standard treatment protocols with respect to the types and dose of progesterone, the treatment period and follow-up methods for assessing response.

In our study, most of our patients were treated with the oral form "Megestrol acetate", nine (60 %) out of the fifteen achieved pathological complete response, which is similar to what is reported in the literature (Ushijima et al., 2007 Jul 1). There was no significant difference in the change in receptors score between AEH and EMCA. However, grade I EMCA demonstrates a significantly greater decrease in AR scores in the post-treatment compared to grade II ($p = 0.048$), indicating a potential grade-specific influence on progestin therapy outcomes which will need to be validated in larger studies.

Megestrol acetate, a synthetic progestin has been shown to regulate varying subsets of genes through PR-A and PR-B isoform, as well as regulate genes by binding to AR, which are similar to genes regulated by the androgen dihydrotestosterone in breast cancer cells (La Vecchia, 2022). In vitro studies conducted on cell lines have shown that MPA can downregulate expression of AR (Rauh-Hain and Del Carmen, 2010). In our study, we find that patients who responded to the treatment had a significant decline in AR and PR expression in the post treatment biopsy when compared to non-responders, but no significant changes were found in ER expression. Similarly, Vereide et al reported a down regulation of ER and PR expression and suggested that it can be used as predictor to response progesterone therapy (Vereide et al., 2006). However, other studies have reached the opposite conclusion (Gunderson et al., 2014).

There are multiple factors that may also play a role in changes in receptor expression. Gaston et al, who reported a racial difference in AR expression among male patients with prostate cancer (Gaston et al., 2003). In our study, AA patients had a significantly greater decrease in AR scores following treatment compared to non-AA patients, a finding which will need to be validated in a larger cohort of racially diverse patients. Additionally, BMI and smoking may contribute to relative expression of AR, PR and ER. Our study did not find an association between BMI and changes in steroid receptors expression. Our study is additionally limited by our small sample size of 15 patients and a majority of AA patients in the sample limits how generalizable our findings are to the general population. Also, due to lost to follow up or unavailability of post treatment blocks, our scores for post treatment IHC is at average of 6 months. Future research should be conducted that analyzes the impact of factors such as race, age, different formulations, and dosing of progesterone therapy on changes in steroid receptor expression in patients undergoing conservative therapy for AEH and EMCA. Additional larger studies will be valuable in analyzing the value of pre and post-treatment biopsies in correlating response to therapy, steroid receptor expression and the molecular classification of EMCA using the ProMisE algorithm (Talhouk et al., 2017). Our data suggest that the change in AR and PR expression between pre and post treatment biopsies may allow practitioners to better counsel patients on when to stop unsuccessful therapy and about their chance for successful resolution of their disease.

Table 3
Receptor expression changes correlation with BMI and smoking.

	Pearson correlation coefficient **(p-value)**			
	AR difference	**PR difference**	**ER difference**	**AR + PR + ER difference**
BMI at diagnosis	−0.06 (0.8)	−0.16 (0.5)	−0.16 (0.5)	−0.24 (0.3)
Smoking	−0.08 (0.7)	0.09 (0.7)	−0.19 (0.4)	−0.08 (0.7)

5. Conclusion

Our study suggests that decrease in AR and PR receptor expression may be a valuable prognostic biomarker for response to progestin therapy. Validation of this finding in a larger cohort of racially diverse patients may allow physicians to use this information to tailor progestin therapy, thereby optimizing treatment response and minimizing

unnecessary interventions for patients undergoing conservative management of AEH or EMCA.

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CRediT authorship contribution statement

Fadi Zaiem: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Mannat Bedi:** Writing – original draft, Investigation, Conceptualization. **Mira Kheil:** Investigation, Conceptualization. **Asem Abujamea:** Investigation. **Deepti Jain:** Investigation. **Dovid Rosen:** Writing – review & editing. **Waed Alkaram:** Investigation. **Seongo Kim:** Formal analysis. **Rouba Ali-Fehmi:** Supervision, Conceptualization. **Radhika Gogoi:** Writing – original draft, Supervision, Conceptualization.

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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