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EVALUATION OF SLUG IMMUNOHISTOCHEMICAL EXPRESSION IN ENDOMETRIAL CARCINOMA

By

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ABSTRACT

Background: SLUG, which is included in the group of zinc finger type proteins, is regarded as major epithelial-mesenchymal transition (EMT) inducers to inhibit the transcription of cell adhesion molecules, including E-cadherin. Some signaling pathways, such as the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, upregulate the expression of SLUG, Slug antisense could prevent EMT indicating that the Slug gene could act a treatment target for tumor invasion and metastasis.

Objective: To studied SLUG immunohistochemical stain expression among Type I (endometrioid) endometrial carcinoma and Type II (serous) endometrial carcinoma.

Patients and methods: Thirty paraffin-embedded endometrial tissue samples were diagnosed as 24 endometrioid endometrial carcinoma (Type I), and 6 serous endometrial carcinoma (Type II) were collected. All endometrial tissue samples of endometrial carcinoma were obtained through hysterectomy. The specimens were collected from archive of surgical pathology files of Pathology Department, Faculty of Medicine, Al-Azhar University, during the period from 2018 till December, 2020.

Results: There was a statistically significant correlation between SLUG expression and grade of endometrial carcinoma (P value<0.001). No case of endometrial carcinoma showed complete absence of SLUG expression. All of the cases (10 cases) of high-grade endometrial carcinoma (4 cases type I and 6 cases type II), showed expression of SLUG in varying degrees of expression, and (5 cases) 50% showed expression of SLUG in more than 50% tumor cells (strong expression), 2 cases 8.3% of type I (EECA) and three cases 50% of type II (serous endometrial ca.). There was no statistically significant correlation between SLUG expression and the age of cases (P value = 0.206). There was no statistically significant correlation between SLUG expression and the types of the endometrial carcinomas (P value 0.002).

Conclusion: SLUG immunohistochemical stain expression was very significantly correlated to the grade and stage of endometrial carcinoma. The correlation between expression of SLUG and high tumor grade, stage are suggesting that SLUG may serve as a prognostic indicator in esophageal carcinoma (EC).

Keywords: SLUG Immunohistochemical Expression, Endometrial Carcinoma.

INTRODUCTION

Endometrial adenocarcinoma is the most common invasive malignant neoplasm of the female genital tract *(Siegel et al., 2012)*.

In Egypt according to the National Cancer Institute (NCI) endometrial carcinoma constituted 1.28% of primary malignant neoplasms and 22.83% of malignant neoplasms of female genital

system, recurrent malignant tumors were reported in 32 cases. Times to recurrence ranged from 1 to 6 years, most of recurrent cases were endometrial adenocarcinoma constituting 65.62% of recurrent cases *(Mokhtar et al., 2016)*.

There are two major classes of endometrial carcinoma. These are commonly described as Type I (the majority) and Type II cancers, which respectively correspond to endometrioid and non-endometrioid histologic types *(Suarez et al., 2016)*.

Type I endometrial cancers are primarily associated with unopposed estrogen exposure and develop in a background of endometrial hyperplasia *(Lax, 2016)*. Endometrioid endometrial carcinoma (EECA) is the prototypical endometrial adenocarcinoma. It is thought to develop following a continuum of premalignant lesions ranging from endometrial hyperplasia without atypia, to hyperplasia with atypia and finally to well differentiated carcinoma *(Boruban et al., 2012)*.

Type II endometrial cancers are unrelated to estrogen exposure and typically arise in a background of atrophic endometrium. They are most commonly of serous and clear-cell morphology. They have not been associated with established risk factors, and no true premalignant lesions have been identified. An early stage of serous carcinoma called serous endometrial intraepithelial carcinoma has been described *(Sherman, 2010)*. The most striking genetic alteration, present in about 90% of serous carcinoma, is p53 mutation *(Tashiro et al., 2010)*.

SLUG, which is included in the group of zinc finger type proteins, is regarded as major EMT inducers to inhibit the transcription of cell adhesion molecules, including E-cadherin. Some signaling pathways, such as the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, upregulate the expression of SLUG *(Gonzalez and Medici, 2014)*.

As a member of the Zinc finger transcription factor family members, Slug is mainly involved in neoplasm malignant phenotype regulation, and could also promote EMT, which is closely related to tumor cell migration and invasion *(Kihara A et al., 2016)*.

Recent researches have indicated that, Slug antisense could prevent EMT, indicating that, the Slug gene could act a treatment target for tumor invasion and metastasis *(Uygur et al., 2015)*.

The aim of the present work was to study SLUG immunohistochemical stain expression among Type I (endometrioid) endometrial carcinoma and Type II (serous) endometrial carcinoma.

PATIENTS AND METHODS

Thirty paraffin-embedded endometrial tissue samples diagnosed as 24 endometrioid endometrial carcinoma (Type I), and 6 serous endometrial carcinoma (Type II) were collected. All endometrial tissue samples of endometrial carcinoma were obtained through hysterectomy. The specimens were collected from archive of surgical pathology files of Pathology Department, Faculty of Medicine, Al-Azhar University, during the period from 2018 till December, 2020.

Sections were routinely stained for hematoxylin and eosin (H&E), to

determine histological grade and stage of endometrial carcinoma. Immunohistochemistry for SLUG (SNAI2) was performed on each paraffin block. Gastric mucosa staining was used as a control for SLUG immunohistochemical staining.

Interpretation of immunohistochemical stains in each case was performed.

Cases of endometrial carcinoma were classified according to FIGO grading of endometrioid carcinoma of the endometrium *(Lax, 2016)*, into low grade (GI) and high grade (G II&III), and to low stage (stage I&II) and high stage (stage III&IV) according to Cancer staging *(American Joint Committee on Cancer, 2017)*.

This study included 30 cases of endometrial carcinoma, 27 cases (23 type I EEC and 4 type I serous ca.) were low stage, and 3 (1 type I EEC and 2 type II serous ca.) cases were high stage.

In according to grading, 20 cases (all of them were type I EEC), were low grade, while 10 cases (4 cases of them were type I EEC and 6 cases were type II serous ca.), were high grade.

To assess SLUG expression, tumor tissue sections were examined and scored under the microscope starting at low power, then higher power magnification for the presence of nuclear staining in tumor cells. Both the extent and intensity of immunostaining were thought. The staining intensity score was graded as follows: weak expression (in less than 50% of tumor cells nuclei), and strong expression (in more than 50% of tumor cells nuclei).

Stain scoring system:

The staining expression of SLUG was evaluated semiquantitatively as follows: 1+ for <25% positive tumor cells, 2+ for 25–50%, 3+ for 51–75% and 4+ for >75%. They were then categorized into low (1+ and 2+) and high (3+ and 4+) for statistical analysis, based on the study by *Wang et al., 2009*.

The protocol of this study was approved by the Ethical Committee Faculty of Medicine, Al-Azhar University on July 2019 (no.Pat._13Med.Research_Evaluation.SLUG>Immunohistochemical.Edometrial carcinoma._0000013), and written consents were taken from all patients.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data was used as mean ± SD (Standard deviation) and range. P value < 0.05 was considered significant.

RESULTS

Thirty paraffin-embedded endometrial tissue samples diagnosed as 24 endometrial endometrioid carcinoma (EECA) (Type I) and 6 endometrial serous carcinomas (Type II) were collected. All endometrial tissue samples were obtained through hysterectomy.

Eighty percent of the cases (24 cases) were EECA (type I) and 20% (6 cases) were serous carcinoma (type II) **(Figure 1)**.

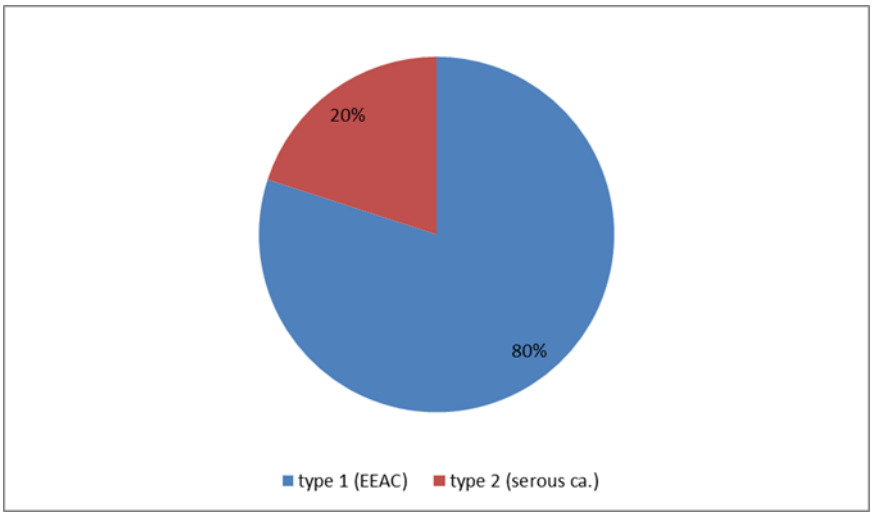

Figure (1): Types of Endometrial Carcinoma

In this study, the patients ranged in age from 42 to 80 years with mean age of 60±9. 40% of EECA (12 cases) and 50% (3 cases) of serous carcinoma were below 60 years old. On the other hand, 50% of serous carcinoma (3 cases) and 60% of EECA (12 cases) were above 60 years old (Figure 2).

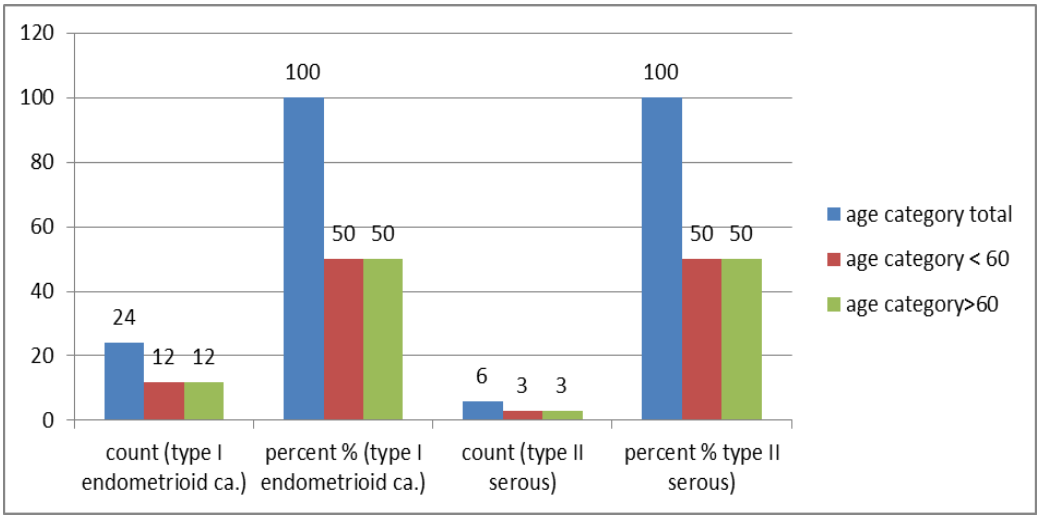

Figure (2): Patient age and types of endometrial carcinoma

In this study, 27 cases (90%) were low FIGO stage and 3 cases (10%) were high FIGO stage. 66.7% of the study cases (20 cases) were low FIGO grade, while 33.3% (10 cases) were high FIGO grade **(Table 2)**.

Table (2): FIGO stage and FIGO grade category among the study cases

Parameters \ Cases		Count	%
FIGO stage	Low (I+II)	27	90%
	High (III)	3	10%
FIGO Grade	Low (I+II)	20	66.7%
	High (III)	10	33.3%
Total		**30**	**100%**

95.8% of type 1 (EECA) (23 cases) and 60% of serous carcinoma (4 case) were low stage, and of ECCA (1 case) and 40% of serous carcinoma (2 cases) were high stage. This was statistically significant (P value <0.033).

78.1% of EECA cases (20 cases) were low FIGO grade. On the other hand, 16.6% of EECA (4 cases) and all cases of serous carcinoma were high FIGO grade. This was statistically significant (P value <0.001) **(Table 3)**.

Table (3): Correlation between the FIGO stage & FIGO grade, and the types of endometrial carcinomas

Parameters \ Types of Endometrial carcinoma		Type 1 (EECA)		Type 2 (serous ca.)		P value
		Count	%	Count	%	
FIGO stage	**Low (I+II)**	23	95.8%	4	60%	**0.033**
	High (III)	1	4.2%	2	40%	
FIGO Grade	**Low (I+II)**	20	83.4%	0	0%	**<0.001**
	High (III)	4	16.6%	6	100%	

There was no significant correlation between SLUG expression and the age of cases (P value = 0.624). SLUG immunoreactivity in more than 50% of cells was noted in 7.4% of cases with low FIGO stage (2 cases) and 100% of cases with high FIGO stage (3 cases). SLUG expression was in less than 50% of cells in 0% of high FIGO stage cases and 92.6% of low FIGO stage cases. This was statistically significant (P value <0.001) **(Table 4)**.

Table (4): Relation between SLUG expression and the age of the cases

Age category \ SLUG Expression	Less than 50%		More than 50%		P value
	Count	%	Count	%	
≤60 years	13	86.7%	2	13.3%	**0.624**
> 60 years	12	80%	3	20%	

There was a significant relation between SLUG expression and the FIGO grade of endometrial carcinoma (P value =0.002). SLUG immunoreactivity was noted in more than 50% of cells in 50% of cases of high grade endometrial carcinoma (5 cases) and showed immunoreactivity in less than 50% of cells in the other 5 cases of high grade endometrial carcinoma. All cases of low grade endometrial carcinoma showed slug immunoreactivity in less than 50% of cells.

Also there was significant relationship between slug expression and FIGO stage of endometrial carcinoma (P value = <0.001). SLUG immunoreactivity was noted in more than 50% of cells in 7.4% of low FIGO stage endometrial carcinoma (2 cases) and showed low immunoreactivity in less than 50% of cells in 92.6% of cases of low FIGO stage endometrial carcinoma (23 cases). All cases of high FIGO stage showed high immunoreactivity in more than 50% of cells 100% (3 cases) **(Table 5)**.

Table (5): Relation between SLUG expression and the FIGO stage and FIGO grade

SLUG Expression / Parameters		Weak positive (<50%)		Strong Positive (>50%)		P value
		Count	%	Count	%	
FIGO stage	Low (I+II)	25	92.6%	2	7.4%	<0.001
	High (III)	0	0%	3	100%	
FIGO Grade	Low (I+II)	20	80%	0	0%	<0.001
	High (III)	5	20%	5	100%	

There was a significant relationship between SLUG expression and type of endometrial carcinoma. 91.7% of cases of type 1 endometrial carcinoma showed expression in less than 50% of cells (22 cases). On the other hand only 8.3% of cases of type 1 endometrial carcinoma showed immunoreactivity in more than 50% of cells (2 cases). While, 50% of type 2 endometrial carcinoma showed immunoreactivity in less than 50% of cells (3 cases). On the other hand 50% of cases of type 2 endometrial carcinoma showed immunoreactivity in more than 50% of cells (3 cases) **(Table 6)**.

Table (6): Relation between types of Endometrial carcinoma and SLUG Expression

Types of Endometrial carcinoma / SLUG Expression	Type 1 (EECA)		Type 2 (serous ca.)		
	Count	%	Count	%	
Weak positive (<50%)	22	91.7%	3	50%	0.014
Strong Positive (>50%)	2	8.3%	3	50%	

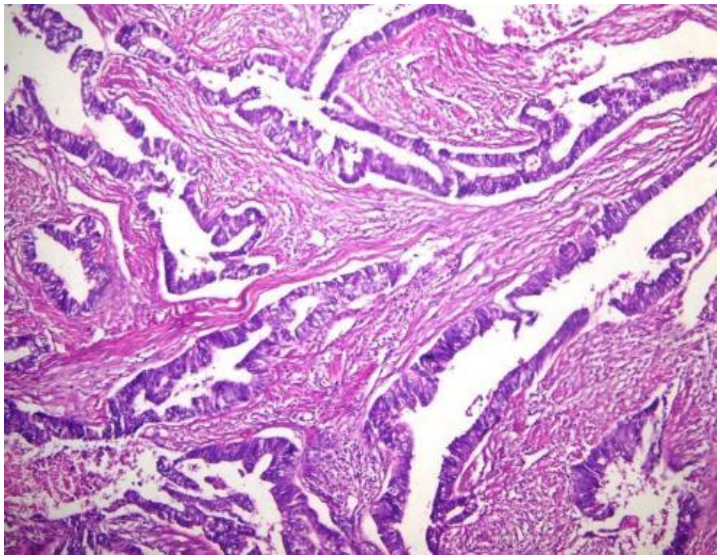

Figure (3): Low grade endometrioid endometrial carcinoma showing, malignant glands lined by malignant cells showing features of malignancy, pleomorphism and heperchromatism. **(H&E, x200).**

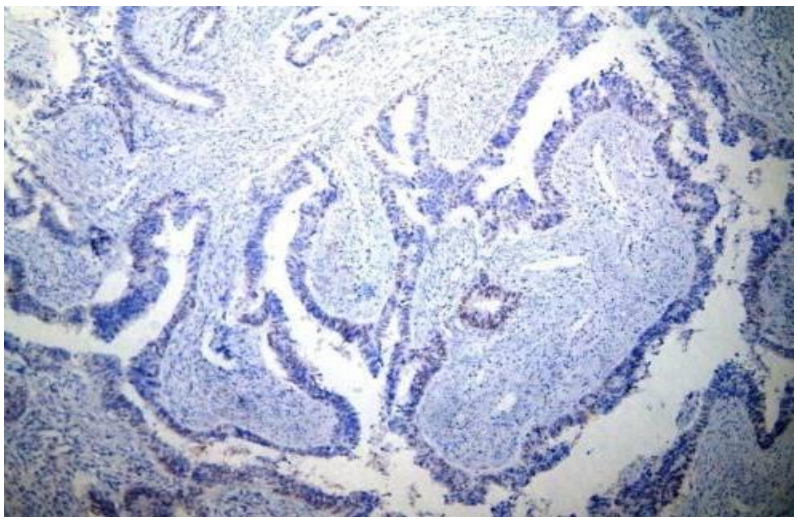

Figure (4): Immunohistochemical staining using SLUG of the previous figure (3) in low grade endometrioid endometrial carcinoma, the glandular epithelium showed positive nuclear immunostaining in less than 50% of cells **(DAB, original magnification x100).**

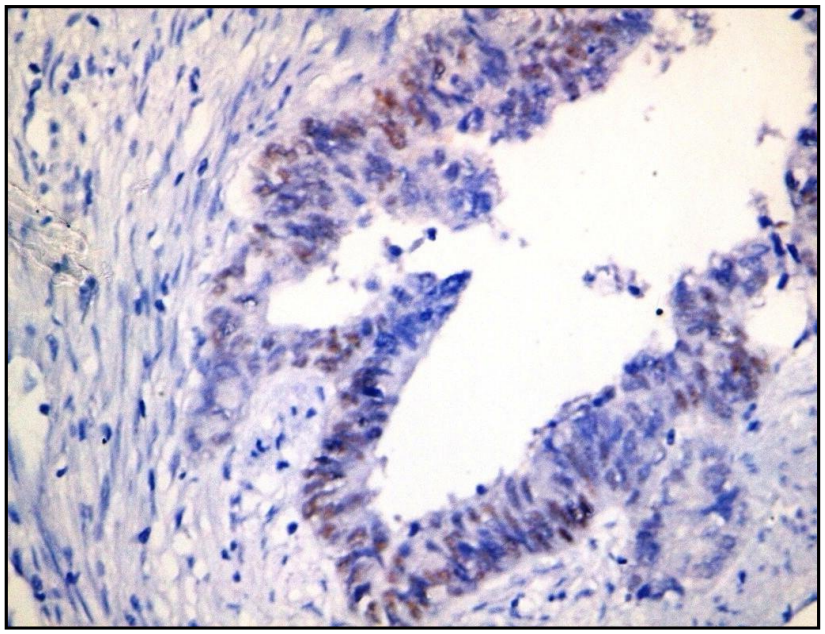

Figure (5): Immunohistochemical staining using SLUG of the previous figure (3) with higher magnification in low grade endometrioid endometrial carcinoma, the glandular epithelium showed positive nuclear immunostaining in less than 50% of cells **(DAB, original magnification x400).**

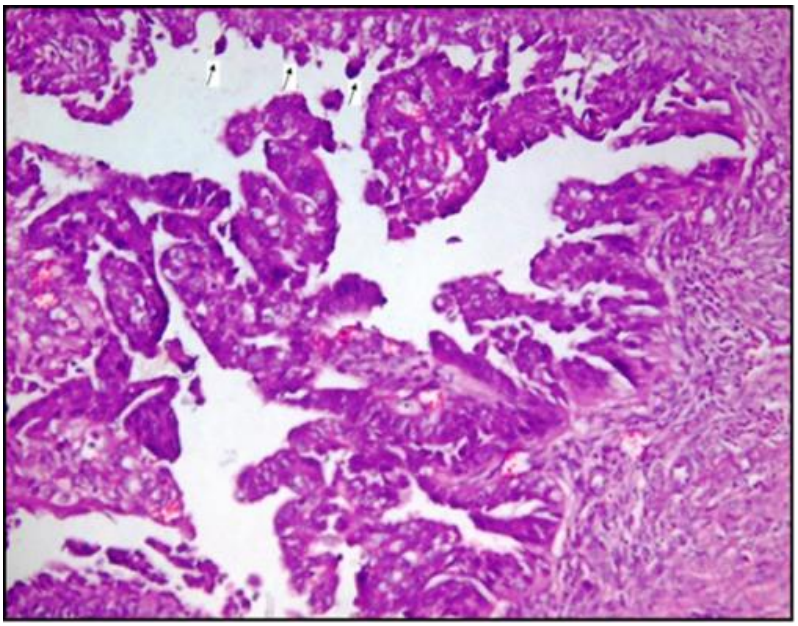

Figure (6): Serous endometrial carcinoma papillary variant, showing malignant cells with pleomorphism, hyperchromatism, and the arrows showed the hobnailing **(H&E, original magnification x200).**

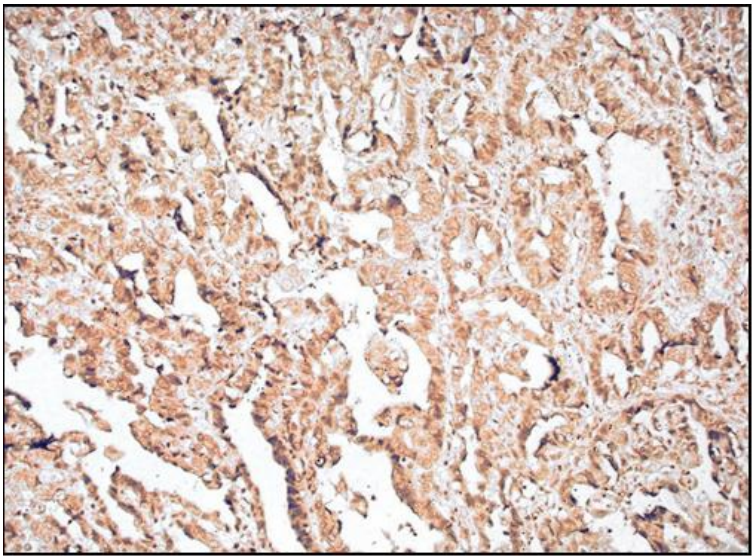

Figure (7): Serous endometrial carcinoma. Immunohistochemical staining of the case illustrated in figures (6) using SLUG. The glandular epithelium showed positive immunostaining in more than 50% of cells nuclei **(DAB, original magnification x200).**

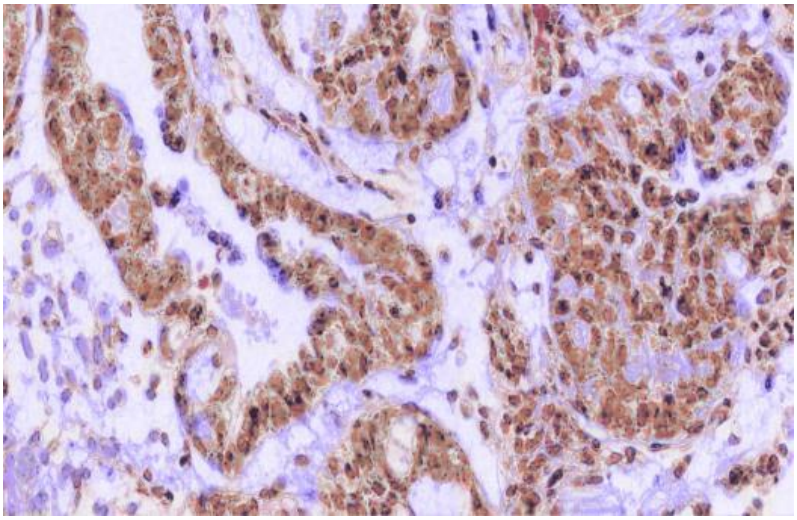

Figure (8): Serous endometrial carcinoma. Immunohistochemical staining of the case illustrated in figures (6) using SLUG with higher magnification. The glandular epithelium showed positive immunostaining in more than 50% of cells nuclei **(DAB, original magnification x400).**

DISCUSSION

Eighty percent of the cases collected during the period from 2018-2021 (24 cases) were EECA (type I) and 20% (6 cases) were serous carcinoma (type II). Similarly, *Saso et al. (2011)* and *Hoffman et al. (2012)* found that Type I (endometrioid) represent 75–90% of endometrial cancers.

In this study, all patients presented with abnormal uterine bleeding. Also in a study done by *Perez et al. (2010),* 81.1%

of cases of endometrial carcinoma presented clinically by abnormal uterine bleeding. Similarly *Doraiswami et al. (2011)* and *Ellenson et al. (2011)* reported that abnormal uterine bleeding is the commonest presenting symptom in endometrial hyperplasia and endometrial carcinoma.

In this study, the mean age of the patients was 60 years old. In agreement with this, *Purdie and Green (2010)* and *Gibson et al. (2014)* showed that the greatest incidence of EC occurs between the ages of 50 and 65 years with peak incidence occurring after menopause.

In our study, 58.3 % of EECA occurred below the age of 60 years and 83.3% of serous carcinoma occurred above the age of 60 years. In keeping with this finding, *Ashley et al. (2010)* stated that type II EC tends to occur at older age relative to type I carcinoma. Also, *Horn et al. (2011)* reported that patients with serous carcinoma are of average 5 years older than those with EECA.

As regard the relation between types of endometrial carcinoma and FIGO grading, this study found that there was statistically significant relation between the EC types and FIGO grade. 66.6% of EECA cases were low FIGO grade. On the other hand, 13.3 % of EECA and all cases of serous carcinoma were high FIGO grade. In keeping with our results, *Lax (2010)* reported that histologically, low-grade endometrioid carcinomas are considered type I, while type II carcinomas are typically high grade and show non-endometrioid features (mainly serous and clear cell).

As regard the relation between types of endometrial carcinoma and FIGO staging of the tumor, this study found that there was statistically significant relation between EC types and FIGO stage. 95.8% of type I (EECA) and 40 % of serous carcinoma were low stage and 4.16% of ECCA and 60% of serous carcinoma were high stage. This was statistically significant. In keeping with our results, *Colombo et al. (2011)* stated that staging is combined with the histologic subtype and grade. The endometrioid type tends to present at a lower stage, while serous carcinomas tend to present at higher stage.

Slug expression in endometrial carcinoma was notably correlated with the histological grade, muscular layer infiltration and lymph node metastasis. But it was not markedly correlated with The International Federation of Gynecology and Obstetrics (FIGO) stage *(Zhu et al., 2020).*

In the current study, there was a statistically significant relation between SLUG expression and grade of endometrial carcinoma. Besides, the Slug and expression was evidently correlated with the endometrial carcinoma development and poor prognosis.

In our study, we found that all of the cases of high-grade endometrial carcinoma showed expression of SLUG in varying degrees of expression, and showed expression of SLUG in more than 50% tumor cells. In keeping with our study *Kihara et al. (2016)* found that the extent of SLUG expression of high-grade endometrial carcinoma. No cases showed a complete absence of SLUG expression, 25% expressed SLUG in more than 50% of the tumor cells. No significant relationship was found between the expression extent of SLUG and the

histological subtypes. Also, *Zhu et al. (2020)* reported that Slug expression in endometrial carcinoma was notably correlated with the histological grade, muscular layer infiltration and lymph node metastasis.

In our study, we found that SLUG expression differed significantly in relation to FIGO stage of tumor, all the high FIGO stage (stage II and III) showed expression of slung in more than 50% of cells.

In keeping with our study, *Sadłecki et al. (2020)* found that the expression of SLUG differed significantly depending on clinical FIGO stage. The expression in patients with FIGO stage III or IV (high FIGO stage) was significantly higher than that in those with less-advanced ECs. The SLUG expression was also significantly higher in type II ECs than in type I malignancies. No statistically significant differences in the SLUG expression were found after stratifying the immunohistochemical results according to histological grade, lymphovascular space invasion (LVSI), cervical invasion, and lymph node involvement. The expressions of SLUG in patients with myometrial invasion ≥ 50% of the uterine wall thickness and adnexal involvement were significantly higher than those in those without these unfavorable prognostic factors. The expression of SLUG was also significantly higher in patients with distant metastases.

In opposition to our study, *Zhu et al. (2020)* found that SLUG expression was not markedly correlated with The International Federation of Gynecology and Obstetrics (FIGO) stage.

In our study, there was no relationship between the slug expression and age in each group. *Zhu et al. (2020)* found that there was no relationship between the Slug expression and age in each group (P>0.05). They reported that Compared with normal endometrial tissues, the Slug expression levels in endometrial carcinoma tissues were remarkably increased. The positive rate of Slug in endometrial carcinoma was 61.3% and the difference was statistically significant compared with that in normal endometrial tissue.

In our study, there was a significant relationship between SLUG expression and type of endometrial carcinoma. 91.7% of cases of type I (EEC) endometrial carcinoma showed expression in less than 50% of cells. On the other hand only 8.3% of cases of type I endometrial carcinoma showed immunoreactivity in more than 50% of cells. While 50% of type II (serous ca.) endometrial carcinoma showed immunoreactivity in less than 50% of cells. On the other hand 50% of cases of type II endometrial carcinoma showed immunoreactivity in more than 50% of cells.

So in our study we found that, higher expression of SLUG in endometrial carcinoma occurs significantly higher in relation to grade and stage of endometrial carcinoma, thus it may be associated with poor prognosis. In agreement with our results, *Zhu et al. (2020)* reported that Slug could be used as a prognostic factor of endometrial carcinoma. Interfering with the expression of Slug in endometrial carcinoma cell lines could effectively inhibit the proliferation, invasion and migration, and its mechanism is related to

the inhibition of EMT. Slug is a potential targets for the treatment of endometrial carcinoma.

CONCLUSION

In this study, SLUG immunohistochemical stain expression was very significantly correlated to the Grade and Stage of endometrial carcinoma.

We can know that SLUG is a member of EMT (Endothelial mesenchymal transition) transcription factors, are regarded as major EMT inducers that inhibit the transcription of cell adhesion molecules.

So in our study we found that, higher expression of SLUG in endometrial carcinoma may be associated with poor prognosis. So, Interfering with the expression of Slug in endometrial carcinoma cell lines could effectively inhibit the proliferation, invasion and migration, and its mechanism is related to the inhibition of EMT. SLUG is a potential targets for the treatment of endometrial carcinoma.

Future therapeutic strategies for endometrial cancer must focus on ways to suppress the SLUG molecules, and prevent further metastasis and improve prognosis.

The correlation between expression of SLUG and high tumor grade, stage are suggesting that SLUG may serve as a prognostic indicator in EC.

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تقييم الصبغ المناعي الهيستوكيميائي ل (سلج) في حالات مرض سرطان بطانة الرحم

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خلفية البحث: يعتبر سلج، المتضمن في مجموعة بروتينات نوع إصبع الزنك، محفزات رئيسية للانتقال الظهاري - اللحمي المتوسط (EMT) لمنع نسخ جزيئات التصاق الخلية، بما في ذلك E-cadherin تعمل بعض مسارات الإشارات، مثل مسار فوسفوينوزيتيد 3-كيناز/ بروتين كيناز ب (PI3K/AKT)، على تنظيم تعبير سلج. وأشارت الأبحاث إلى أن مضادات تحسس سلج يمكن أن تمنع EMT، مما يشير إلى أن جين سلج يمكن أن يعمل كهدف علاجي لغزو الورم والورم الخبيث.

الهدف من البحث: دراسة التعبير عن الصبغة النسيجية المناعية SLUG بين سرطان بطانة الرحم من النوع الأول (بطانة الرحم) وسرطان بطانة الرحم من النوع الثاني (المصلي).

المرضى وطرق البحث: تم جمع ثلاثين عينة من أنسجة بطانة الرحم مدمجة بالبارافين تم تشخيصها على أنها: 24 سرطان بطانة الرحم (النوع الأول) و 6 سرطان بطانة الرحم المصلي (النوع الثاني). وقد تم الحصول على جميع عينات أنسجة بطانة الرحم من سرطان بطانة الرحم من خلال استئصال الرحم. جمعت العينات من أرشيف ملفات الباثولوجيا الجراحية بقسم الباثولوجيا بكلية الطب وجامعة الأزهر خلال الفترة من 2018 حتى ديسمبر 2020.

نتائج البحث: كانت هناك علاقة ذات دلالة إحصائية بين تعبير SLUG ودرجة سرطان بطانة الرحم (قيمة P <0.001)، ولم تظهر أي حالة من حالات سرطان بطانة الرحم الغياب التام لتعبير SLUG. وكانت جميع الحالات (10 حالات) من سرطان بطانة الرحم عالي الدرجة (4 حالات من النوع الأول و 6 حالات من النوع الثاني)، كما أظهرت تعبيرًا عن SLUG بدرجات متفاوتة من التعبير، و

(5 حالات) أظهر 50٪ تعبيرًا عن SLUG في أكثر من 50٪ من الخلايا السرطانية (تعبير قوي)، وحالتان 8.3٪ من النوع الأول (EECA)، وثلاث حالات 50٪ من النوع الثاني (بطانة الرحم المصلية). ولا توجد علاقة ذات دلالة إحصائية بين تعبير SLUG وعمر الحالات (قيمة 0.206 = P). ولم يكن هناك ارتباطاً ذا دلالة إحصائية بين تعبير SLUG وأنواع سرطان بطانة الرحم (قيمة P 0.002).

الاستنتاج: إرتبط تعبير البقعة الكيميائية المناعية SLUG إرتباطًا وثيقًا بدرجة ومرحلة سرطان بطانة الرحم. وتشير العلاقة بين التعبير عن SLUG ودرجة الورم العالية إلى أن SLUG قد يكون بمثابة مؤشر تنبؤي في سرطان المريء.

الكلمات الدالة: الصبغ المناعي الهيستوكيميائي ل (سلج)، مرض سرطان بطانة الرحم.

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