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ORIGINAL ARTICLE

Immunohistochemical Expression of Hepatocyte Growth Factor Receptor and Epidermal Growth Factor Receptor in Serous Ovarian Tumors

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ABSTRACT

Background: Ovarian cancer mostly shows no symptoms and discovered at advanced stages, so high mortality is expected. Therefore, is considered a highly lethal gynecological cancer in women. More improvement could be achieved if there were sensitive and specific biomarkers for the disease in the early stages. We aimed to evaluate the correlation between the expression of Hepatocyte Growth Factor Receptor (HGFR) and Epidermal Growth Factor Receptor (EGFR) in ovarian serous tumors and their relationship with pathological criteria.

Methods: Seventy paraffin-embedded tissue blocks of ovarian serous tumors were included, and categorized as 20 benign, 25 borderline and 25 malignant tumors. HGFR and EGFR immunohistochemical staining was done.

Results: Among benign tumors, negative HGFR was in 70% of benign tumors, and EGFR was negative in 60%. In borderline tumors, HGFR was positive in 76%, and EGFR was positive in 68%. All malignant tumors were positive for HGFR and EGFR. A substantially significant variations were found between HGFR expression and both grade and stage (P=0.006, P=0.009, respectively), and EGFR expression with grade and stage (P=0.004, P<0.001, respectively). HGFR had a significant positive correlation with EGFR expressions among all studied cases (r=0.846, P<0.001), with also a significant positive relationship between HGFR and EGFR regarding grade (r=0.544, P=0.005) (r=0.500, P=0.01), respectively, as well as stage (r=0.550, P=0.004), (r=0.778, P<0.001), respectively in malignant cases.

Conclusions: HGFR and EGFR expressions are strongly overexpressed in ovarian serous carcinoma than borderline and benign tumors and correlated with poorer prognostic outcomes as higher grades and advanced disease stages.

Keywords: Ovarian cancer; Serous tumors; Hepatocyte Growth Factor Receptor; Epidermal Growth Factor Receptor.

INTRODUCTION

Ovarian cancer is ranked the 7th most common gynecological cancer and cancer-related mortality in the world [1] and occupies a higher rank among Egyptian women as it is considered the 12th most common diagnosed cancer [2].

On a histopathologic base, ovarian tumors can be epithelial surface cell, germ cell, sex cord–stromal, or metastatic tumor with the majority of ovarian cancers, having epithelial origin. The most common epithelial ovarian cancer is serous tumors constituting 70%, which are divided into high grade and low grade. Epithelial ovarian tumors are classified into benign, borderline and malignant [3, 4].

Serous tumors are classified as benign if cellular proliferation and invasive behavior are absent, as borderline if there is abundant proliferation without invasion, and as malignant if invasion is present [5, 6].

Ovarian cancer is known as the silent killer because it's asymptomatic disease with delayed onset of

symptoms [4]. Furthermore, due to inadequate screening, it carries a significant mortality risk. Histological type and grade, as well as the patient's age at diagnosis, are prognostic markers that impress the outcome of ovarian cancer [7].

Epithelial-mesenchymal transitions involve epithelial cells acquiring mesenchymal characteristics. These transitions occur in various biological processes and may happen during embryonic development, be linked to adult tissue regeneration, or be associated with cancer progression [8].

As a tyrosine kinase receptor, HGFR is also called c-mesenchymal-epithelial transition factor (c-MET). The cell cycle, proliferation, differentiation, motility, and death are all regulated by this protein through the solitary ligand, hepatocyte growth factor (HGF) [9]. The activation of actin-rich adhesion sites and lamellipodia is facilitated by HGF-induced integrin clustering, which in turn enhances cancer cell motility and invasion [10].

A family of transmembrane kinase-related proteins, the epidermal growth factor receptors (EGFRs) activate many signalling pathways, these signaling pathways are considered the main regulators for cancer behavior including invasiveness, apoptotic resistance, angiogenesis, cell proliferation and adhesion [11]. The tumor grade, cell proliferation index, aberrant P53 expression, and patient outcome are all associated with increased EGFR expression. [12]. Many factors, like epidermal growth factor as well as HGF, are among the numerous signals that induce epithelial-mesenchymal transition in cancer progression [13].

The hypothesis of the current research is that HGFR and EGFR could be significantly associated with the grade and stage of ovarian serous tumors. Overexpression of these receptors is more prevalent in high-grade and advanced-stage malignant tumors, indicating their potential role as biomarkers for early diagnosis, as well as targeted therapy among ovarian cancer cases. So, this work aimed to evaluate the correlation between the expression levels of Hepatocyte Growth Factor Receptor (HGFR) and Epidermal Growth Factor Receptor (EGFR) in ovarian serous tumors and their relationship with pathological criteria.

METHODS

We conducted a cross-sectional study for ovarian serous tumors prepared at the Pathology Department of Zagazig University Hospital from 2023 to 2025 after receiving approval number (10534) from the local ethical committee and institutional review board (IRB) of the Faculty of Medicine, Zagazig University. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. Seventy formalin-fixed paraffin-embedded tissue blocks that were categorized as 20 cases of benign tumors, 25 cases of borderline tumors and 25 cases of malignant tumors. Cases with other associated cancers were excluded.

The clinical data were reviewed from patients' medical files from the Pathology department regarding age, site (right, left or bilateral) and tumor size (measured in centimeters, for bilateral tumors the mean was calculated).

Histopathological study

Sections of paraffin blocks of all studied cases were cut at 2-5 µm thickness by a rotatory microtome and stained with Hematoxylin and Eosin (H&E) for diagnosis and histopathological findings confirmation. The pathological data as tumor grade (low or high) and stage (I-IV) were determined.

Immunohistochemical procedure

Formalin-fixed paraffin-embedded blocks were serially sectioned into 2–5 µm and deparaffinized in xylene and then rehydrated in descending series of alcohols. Immunohistochemical staining was done with 2 monoclonal antibodies, HGFR (Medaysis, USA, MC0060RTU7, dilution 1:25-100) and EGFR (Cell marque, USA, EP22, dilution 1:100). The staining process was performed using the Leica BONDMAX automated immunohistochemistry platform, with antibody detection carried out through a biotin-free Bond Polymer Defined Detection System (Leica Microsystems). To ensure accuracy and reliability, quality control was conducted using well-established positive and negative controls. Non-small cell lung carcinoma served as the positive control for HGFR, while breast carcinoma was used as the positive control for EGFR.

Evaluation of HGFR immunostaining

HGFR expression was observed as a membranous or cytoplasmic stain and assessment of was done by multiplying the staining intensity and percentage scores of immunoreactive tumor cells based on the following scoring: Staining intensity was scored as 0 (negative), 1 (low), 2 (moderate), and 3 (high), while the proportion of positive cells was categorized as 0 (no expression), 1 (<10%), 2 (10–50%), 3 (51–80%), and 4 (>80%). The resulting score ranged from 0 to 12, with scores classified as 0 (negative), 1–4 (weak expression), 6–8 (moderate expression), and 9–12 (strong expression) [14].

Evaluation of EGFR immunostaining

EGFR expression was evaluated as a membranous or cytoplasmic stain using a semiquantitative scoring system based on staining intensity and the percentage of positive cells, with expression detected as either cytoplasmic or membranous staining. Staining intensity was scored as 0 (negative), 1 (weak), 2 (intermediate), and 3 (strong). The percentage of positive cells was categorized as 0 (no positive cells), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (>75%). The final score, ranging from 0 to 12, was calculated by multiplying the intensity and percentage scores. Scores were interpreted as follows: 0 (no expression), 1–4 (weak expression), 6–8 (moderate expression), and 9–12 (strong expression) [15].

Statistical Analysis

Using IBM Corp., we gathered, tabulated, and statistically analysed all data. With a 2015 release. This is Version 23.0 of IBM SPSS Statistics for Windows. The IBM Corporation is based in Armonk, NYC. After ensuring normality with the Shapiro-Wilk test, normally distributed data was displayed with a standard deviation (±SD) for quantitative data. The percentage was used to express the qualitative data. Quantitative data were analyzed using one-way ANOVA, while qualitative data were evaluated using chi-square and Fisher's exact tests. All statistical tests were two-tailed. A p-value of ≤0.05 was considered statistically significant, indicating a meaningful association or difference, whereas a p-value >0.05 was interpreted as statistically insignificant.

RESULTS

Out of 70 cases of ovarian serous tumors, about 54 % were less than 50 years old. The age range was 15-73 years with the mean age 46.14±14.14 years. Most of the cases (58.6%) had tumor size more than 10 cm. The size range was 2-19 cm with the mean size was 10.4 ± 4.67. Most cases were unilateral with nearly equal percentage for right and left-sided tumors. Regarding the malignant cases, 60% were high grade cases and 28 % were stage II, while other stages (I, III, IV) were present equally. (Table 1)

HGFR expression

In benign tumors, negative HGFR expression was in 70% of benign tumors, and positive HGFR was only weak (Figure 1B). In borderline tumors, expression was positive in 76%, mainly moderate in 52% of cases (Figure 1E). All cases of malignant tumors were positive for HGFR expression with 96% moderate to strong expression (Figure 2B, 2E). A substantially significant variation was revealed between negativity and positivity of HGFR and the studied (benign, borderline and malignant) groups (P<0.001) and also with HGFR scores (P<0.001, 0.07, <0.001, respectively) (Table 2). A significant difference was statistically recognized between HGFR expression and both grade as well as stage, where strong expression was found in 80% of high grade (P=0.006), 66.7% of stage III and 100% of stage IV (P 0.009). (Table 4)

EGFR expression

EGFR was negative in 60% of benign tumors and only weak in the remaining benign tumors (Figure 1C). While it was positive in 68% of borderline tumors, mainly moderate in 44% of cases (Figure 1F). It was noticeably positive in 100% of malignant tumors with 84% moderate to strong expression (Figure 2C, 2F). A significant statistical difference was identified between EGFR-negative and EGFR-positive cases across the three studied groups (P < 0.001) and in relation to EGFR scores (P < 0.001, P = 0.002, and P < 0.001, respectively) (Table 3).

Additionally, EGFR expression was significantly associated with both tumor grade and stage, where strong expression was observed in 86.7% of high-grade tumors (P = 0.004) and in 100% of tumors classified as stage III and IV (P < 0.001) (Table 4)

Correlation between HGFR and EGFR expressions

There was a strong positive correlation between the expressions of HGFR and EGFR in all instances that were investigated (r=0.846, P<0.001). Regarding malignant cases, positive correlation with high significance between HGFR and tumor grade (r=0.544, P=0.005) and tumor stage (r=0.550, P=0.004). In addition, there is a significant positive correlation between EGFR and both tumor grade (r=0.500, P=0.01) and tumor stage (r=0.778, P<0.001). (Table 5 and 6)

Table (1): Clinico-pathologic characteristics of studied groups

Parameter	Number (N=70)	%
Age		
< 50	38	54.3
≥ 50	32	45.7
	Mean ± SD Range	46.1 ± 14.1 (15 – 73)
Size		
< 10 cm	29	41.4
≥ 10 cm	41	58.6
	Mean ± SD Range	10.4 ± 4.67 (2 – 19)
Site		
Right	31	44.3
Left	32	45.7
Bilateral	7	10
Tumor type		
Benign tumor	20	28.6
Borderline tumor	25	35.7
Malignant tumor	25	35.7
Malignant tumor characters		
	Number (N=25)	%
Grade		
Low	10	40
High	15	60
Stage		
I	6	24
II	7	28
III	6	24
IV	6	24

Table (2): Immunohistochemical expression of HGFR among the studied groups

	HGFR expression		Test	P Value	HGFR expression				Test	P Value
	Negative	Positive			Negative	Weak	Moderate	Strong		
Benign tumor (n=20)	14 (70%)	6 (30%)	Fisher	**<0.001**	14 (70%)	6 (30%)	0 (0%)	0 (0%)	Fisher	**<0.001**
Borderline tumor (n=25)	6 (24%)	19 (76%)			6 (24%)	3 (12%)	13 (52%)	3 (12%)	Fisher	0.07
Malignant tumor (n=25)	0 (0%)	25 (100%)			0 (0%)	1 (4%)	10 (40%)	14 (56%)	Fisher	**<0.001**

**Fisher exact test, Non-significant: P >0.05, Significant: P ≤0.05*

Table (3): Immunohistochemical expression of EGFR among the studied groups

	EGFR expression		Test	P Value	EGFR expression				Test	P Value
	Negative	Positive			Negative	Weak	Moderate	Strong		
Benign tumor (n=20)	12 (60%)	8 (40%)	Fisher	**<0.001**	12 (60%)	8 (40%)	0 (0%)	0 (0%)	Fisher	**<0.001**
Borderline tumor (n=25)	8 (32%)	17 (68%)			8 (32%)	5 (20%)	11 (44%)	1 (4%)	Fisher	**0.002**
Malignant tumor (n=25)	0 (0%)	25 (100%)			0 (0%)	4 (16%)	5 (20%)	16 (64%)	Fisher	**<0.001**

**Fisher exact test, Non-significant: P >0.05, Significant: P ≤0.05*

Table (4): Interpretation of the results of HGFR and EGFR expression regarding tumor grade and stage among the malignant cases

		Total (n=25)	Positive HGFR expression			Test	P value	Positive EGFR expression			Test	P value
			Weak (n=1)	Moderate (n=10)	Strong (n=14)			Weak (n=4)	Moderate (n=5)	Strong (n=16)		
Grade	**Low**	10	1 (10%)	7 (70%)	2 (20%)	Fisher	**0.006**	4 (40%)	3 (30%)	3 (30%)	Fisher	**0.004**
	High	15	0 (0%)	3 (20%)	12 (80%)			0 (0%)	2 (13.3%)	13 (86.7%)		
Stage	**I**	6	1 (16.7%)	3 (50%)	2 (33.3%)	Fisher	**0.009**	3 (50%)	3 (50%)	0 (0%)	Fisher	**<0.001**
	II	7	0 (0%)	5 (71.4%)	2 (28.6%)			1 (14.3%)	2 (28.6%)	4 (57.1%)		
	III	6	0 (0%)	2 (33.3%)	4 (66.7%)			0 (0%)	0 (0%)	6 (100%)		
	IV	6	0 (0%)	0 (0%)	6 (100%)			0 (0%)	0 (0%)	6 (100%)		

**Fisher exact test, ^{2}Chi-square test, Non-significant: P >0.05, Significant: P ≤0.05*

Table (5): Correlation of EGFR with HGFR expression among studied patients

Variable	EGFR expression	
	r	***P***
HGFR expression	0.846	**<0.001**

**Spearman rank correlation test, Non-significant: P >0.05, Significant: P ≤0.05*

Table (6): Correlation of EGFR and HGFR with tumor grade and stage among the malignant cases

Variable	EGFR expression		HGFR expression	
	r	***P***	***r***	***P***
Tumor grade	0.500	**0.01**	0.544	**0.005**
Tumor stage	0.778	**<0.001**	0.550	**0.004**

**Spearman rank correlation test, Non-significant: P >0.05, Significant: P ≤0.05*

DISCUSSION

Ovarian cancer is a challenging malignancy with late-stage diagnosis and poor prognosis. Tumor biology complexity and the interaction of growth factors and their receptors play remarkable roles in progression and metastasis of the tumor. The insufficiency of adequate screening methods and increased resistance for chemotherapy resistance highlight the need for new markers to improve management and prognosis [15].

Key actors in the formation and spread of cancer include hepatocyte growth factor (HGF) and its receptor, c-Met. These proteins play a crucial role in regulating key physiological processes, including cell proliferation, survival, motility, and differentiation, ensuring proper cellular function and tissue homeostasis. [16]. Receptors for epidermal growth factor also control cell proliferation, differentiation, and survival. Cell proliferation and metabolic processes are impacted by the signalling pathways activated when EGFR interacts with its ligands. Cancers, particularly ovarian cancer, are associated with aggressive tumors and poor outcomes when these receptors are activated abnormally [17].

HGF secreted by ovarian tumor cells can induce a mesothelial-to-mesenchymal transition in peritoneal mesothelial cells, stimulating their invasion. Manipulating HGF activity affects the extent of ovarian cancer spread and developing ascites [18]. High levels of HGF can drive aggressive growth and invasiveness, characteristics often seen in serous ovarian carcinomas. The ability of cancer cells to invade neighboring tissues and metastasize to faraway places is enhanced by HGF-facilitated processes such epithelial-to-mesenchymal transition. Malignant serous ovarian tumors may exhibit genetic alterations that upregulate HGF or its receptor, contributing to enhanced signaling and tumor growth [9].

HGFR was highly expressed in 76% of borderline cases and all malignant cases with a statistically significant difference between receptor expressions, in borderline and malignant cases. In agreement with our findings, the study done by Nakamura et al. (2015) illustrated that HGF expression shows higher levels with more advanced stages of ovarian cancer [18].

The majority of high-grade cases (80%) had a strong expression of HGFR, and all cases of stage ɜ had a strong expression as well, indicating a statistically significant relationship between the two variables. Similar findings were obtained by **Czogalla et al. (2022)** who stated that the increased HGFR expression in ovarian cancer of epithelial origin is related to higher grades, higher FIGO stages, distant spread and reduced survival rates [9]. CA 125 and HGF levels improved the ability to predict whether a tumor was malignant. Advanced stages of ovarian cancer and high preoperative HGF levels had decreased disease-free survival compared to those with lower HGF levels [19].

Negative HGFR expression in benign ovarian tumors, compared to positive expression in malignant ones, indicates key differences in tumor biology, growth mechanisms, molecular traits, and environmental factors. This divergence highlights how HGF and HGFR contribute to the aggressiveness of ovarian cancer [19].

Individuals with epithelial ovarian cancer who express high levels of HGFR are more likely to have poor progression-free and overall survival rates [9]. Increased circulating HGF levels indicates worse prognosis. In ovarian carcinomas, patients have significantly increased preoperative HGF serum levels compared to those with benign or borderline tumors [19].

In advanced stages, the tumor microenvironment can enhance HGFR expression, promoting tumor growth and invasiveness. One of the factors that contributes to the aggressive behavior and metastasis of higher-grade tumors is the upregulation of the HGF/HGFR signalling pathway, which is essential for cell motility, invasion, and growth. HGFR plays a crucial role in supporting cellular signaling pathways and influencing overall tumor behavior [9].

Our results showed that, regarding EGFR expression, a statistically significant difference was found as all the malignant cases had positive expression followed by 68% of the borderline cases. In one study, about 46% of examined cases were EGFR positive as it was expressed in 25% and 70% of borderline and malignant cases, respectively [20]. Supporting studies as Kamal et al. (2022) and Mehner et al. (2017) demonstrated positive EGFR expression in 66% and 52% of ovarian carcinoma cases, respectively [11, 21]. A statistically significant difference between the studied groups. EGFR expression in both malignant serous carcinoma and borderline tumors was 77.7% and 21.4%, respectively [22]. Ranjbar et al. (2015) supported our work concluding that EGFR was expressed at significantly higher rates in ovarian cancer patients compared to healthy controls [23]. Several studies reported that positive expression

was more common in ovarian carcinomas than borderline tumors [24, 25]. Additionally, another study revealed a significant association between EGFR amplification and its overexpression in serous carcinomas [26].

EGFR expression showed a statistically significant correlation with both tumor grade and stage. Strong expressions were detected in 86.7% of high-grade tumors, whereas weak expression was observed in 40% of low-grade cases. Furthermore, 50% of stage I tumors exhibited weak expression, while strong expression was predominantly seen in stage III and IV tumors. These findings align with previous studies, which have reported higher EGFR expression in high-grade serous carcinomas compared to low-grade and borderline tumors. Elevated EGFR expression has also been associated with poor clinical outcomes, including larger tumor size, capsule disruption, lymph node metastasis, and advanced tumor stages [11, 15, 25].

EGFR plays a crucial role in driving tumor aggressiveness, cellular signaling pathways, and overall biological behavior. Higher-grade tumors, which are more aggressive and poorly differentiated, rely heavily on growth factors signaling and exhibit higher EGFR levels. In contrast, low-grade tumors are more differentiated and less dependent on growth factor signaling. EGFR is essential in regulating cell growth and division [24].

The positive expression of EGFR in malignant ovarian serous tumors is related to its contribution in proliferation, tumor microenvironment interactions, and specific molecular characteristics. EGFR signaling is essential for tumor growth and metastasis because it increases angiogenesis, which is particularly important for tumors that require an increase in blood supply. Chronic inflammation in ovarian cancer can increase EGFR expression and activation, driving tumor progression. It is involved in pathways that promote cell proliferation and survival, with heightened expression leading to uncontrolled growth and tumor aggressiveness [11].

In the current study, HGFR expression shows a positive correlation with EGFR expression in ovarian serous tumors. A study supported our results as combined higher expressions of both receptors were associated with shorter progression free survival and chemotherapy free interval [27, 28]**.** In epithelial ovarian cancer, HGFR expression is also linked to poor prognosis, with high HGFR expression independently predicting shorter progression-free and overall survival. Furthermore, HGFR expression combined with other biomarkers, including EGFR, significantly linked to poor progression-free survival, platinum-free interval, and overall survival [9]. In a study done by Farrag et al., (2021), they assessed the expression of EGFR in high grade carcinomas in relation to taxol-carboplatin neoadjuvant treatment and found a significant association with lower expression among patients who received neoadjuvant therapy compared to patients not receiving the therapy. This may be attributed to suppression of tumor cells' growth affected by chemotherapy administration [29].

These results raise the possibility that combination expressions are a useful diagnostic and prognostic indicator for ovarian cancer. Therefore, assessment of EGFR combined with HGFR underlines the possible efficiency of binary combination therapies. In a study, the usage of combined EGFR/Her-2 as canertinib and HGFR (c-Met) inhibitors as PHA665752 was effective to cause suppression of multiple pathways leading to weakened growth of cancer cells and their impaired survival in patients, having these positive receptors on tumor cells [30].

Conclusion

The immunohistochemical expressions of HGFR as well as EGFR are strongly overexpressed in ovarian serous carcinoma than borderline and benign tumors and correlated with poorer prognostic outcomes as higher grades and advanced disease stages. Assessing HGFR and EGFR expressions levels, especially when combined, can help in the prediction of serous ovarian tumors advancement and suggest a possible beneficial targeted therapy".

Conflict of interest

The authors declared that they have no conflicts of interest with respect to the authorship and/or publication of this article.

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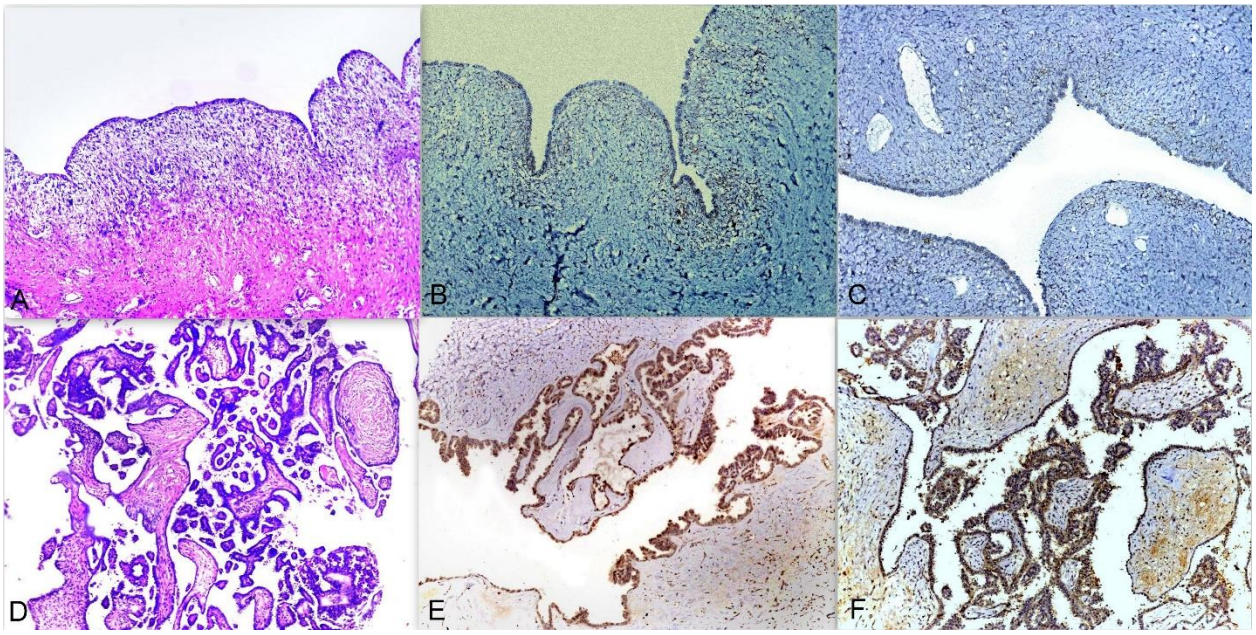

Figure (1): Benign serous tumor (ovarian serous cystadenoma) showing **A)** simple serous lining without papillae or complexty in the architicture (H&E, x100), **B)** negative HGFR expression (IHC, HGFR x100), and **C)** negative EGFR expression (IHC, EGFR x100). **Borderline ovarian serous tumor** showing **D)** papillae arborizing into smaller ones, lined by pseudostratified ciliated, fallopian serous epithelium (H&E, x100), **E)** moderate cytoplasmic HGFR expression (IHC, HGFR x100) and **F)** moderate cytoplasmic EGFR expression (IHC, EGFR x100).

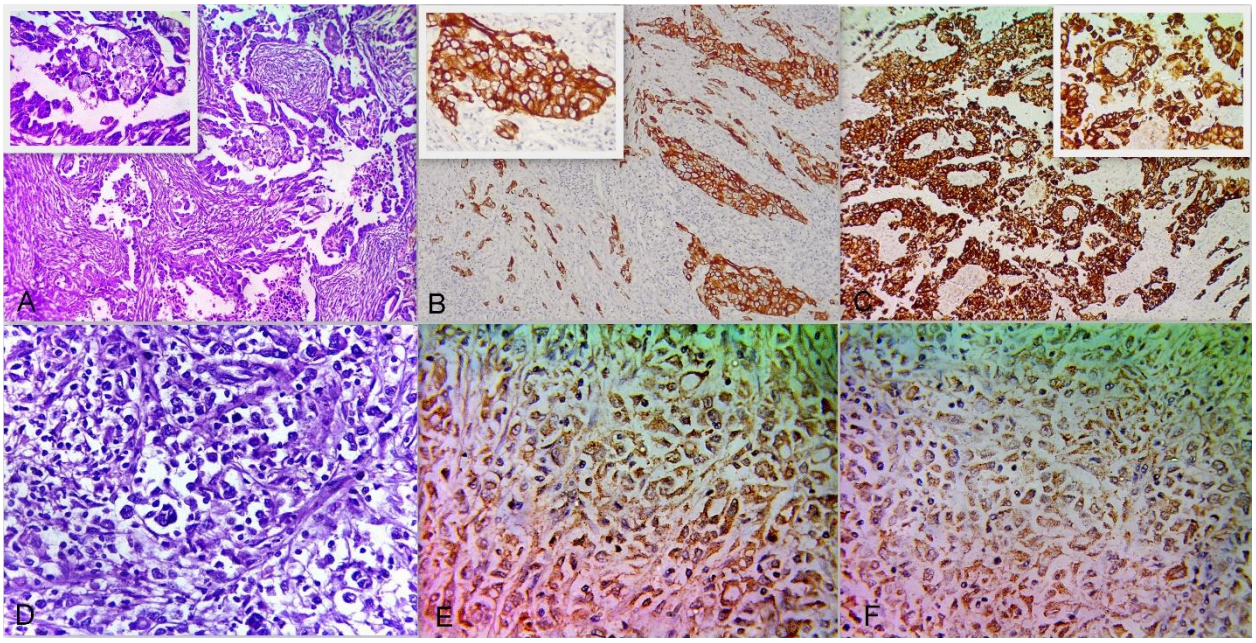

Figure (2): Malignant ovarian serous carcinoma showing **A)** malignant cells arranged in complex papillary growth with psammoma bodies (inset x400) (H&E, x100), **B)** strong cytoplasmic and membranous HGFR expression (inset x400) (IHC, HGFR x100) and **C)** strong cytoplasmic and membranous EGFR expression (inset x400) (IHC, EGFR x100). **Malignant ovarian serous carcinoma** showing **D)** malignant cohesive cells with marked hyperchromatism and pleomorphism (H&E, x100), **E)** strong cytoplasmic HGFR expression (IHC, HGFR x400) and **F)** moderate cytoplasmic EGFR expression (IHC, EGFR x400).

Citation

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