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Significance of Glucose Transporter Isoform-1(GLUT-1) and Progesterone Receptor Immunohistochemical Expression in Uterine Leiomyomas Associated with Endometrial Hyperplasia or Carcinoma

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ABSTRACT

Background: The most typical solid benign uterine tumors are called uterine leiomyomas. The most prevalent gynecologic malignancy worldwide is endometrial cancer. It is mandatory to search for new markers that could facilitate early diagnosis and prognosis of endometrial cancer biopsy specimens; among these are Glut-1, and progesteron receptor (PR).

Aim: To investigate if there is relation between uterine leiomyoma and the associated benign or malignant endometrial lesions.

Materials and methods: This study included 109 patients who underwent a total abdominal hysterectomy, the specimens were fixed in 10% formalin solution and sent to Pathology Department, Faculty of Medicin, Zagazig University and processed for histological routine H&E investigation. Patients were divided into: GI (control group) and included 24 patients diagnosed with uterine leiomyomas with normal endometrium, GII included 60 patients diagnosed with uterine leiomyoma associated with endometrial carcinoma, and GIII included 25 patients diagnosed with uterine leiomyoma associated with atypical endometrial hyperplasia.

Results: Patients with leiomyoma associated with endometrial cancer and coupled negative PR expression were substantially linked with high GLUT-1 expression 26.

Conclusion: High GLUT-1 and low PR expression in leiomyomas could serve as useful additional marker in predicting the increased future risk of hyperplastic atypia and malignancy and differentiate benign endometrium from atypically hyperplastic endometrium.

Keywords: GLUT-1, PR, immunohistochemical, leiomyoma, endometrial carcinoma.

INTRODUCTION

The most typical solid benign uterine tumors are called uterine leiomyomas, likewise called uterine fibroids. Hysterectomy is most frequently performed due to uterine leiomyomas. Uterine leiomyomas affect one in every four women. By age 50, the incidence is greater than 70% [(1)].

Uterine leiomyomas can be divided into common leiomyomas and a few relatively uncommon subtypes, including cellular, atypical, mitotically active, epithelioid, and myxoid leiomyomas, based on histology. Many pelvic illnesses, such as endometrial hyperplasia and endometrial cancer, frequently coexist with fibroid uterus, indicating the presence of shared etiological causes [(2)].

Uterine leiomyomas may put women at risk for developing uterine cancer. Numerous studies found that women with uterine leiomyomas had a 2- to 3-fold higher risk of uterine malignancies and that there was a correlation between uterine leiomyoma and risk of uterine cancer. Uterine leiomyomas have been shown in case series to be more frequent among women having hysterectomy for endometrial carcinoma [(3)].

Uterine cancer is the tenth most prevalent type of cancer among women in Egypt. Endometrial cancer incidence is rising worldwide, according to the Middle East Cancer Consortium (MECC), with 382,069 new cases recorded in 2018 [(4)].

Endometrioid and mucinous carcinoma are under Type (1) of endometrial cancer, while serous, clear cell, undifferentiated carcinoma, and carcinosarcoma go under Type (2). A pathological disease known as endometrial hyperplasia (EH) is marked by hyperplastic alterations in the endometrial glandular and stromal tissues lining the uterine cavity. Endometrioid intraepithelial neoplasia (EIN), also known as atypical endometrial hyperplasia, is thought to be the precursor lesion of endometrial cancer [(5)].

The major fuel used to keep the human metabolism running is glucose. Glucose transport proteins (GLUT) are the main transport proteins controlling glucose entrance into cells in humans. These stages are interdependent and govern glucose hemostasis. There are 14 different kinds of GLUT, each with a unique tissue distribution pattern, sensitivity to the insulin stimulus, and glucose affinity [(6)].

The most popular transport protein, known as GLUT-1, is mostly present in erythrocytes, the blood-brain barrier, the liver, and capillary endothelium. Due to their elevated metabolic rates and glucose needs, malignant cells require a greater expression of the glucose transporter gene. Numerous human malignancies, including bladder, lung, gallbladder, gastric, head and neck, colorectal, ovarian, pancreatic, esophageal, breast, and gallbladder

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carcinoma, have been linked to increased GLUT-1 expression [7].

Increased GLUT-1 expression in uterine leiomyomas may indicate that fibroid cells proliferate more quickly (and hence use more energy) than healthy myometrium does. The use of GLUT-1 immunostaining, on the other hand, may be advantageous as a further marker to distinguish between cases of hyperplasia with and without atypia. This differentiation would aid in the detection of endometrial hyperplasia with atypia, a significant risk factor for endometrial cancer and a known contributor to the development of endometrial tumors, particularly Type 1 endometrial tumors [8].

The ability to distinguish between benign endometrium and atypically hyperplastic endometrium is made possible by the elevated expression of GLUT-1 in endometrial cancer. The uterus is exposed to estrogen and progesterone, two steroid hormones that both have an opposing effect on the endometrial glandular epithelium and myometrium during the normal course of the menstrual cycle [9].

Particularly through the estrogen receptor (ER), estrogen has a mitogenic impact that promotes the growth of the endometrial epithelium. Endometrial hyperplasia and, ultimately, endometrial cancer (EC), can develop quickly if estrogen is not countered [10].

However, by reducing ER expression, preventing active cell division, and encouraging cell differentiation through the progesterone receptor (PR), progesterone functions as an antagonist to estrogen. The lining of the uterus is extremely responsive to hormone action because the endometrium and myometrium express both ER and PR [11].

When compared to normal myometrium, uterine leiomyomas have higher concentrations of estrogen and progesterone receptors, and their volume decreases when ovarian function is suppressed. These factors all play a role in the pathophysiology of uterine leiomyomas [12].

MATERIAL AND METHODS

This study included 109 patients who underwent a total abdominal hysterectomy and were admitted to the department of obstetrics and gynaecology, Faculty of Medicine, Zagazig University and the operation was done during the follicular phase of the menstrual cycle, the specimens were fixed in 10% formalin solution and sent to Pathology Department, Faculty of Medicin, Zagazig University and processed for histological routine H&E investigation. Patients were divided into three groups according to their diagnosis. GI served as the control group and included 24 patients diagnosed with uterine leiomyomas with normal endometrium, GII included 60 patients diagnosed with uterine leiomyoma associated with endometrial carcinoma, and GIII included 25 patients diagnosed with uterine leiomyoma associated with atypical endometrial hyperplasia.

Patients with uterine leiomyomas with normal endometrium, patients with uterine leiomyomas associated with endometrium carcinoma and patients with uterine leiomyomas associated with atypical endometrium hyperplasia were included in the study respectively.

Due to insufficient patient material being obtained for histopathology biopsy, patients with other malignancies, a history of taking hormonal or other medications for at least six months, and a history of internal disease (hypertension, diabetes, or other endocrine diseases) were excluded from the study.

Clinical data: Accurate and complete patient clinicopathological data from archives regarding age, tumor size, FIGO stage, grade, LVSI, LN metastasis and distant metastasis

Methods:

A. Histopathological examination:

Paraffin blocks of all studied cases were recut 3-5 μ thickness sections by a rotatory microtome and stained with Hematoxylin and Eosin (H&E). Two pathologists reviewed slides of all cases to evaluate tumor characteristics.

All cases of endometrial carcinoma were histologically classified according to the current WHO classification of endometrial carcinoma [13].

B-Immunohistochemical study:

Representative samples of 109 leiomyomas associated with the three groups were processed, and their Paraffin-embedded tissue blocks were stained with anti-GLUT-1(Rabbit monoclonal anti GLUT-1antibody , clone(EP141), isotypeIgG, cataloguenumber(BSB6782), diluted1:100, Bioscience for the world). And anti-progesterone receptor antibodies(Rabbit monoclonal anti PR antibody , clone(RBT22), isotypeIgG , ready to use, Bioscience for the world).

Immunohistochemical procedure:

Serial sectioning 3-5 μ thickness intervals of formalin-fixed, paraffin-embedded blocks, deparaffinization in xylene, and rehydration in descending series of alcohols were all done. A 10 mM citrate buffer (pH 6.0) was heated in the microwave for about 20 minutes to perform the antigen retrieval. Using 3% hydrogen peroxide for 10 minutes, endogenous peroxidase was blocked. The slides were repeatedly washed in PBS before being treated with the primary antibody for Rabbit monoclonal anti-GLUT-1 antibody, clone (EP141), isotypeIgG, catalogue number (BSB6782), diluted 1:100, Bioscience for the world, and Rabbit monoclonal anti PR antibody, clone(RBT22), isotypeIgG, ready to use, Bioscience for the world. The slides were kept in a humidity chamber overnight at 2 to 8 C. To prevent flow directly on tissue;

a buffer solution was used to rinse the slides gently. As previously mentioned, immediately tap off any extra buffer, then wipe the slides. After which, the sections underwent a 15-minute at room temperature incubation with an immunohistochemistry kit using a biotin-labelled secondary antibody and a streptavidin-linked peroxidase, and then they were washed after 15 minutes. Tissue sections were treated with the diaminobenzidine (DAB) substrate, incubated for 5 to 10 minutes, and then distilled water was used to gently wash. A solution was used to immerse the slides of Mayer's hematoxylin and incubated for 2 to 5 minutes, depending on the hematoxylin's strength. The distilled water bath was used to rinse the slides gently to remove extra utilized hematoxylin stains, slides were dipped 10 times into an ammonia water bath. Slides were washed for two to five minutes in a distilled water bath. Slides were carefully mounted with a cover slip using D.P.X. after being cleared in xylene for three changes. In the same environment as the examined patients, positive and negative controls were stained. GLUT-1 was tested using placental tissue as a positive control, and sections of human breast cancer tissue were used as a positive control for the PR marker, while the negative control was prepared by substituting PBS for the main antibodies.

Evaluation of GLUT 1 immunostaining :

GLUT-1 expression is considered positive if cytoplasmic or membranous staining of the smooth muscle. In order to accurately calculate the percentage of positively stained tumor cells in tissue samples, all cases with brown color in less than 5% of neoplastic cells were counted as negatively stained. Negative, weak, modest, and severe stains were given grades of 0, 1, 2, and 3, respectively. These results are presented as excellent (2 and 3), poor (1), and negative (0) [14].

A semi-quantitative score that assigns marks based on the percentage of GLUT-1 positive cells was used for the evaluation. a four-Score 0 negative was defined as the absence of tumor cell membrane staining; Score 1+, slightly positive (10% of tumor cells show membrane staining); Score 2+, moderately positive (10 and 50% of tumor cells show membrane staining); Grade 3, strongly positive (50% of tumor cells show membrane staining). Tumors classified as score 2+ or 3+ were considered to overexpress GLUT-1**,** negative Glut1 =score 0, low Glut1 =score 1, high Glut1 =score 2,3 [15].

Evaluation of PR immunohistochemical :

Based on the number of stained nuclei and staining intensity, PR expression was categorized as either negative (absence or weak staining in 10% of the cell nuclei) or positive which was graded as 1+ (up to 25%), 2+ (26%–50%), 3+ (51%–75%), and 4+ (76%–100%) [16, 17].

Pr expression was graded as: grade1+ =up to25%, grade2+ =26%-50%, grade3+ =51%-75% and Grade4+ =76%-100%. Negative Pr expression <10% or weak expression, low Pr expression =grade1+ and grade2+, high Pr expression =grade 3+ and grade4+.

Ethics approval: The study has been conducted according to the guidelines of the local ethical committee of faculty of medicine, Zagazig University ZU-IRB#9125/30-11-2021.

Statistical analysis

The SPSS application (Statistical Package for Social Science), version 26, was used to computerize and statistically evaluate the data that had been gathered. When applicable, data were shown as tables and graphs. Frequencies and relative percentages were used to depict qualitative data. The difference between qualitative variables was calculated using the chi square test (2) and the Fisher exact test, as shown.

RESULTS

Table 1. Association between GLUT-1 expression and endometrial carcinoma.

Variable	GLUT-1			P value
	Negative (n= 26)	Low (n= 14)	High (n= 44)	
Normal endometrium (n= 24)	24 (100%)	0	0	**<0.001***
Endometrial carcinoma (n= 60)	2 (3,3%)	14 (23,3%)	44 (73,3%)	

Fisher Exact test; *: significant at <0.05

There was a statistically significant association between GLUT-1 expression and endometrial carcinoma. High levels of Glut-1 expression were found among those with endometrial carcinoma 44 (73,3%) (Table 1).

Table 2. Association between PR expression and endometrial carcinoma.

Variable	PR, n (%)			P value
	Negative (n= 32)	Low (n= 26)	High (n= 26)	
Normal endometrium (n= 24)	1 (4.2%)	2 (8.3%)	21 (87.5%)	**<0.001***
Endometrial carcinoma (n= 60)	31 (51.7%)	24 (40%)	5 (8,3%)	

Chi-square test; *: significant at <0.05

There was statistically significant association between negative PR expression and patients with endometrial carcinoma associated with leiomyoma. Wherese it was negative in 31 (51.7%)of the patients (Table 2).

Table 3. Association between combined PR & GLUT-1 expression and endometrial carcinoma

Variable		Endometrium		P value
		Normal (n= 24)	Carcinoma (n= 60)	
Combined PR-GLUT-1	Negative-Negative (n= 3)	1 (4.2%)	2 (3.3%)	**<0.001***
	Low- Low (n= 9)	0	9 (15%)	
	High-High (n= 3)	0	3 (5%)	
	Negative-Low (n= 3)	0	3 (5%)	
	Negative-High (n= 26)	0	26 (43.3%)	
	Low-Negative (n= 2)	2 (8.3%)	0	
	Low- High (n= 15)	0	15 (25%)	
	High-Negative (n= 21)	21 (87.5%)	0	
	High-Low (n= 2)	0	2 (3.3%)	

Fisher Exact test; *p is significant at <0.05

Patients with leiomyoma associated with endometrial carcinoma were significantly associated with combined negative PR expression and high GLUT-1 expression 26 (43.3%) (Table 3).

Table 4. Association between GLUT-1 expression and atypical hyperplasia.

Variable	GLUT-1		P value
	Negative (n= 27)	Positive (n= 22)	
Normal endometrium (n= 24)	24 (100%)	0	**<0.001***
Atypical hyperplasia (n= 25)	3 (12%)	22 (88%)	

Fisher Exact test; *: significant at <0.05

There was a statistically significant association between the GLUT-1 expression and atypical hyperplasia associated with leiomyoma. Positive GLUT-1 expression was associated with leiomyoma with atypical hyperplasia (Table 4).

Table 5. Association between PR expression and atypical hyperplasia

Variable	PR			P value
	Negative (n= 19)	Low (n= 9)	High (n= 21)	
Normal endometrium (n= 24)	1 (4,2%)	2 (8.3%)	21 (87,5%)	**0.001***
Atypical hyperplasia (n= 25)	18 (72%)	7 (28%)	0	

Fisher Exact test; *: significant at <0.05

There was a statistically significant association between the PR expression and atypical hyperplasia associated with leiomyoma. Leiomyoma with atypical hyperplasia associated with negative to low PR expression (Table 5).

Table 6. Association between combined PR & GLUT-1 expression and atypical hyperplasia.

Variable		Normal endometrium (n= 24)	Atypical hyperplasia (n= 25)	P value
Combined PR-GLUT-1	Negative-Negative (n= 1)	1 (4.2%)	0	**<0.001***
	Negative-Low (n= 18)	0	18 (72%)	
	Low-Negative (n= 5)	2 (8.3%)	3 (12%)	
	Low-High (n= 4)	0	4 (16%)	
	High-Negative (n= 21)	21 (87.5%)	0	

Fisher Exact test; *p is significant at <0.05

Atypical hyperplasia was significantly associated with combined negative PR expression and low GLUT-1 expression 18 (72%) (Table 6).

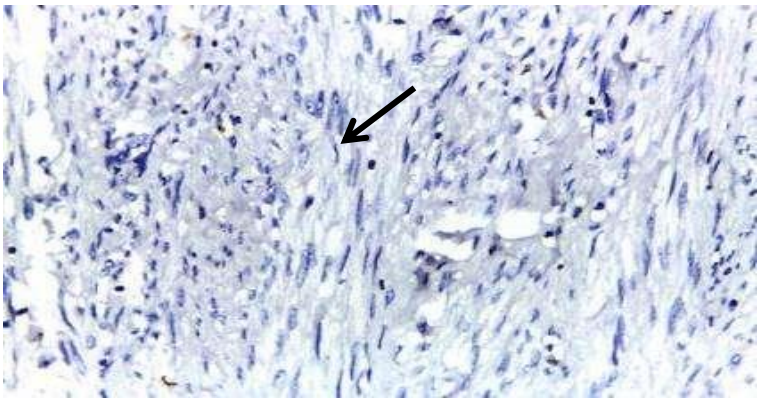

Figure (1): Photomicrograph of section in leiomyoma in a case with normal endometrium showing negative Glut-1 expression (IHC, Glut1, X:400).

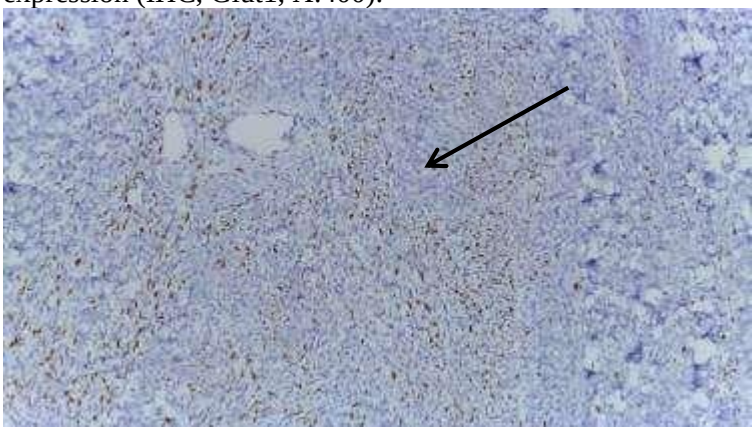

Figure (2): Photomicrograph of section in leiomyoma in a case with normal endometrium showing high PR expression (IHC, PR, X:100).

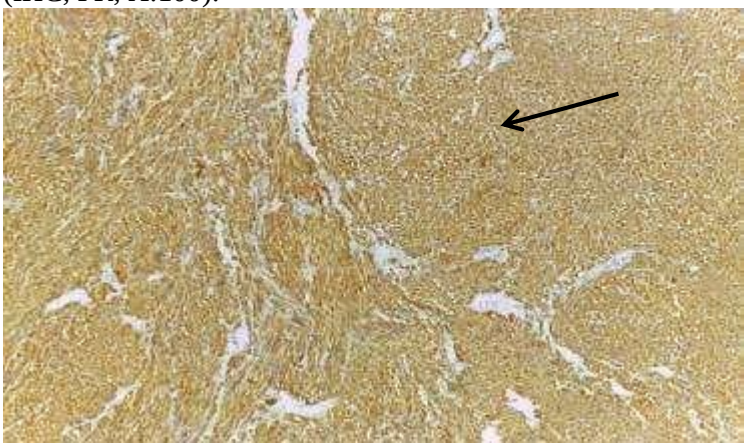

Figure (3): Photomicrograph of section in leiomyoma in a case with high grade endometrial carcinoma showing high Glut-1 expression (IHC, Glut1, X:200).

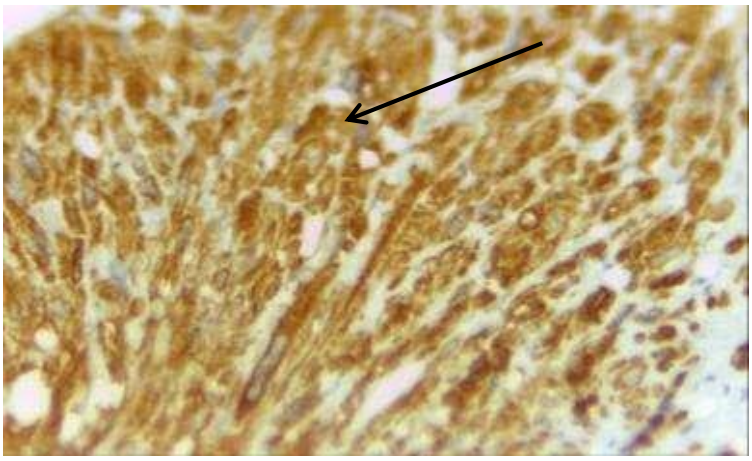

Figure (4): Photomicrograph of section in leiomyoma in a case with high grade endometrial carcinoma showing high Glut-1 expression (IHC, Glut1, X:400).

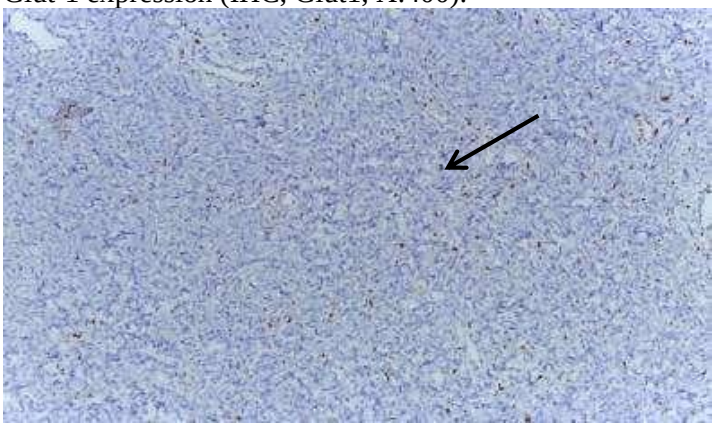

Figure (5): Photomicrograph of section in leiomyoma in a case with high grade endometrial carcinoma showing negative PR expression (IHC, PR, X:100).

DISCUSSION

GLUT-1 expression is enhanced in uterine leiomyoma, suggesting that fibroid cells proliferate more rapidly (and therefore demand more energy) than the healthy myometrium. GLUT-1 immunostaining, on the other hand, might be useful as a further indicator distinguishing cases of hyperplasia with atypia from those without atypia. This differentiation would be helpful in identifying endometrial hyperplasia with atypia, which is known to play a significant role in the formation of endometrial malignancies and is a major risk factor for endometrial cancer particularly Type 1 endometrial tumors [(8)].

Endometrial cancer has a high expression of GLUT-1, which may be used to differentiate between benign and abnormally hyperplastic endometrium. The uterus is exposed to the steroid hormones progesterone and oestrogen during the menstrual cycle which have opposing effects on the endometrial glandular epithelium and myometrium [(18)].

Estrogen hormone, particularly, has a mitogenic action that promotes endometrial epithelial proliferation via oestrogen receptors (ER). If oestrogen is not inhibited, it can cause endometrial hyperplasia's quick onset and the subsequent growth of endometrium cancer (EC) [(19)].

Conversely, Progesterone inhibits oestrogen's ability to cause active cell division while encouraging cell differentiation via the progesterone receptor (PR). Because the endometrium and myometrium express the uterine lining is highly susceptible to hormone action in both ER and PR. [(20)].

The results of the current study revealed that the GLUT-1 was negative among 31 (28.4%) patients, low among 34 (31.2%) patients and high among 44 (40.4%) patients. In addition there was a statistically significant association between GLUT-1 expression in leiomyomas and the presence of endometrial carcinoma. whereas high levels of Glut-1 expression were found among those with endometrial carcinoma 43 (97.7%).

Since it was discovered that cancer cells exhibit a greater glucose consumption than normal tissue, glucose transporters have emerged as one of the central topics in cancer biology. The consequent significant increase in glucose need suggests a need for steadily increased glucose transit via the cell membrane. **Knapp *et al.*** discovered a statistically significant connection between

GLUT-1 and endometrial cancer, supporting our results and going in the same direction [8].

Yang *et al.* [21] shown that the majority of cancers exhibit elevated GLUT1 expression compared to relevant normal counterpart tissues in non-cancerous situations. Additionally, GLUT1, which would not normally be expressed in cells under normal conditions, is frequently expressed in neoplastic cells due to the necessity for power to support unchecked proliferation.

An appropriate biomarker of glucose metabolism that might be simply and affordably evaluated as part of the histologic assessment routine of neoplasms is the level and membrane GLUT1 expression. Numerous research attempted to identify a comparable correlation and confirm that the GLUT1 might be used as a diagnostic and prognostic tissue marker in endometrial neoplasia, but the results were conflicting. **Khabaz *et al.*** [14] found a statistically significant correlation between GLUT-1 and endometrial cancer along the same lines.

The findings of the present study revealed that PR showed negative results among 50 (45.9%) low PR among 33 (30.2%) and high among 26 (23.9%). There was statistically significant association between the negative and low PR expression in leiomyomas associated with endometrial carcinoma. wheares PR expression was negative in 31 (51,7%) of patients and showed low expression in 24 (40%) of paients. Endometrial carcinoma was significantly associated with combined negative PR and high GLUT-1 expression in (41.7%) of patients and with combined low PR and high GLUT-1 in (25%) of patients.

According to **Raffone *et al.*** [22] Progesterone receptor immunohistochemistry expression was evaluated as a potential predictive measure of response in conservatively treated atypical endometrial hyperplasia (AEH) and early endometrial carcinoma (EEC), considering its critical role in mediating the effects of progestogens. The outcomes in this area, meanwhile, seem contradictory.

In a huge meta-analysis, **Travaglino *et al.*** [23] found revealed the reaction of AEH and EEC to the insertion of a levonorgestrel-releasing intrauterine device (LNG-IUD) was correlated with progesterone receptor expression. However, they also discovered that the prediction accuracy was insufficient for the marker to be used alone in clinical settings.

In addition, **Kreizman *et al.*** [24] stated that the characteristics of the disease include the molecular tumor classification, including PR and ER expression. Steroid receptors ER and PR are quantitatively related to histologic differentiation, therapeutic response, and metastatic potential. It was discovered that ER-α expression was lowered in EC and that this decrease continued as EC grading advanced.

Regarding atypical hyperplasia in the present study, statistically significant correlation was present between low GLUT-1 and negative to low PR expression in leiomyomas with atypical hyperplasia. Also atypical hyperplasia was significantly associated with combined negative PR and low GLUT-1 25 (64%).

To our knowledge, the first study to demonstrate GLUT-1 expression in EH and malignancies is that of **Wang *et al.*** In that investigation, endometrial carcinomas and atypia in all EHs were found to have GLUT-1 expression [25].

In contrast to the current results, **Ma *et al.*** [26] observed that 25% of instances of endometrial hyperplasia had positive GLUT-1 expression. While GLUT-1 expression in that study was lower in atypical hyperplasia patients than in the current investigation, it was not stated whether or not atypia existed in the hyperplasia cases.

In this direction, **Xiong *et al.*** [27] cleared that the ability to distinguish between benign endometrium and atypically hyperplastic endometrium is made possible by the elevated expression of GLUT-1 in endometrial cancer. Since elevated GLUT-1 expression is already known to occur in many neoplasms, researchers have looked into how it may affect prognostic factors. The colon cancer study is the first and most notable research on this topic to date.

Consistent with the present study, **Hewedi *et al.*** [28] showed that 100% of leiomyomas and atypical leiomyomas had high PR expression, but the number of leiomyosarcomas had significantly decreased. Along with the outcomes of **Soltan *et al.*** [29] in the non-sarcomatous group compared to the leiomyosarcoma group, there was a statistically significant increase in nuclear PR immunoreactivity.

Furthermore, compared to 47% of leiomyosarcomas, progesterone receptors were discovered to be expressed in 100% of leiomyomas and 96% of atypical leiomyomas [30].

The work by **Llaurado *et al.*** [31] demonstrated a link between the decreased PR expression in EC and the myometrial invasion, supporting the findings of the current investigation. The epithelial to mesenchymal transition (EMT), which is strongly associated with the invasive properties of EC, may be the source of a significant myometrial invasion.

As a result, the aforementioned invasive properties of the tumor may be shown by the lower expression of PR in the tumor cells by **Wik *et al.*** [32].

CONCLUSION

We concluded that high GLUT-1 and low PR expression in leiomyomas could serve as useful additional marker in predicting the increased future risk of atypical endometrial hyperplasia and malignancy and

differentiate benign endometrium from atypically hyperplastic endometrium. Furthermore, their association with the poor prognostic clinicopathological parameters of endometrial adenocarcinoma.

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