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Evaluation of Immunohistochemically Expression of GLUT-1 in Benign Proliferative, Hyperplastic Endometrium and Endometriosis Adenocarcinoma

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Abstract

Objectives: The aim of this study is to evaluate the GLUT-1 expression in benign proliferative, hyperplastic, and malignant endometrial tissues, to evaluate the usefulness of GLUT-1 expression in endometrial hyperplasia, and to determine its role in the neoplastic progression to endometrioid type adenocarcinoma. We also aimed to analyze some prognostic clinical parameters (age, stage, grade).

Methods: This cross sectional study was carried out on paraffin embedded surgical specimens of endometrial tissue. Applying the immune histochemical techniques by using the GLUT-1 as a primary antibody, statistical analysis was done and the correlation with different clinical and pathological parameters were assessed.

Results: 98 cases of endomertial tissue, 17.4% disordered proliferative endometrium, 22.4% endometrial hyperplasia without atypia, 18.4% endometrial hyperplasia with atypia, 41.8% endometrioid adenocarcinoma, 56.1% were GLUT-1 positive. Significant correlation was found between GLUT-1 expression and increasing degree of atypia as it was negative in benign proliferative and hyperplasia without atypia meanwhile positive in hyperplasia with atypia and endometrioid carcinoma. Significant correlation with grade of carcinoma, patient age, no correlation was found with ovarian and cervical metastasis, no significant correlation was found with tumor stage.

Conclusions: GLUT-1 immunostaining may be useful in distinguishing hyperplasia without atypia from hyperplasia with atypia; GLUT-1 overexpression is a consistent feature of endometrioid adenocarcinoma.

Keywords: Immunohistochemically expression, GLUT-1, benign proliferative, endometriosis, adenocarcinoma

Introduction

Endometrial hyperplasia (EH) is an irregular proliferation of endometrial glands, which can progress to endometrial cancer (EC).[1,2] The likelihood of EH progressing to EC is determined by the type of the lesion, which can be a benign response to an unopposed activity of estrogens, or a neoplastic premalignant process.[2] These two conditions require two different therapeutic approaches: benign EH may be managed with observation alone, with progestin reserved to symptomatic cases.[3] On the other hand, premalignant EH could be treated with hysterectomy, although a conservative treatment can be chosen in selected cases (strong wish to preserve fertility or contraindication for surgery). Endometrial cancer (EC) is the second most frequent malignant neoplasm of the female reproductive system in USA.[3] The most common morphological type is endometrioid carcinoma, serous uterine carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma and others.[4] Diagnosis and management of endometrial neoplasms depend greatly on patients' clinicopathological factors [patient age, tumor size and histological type as well as Federation International of Gynecology and Obstetrics (FIGO) grade as prognostic signs]. Yet, these clinical factors are not adequate to predict disease's outcomes due to endometrial tumors heterogeneity.[5] Regardless of significant improvements in cancer management and the good prognosis of endometrial tumors, about 15% of all endometrial tumors recur, of which up to 90% of recurrent tumors happen within 3 years.[6] The recurrent disease prognosis is poor; the median survival barely surpasses twelve months.[7] The aim of this study is to evaluate the GLUT-1 expression in benign proliferative, hyperplastic, and malignant endometrial tissues, to evaluate the usefulness of GLUT-1 expression in endometrial hyperplasia, and to determine its role in the neoplastic progression to endometrioid type adenocarcinoma. We also aimed to analyze some prognostic clinical parameters (age, stage, grade).

Methods

The specimens were formalin-fixed, paraffin embedded tissue blocks; from these blocks, 4 micrometer-thick tissue sections were obtained, then deparaffinized and stained with hematoxylin eosin staining method and immunohistochemical 3 steps polymeric detection staining method. Steps: a) Deparaffinization: This had been performed by immersion in the followings:

1. Incubate the sections in an oven at 65°C for 1 hour.
2. Two changes in xylene, each for 5 minutes for clearing and dissolve the paraffin.
3. Ethanol in gradually decreasing concentration to rehydrate the tissue (100%, 70%, 50%) each for 5 minutes.
4. Distilled water.

b) Hematoxyline and eosine staining method

1. Dewax sections (Deparaffinization as in above).
2. Stain in Harris hematoxylin for 3–10 minute.
3. Wash well in running tap water.
4. Remove excess stain by differentiating the sections in 1% acid alcohol (1% in HCl 70% alcohol) for 5–10 seconds.
5. Wash well in tap water until sections regain their blue color.
6. Stain in eosin for 2–5 minutes.
7. Dehydrate slowly through increasing grades of alcohols (i.e. 70%, 90% and 100%).
8. Clearing by xylene.
9. Mount with DPX (distyrene, plasticiser, xylene).

c) Immunohistochemical staining protocol

The immunostaining method used in the current study was the 3-steps polymeric detection system and included the following steps:

1. Cut and mount 3–4-micron formalin-fixed paraffin-embedded tissues on positive charged slides.
2. Deparaffinization was done by incubating the sections in an oven at 60°C for 2 hours followed by two changes of xylene then rehydrate tissue in decreasing concentration of alcohol (100%, 70%, 50%).
3. The sections were retrieved by using EDTA buffer (Pathn-Situ Cat # PS008) under steam pressure for 15 minutes using PathnSitu s MERS (Multi Epitope Retrival System), then allow to cool for 10 minutes.
4. Wash with 3 changes of IHC wash buffer each for 5 minutes.
5. Place slides in PolyDetector Peroxidase Blocker for 5 minutes.
6. Wash with 2 changes of IHC wash buffer each for 5 minutes.
7. Cover tissue with the Primary Antibody (GLUT-1) which is ready to use and incubate for 30 minutes at room tempreture.
8. Wash with 2 changes of IHC wash buffer each for 5 minutes.
9. Cover tissue with PolyDetector plus Link and incubate for 15 minutes.
10. Wash with 2 changes of IHC wash buffer each for 5 minutes.
11. Cover tissue with Polydetector HRP Label and incubate for 15 minutes.
12. Wash with 2 changes of IHC wash buffer each for 5 minutes.
13. Prepare DAB by adding one drop of PolyDetector DAB Chromogen per mL of PolyDetector DAB Buffer and mix.
14. Cover tissue with prepared DAB substrate-chromogen solution, incubate for 10 minutes.
15. Rinse with 3 changes of IHC wash buffer each for 5 minutes.
16. Counterstain with Mayer's hematoxylin for 2 minutes and then dehydrate.
17. Coverslip.

The evaluation of positive immunoreaction for GLUT-1 antibody is by the diffuse brownish staining of the cytoplasm and membrane and two aspects of the immunostaining parameters were evaluated semiquantitively according to immunereactive scoring:

1. The extent of immunostaining according to the percentage of stained neoplastic cells.
2. The intensity of immunostaining according to the staining of red blood cells as positive internal controls. Then for each case, a combined immunoreactivity score was evaluated by multiplying the score for extent by the score for intensity so the combined immunoreactivity score (IRS) ranged from 0–12.

Statistical analysis was carried out using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student *t*-test was used to compare means between two groups, ANOVA test was used to compare means between three groups or more. Pearson Chi-Square and Fisher's exact tests were used to find the association between categorical variables. A *P*-value of ≤ 0.05 was considered as significant.

Results

Distribution of patients with endometroid adenocarcinoma according to study parameters including (age, glut 1 immune staining, type of biopsy, glut 1 score, staging, grading, cervical involvement, ovarian involvement and myometrium involvement), as shown in Tables 1&2.

Association between GLUT 1 immunostaining score and (endometroid adenocarcinoma, endometrial hyperplasia without atypia, endometrial hyperplasia with atypia and disordered proliferative endometrium) as shown in Table 3.

The association between stage and grade of endometroid adenocarcinoma and glut 1 score including (Mild reaction score (2–3), Moderate reaction score (4–8) and Strong reaction score (9–12) after exclusion of (11 patients) with dilation and curettage biopsy). There was significant association between grade of endometroid adenocarcinoma and glut 1 score as shown in Table 5.

The association between cervical and myometrium involvement and glut 1 score including (Mild reaction score (2–3), Moderate reaction score (4–8) and Strong reaction score (9–12) among patients with endometroid adenocarcinoma. There was significant association between cervical and myometrium involvement and glut 1 score as shown in Table 6.

Discussion

Glucose transporters have become one of the core subjects in cancer biology since it has been found that neoplastic cells show higher glucose metabolism in comparison with normal tissue. The resultant big growth in glucose necessity indicates a

Table 1. **Clinic pathological parameters**

Clinico-pathological variables		Number	%
Age groups	30–39	15	15.3
	40–49	39	39.7
	50–59	20	20.4
	60–69	14	14.2
	>70	10	10.2
Diagnosis	Disordered proliferative	17	17.3
	Hyperplasia without atypia	22	22.4
	Hyperplasia with aypia	18	18.3
	Endometrial carcinoma	41	41.8
Endometrial carcinoma cases	TAH D & C	30 11	73.17 26.82
TAH cases stages	Stage 1	21	70
	Stage 2	9	30
TAH cases grades	Grade 1	19	63.33
	Grade 2	11	36.66
Glut-1 immunereactivity	Positive Negative	55 43	56.1 43.9

Table 2. **The distribution of patients with endometroid adenocarcinoma according to study parameters**

Study variables	Number	%
Age (years)		
30–39	4	9.8%
40–49	9	22.0%
50–59	9	22.0%
60–69	11	26.8%
≥70	8	19.4%
Total	41	100.0%
Type of biopsy		
Hysterectomy	30	73.2%
D and C	11	26.8%
Total	41	100.0%
glut 1 immune staining		
Positive	39	95.1%
Negative	2	4.9%
Total	41	100.0%
glut 1 score		
No reaction (0–1)	2	4.9%
Mild reaction (2–3)	18	43.9%
Moderate reaction (4–8)	8	19.5%
Strong reaction (9–12)	13	31.7%
Total	41	100.0%
Staging		
Stage 1	21	70.0%
Stage 2	9	30.0%
Total	30	100.0%
Grading		
Grade 1	19	63.3%
Grade 2	11	36.7%
Total	30	100.0%
Cervical involvement		
Yes	10	33.3%
No	20	66.7%
Total	30	100.0%
Ovarian involvement		
Yes	0	0.0%
No	30	100.0%
Total	30	100.0%
Myometrium involvement		
<50%	17	56.7%
>50%	13	43.3%
Total	30	100.0%

demand for a consistent rise in the transportation of glucose through the cell membrane. The greater part of tumors shows increased expression of GLUT1 than that has been existed in relevant normal counterpart tissues in non-cancerous states. Furthermore, because of the need for power to serve unrestrained proliferation, neoplastic cell frequently expresses GLUT1 that would not be expressed in the cells in ordinary circumstances.[8] The level and membranous location of GLUT1 expression could be an appropriate biomarker of glucose metabolism that might be assessed easily and economically as part of the histologic assessment practice of neoplasms.[9] Since increased expression of GLUT1 is already known in many neoplasms, its relationship with prognostic parameters has been studied.[10-12] The earliest and the most striking study on this subject to date is the one that was conducted on colon cancer. In addition to indicating GLUT1 as a good marker to determine aggressive biological behavior of colorectal carcinomas, it also showed a direct correlation between lymph node metastases and GLUT1 expression.[12] In endometrial neoplasms, nevertheless, many studies tried to find a comparable association and verify that the IHC GLUT1 phenotype could be utilized as a diagnostic and prognostic tissue marker.[13] This study includes a review of 98 cases, 17 with disordered proliferative disorder, 30 with EH, 41 with endometriod carcinoma. 30 cases were TAH which was graded according to FIGO classification and staged according to AJCC/ISUP for evaluation of various clinical (age) and histopathological (grade, stage, cervical invasion, myometrial involvement) parameters with GLUT-1 expression. Table 4 Our study showed increase membranous &/or cytoplasmic expression of GLUT-1 in EC as compared to normal endometrium, decreased GLUT-1 expression in normal endometrium as well as its weak expression in non-cancerous lesions suggests that this molecule might be involved in endometrial carcinogenesis as the finding of this study. Our study showed increased risk of developing EC with increasing patient age especially in those aged >60 years ($P < 0.001$). Pal N et al. 2018,[14] Alcazar JL et al. 2018,[15] Rosen MW et al. 2019[16] found increase risk of EC with increasing age. A. Corbacioglu et al. 2014,[17] found no relation between increasing age and the risk of developing EC, this probably related to the larger sample number they used. This study was significant regarding differentiating between hyperplasia with and without atypia as GLUT-1 expression was negative in endometrial hyperplasia without atypia, meanwhile its expression was positive with varrying degree of intensity in endometrial hyperplasia with atypia, Max, hui, linli et al. 2015[18] showed significant difference in GLUT-1 expression between endometrial hyperplasia with and without atypia as GLUT1 expression was negative in hyperplasia without atypia, positive expression with varying degree of intensity was noticed in endometrial hyperplasia with atypia. This study showed increasing expression of GLUT-1 with increasing degree of dysplasia from benign proliferative, hyperplasia without atypia through hyperplasia with atypia to carcinoma, the vast majority of EC cases were positive for GLUT-1. Ma X et al. 2015,[18] Al-Sharaky Dr. et al. 2016,[19] mohamad Nidal Khabaz et al. 2019,[20] also found increasing expression with increasing degree of dysplasia, with remarkable expression of GLUT-1 in EC cases. This study showed significant relation between tumor grade and GLUT-1 expression P (0.001) with decreasing intensity of expression as the tumor

Table 3. **Association between GLUT 1 immunostaining score and (endometroid adenocarcinoma, endometrial hyperplasia without atypia, endometrial hyperplasia with atypia and disordered proliferative endometrium)**

Study variables	Diagnosis				Total	*P*-value
	Endometroid adenocarcinoma	Typical endometrial hyperplasia without atypia	Endometrial hyperplasia with atypia	Disordered proliferative endometrium		
glut 1 immune staining						
Positive	39 (95.1)	0 (0.0)	16 (88.9)	0 (0.0)	55 (56.1)	<0.001*
Negative	2 (4.9)	22 (100.0)	2 (11.1)	17 (100.0)	43 (43.9)	
Total	41 (100.0)	22 (100.0)	18 (100.0)	17 (100.0)	98 (100.0)	
glut 1 score						
No reaction (0–1)	2 (4.9)	22 (100.0)	6 (33.3)	17 (100.0)	47 (48.0)	<0.001*
Mild reaction (2–3)	18 (43.9)	0 (0.0)	12 (66.7)	0 (0.0)	30 (30.5)	
Moderate reaction (4–8)	8 (19.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (8.2)	
Strong reaction (9–12)	13 (31.7)	0 (0.0)	0 (0.0)	0 (0.0)	13 (13.3)	
Total	41 (100.0)	22 (100.0)	18 (100.0)	17 (100.0)	98 (100.0)	

*$P \leq 0.05$ was significant.

Table 4. **Association between type of endometrial hyperplasia and glut 1 immune staining and glut 1 score ($N = 40$)**

Study variables	Type of endometrial hyperplasia		Total	*P*-value
	Hyperplasia without atypia	Hyperplasia with atypia		
glut 1 immune staining				
Positive	0 (0)	16 (88.9)	16 (40.0)	<0.001*
Negative	22 (100.0)	2 (11.1)	24 (60.0)	
Total	22 (100.0)	18 (100.0)	40 (100.0)	
glut 1 score				
No reaction (0–1)	22 (100.0)	6 (33.3)	28 (70.0)	<0.001*
Mild reaction (2–3)	0 (0.0)	12 (66.7)	12 (30.0)	
Total	22 (100.0)	18 (100.0)	40 (100.0)	

*$P \leq 0.05$ was significant.

Table 5. **Association between grade and stage of endometroid adenocarcinoma and glut 1 score ($N = 30$)**

Study variables	glut 1 score			Total	*P*-value
	Mild reaction (2–3)	Moderate reaction (4–8)	Strong reaction (9–12)		
Stage					
Stage 1	6 (46.2)	4 (100.0)	11 (84.6)	21 (70.0)	0.069
Stage 2	7 (53.8)	0 (0.0)	2 (15.4)	9 (30.0)	
Total	13 (100.0)	4 (100.0)	13 (100.0)	30 (100.0)	
Grade					
Grade 1	2 (15.4)	4 (100.0)	13 (100.0)	19 (63.3)	<0.001*
Grade 2	11 (84.6)	0 (0.0)	0 (0.0)	11 (36.7)	
Total	13 (100.0)	4 (100.0)	13 (100.0)	30 (100.0)	

*$P \leq 0.05$ was significant.

Table 6. **Association between cervical and myometrium involvement and glut 1 score among patients with endometroid adenocarcinoma ($N = 30$)**

Study variables	glut 1 score			Total	*P*-value
	Mild reaction (2–3)	Moderate reaction (4–8)	Strong reaction (9–12)		
Cervical involvement					
Positive	8 (61.5)	0 (0.0)	2 (15.4)	10 (33.3)	0.027*
Negative	5 (38.5)	4 (100.0)	11 (84.6)	20 (66.7)	
Total	13 (100.0)	4 (100.0)	13 (100.0)	30 (100.0)	
Myometrium involvement					
<50%	3 (23.1)	4 (100.0)	10 (76.9)	17 (56.7)	0.003*
>50%	10 (76.9)	0 (0.0)	3 (23.1)	13 (43.3)	
Total	13 (100.0)	4 (100.0)	13 (100.0)	30 (100.0)	

*$P \leq 0.05$ was significant.

grade increase, also found insignificant relation to tumor stage, which might indicate a prognostic role for GLUT1 as its expression decreased with increased tumor grade. Anagnostou E 2017[21] Mohamad Nidal Khabaz et al. 2019,[20] was found significant correlation between GLUT-1 expression and tumor grade with decreasing expression as the tumor stage increase. This study showed significant correlation with myometrium invasion (P 0.001), also significant correlation with cervical invasion (P 0.027), as GLUT1 expression decrease with the presence of cervical and myometrium invasion thus might give a clue that GLUT1 expression may be decreased with increasing tumor aggressiveness, which might be of prognostic value. Max, hui, linli et al. 2015[18] showed significant correlation between GLUT-1 expression with myometrium and cervical invasion. Canpolat et al. 2015,[22] Anagnostou E 2017[21] Kristyna Nemejcova 2017[23] Mohamad Nidal Khabaz et al. 2019[20] all did not show significant correlation with myometrium and cervical invasion, this could be explained by the larger number of specimens they used in their studies and the possible difference in race and environmental factors.

Conclusion

The absence of GLUT-1 expression in EH without atypia and increased expression in EH with atypia may play a role in distinguishing between them. GLUT-1 could be used as a predictable factor to determine cases with atypical hyperplasia who are at high risk for cancer development. Decreased expression of GLUT1 with increasing tumor stage, myometrium invasion, cervical invasion could be used as a prognostic factor to predict patients at high risk of metastasis.

Conflict of Interest

None.

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