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ORIGINAL ARTICLE

FOX A1 expression as a prognostic factor in cases of invasive serous and mucinous ovarian carcinoma in association with p53 status and CEA expression

Shaimaa M.M. Bebars[1*], AfafTahaEbrahim El-Nashar[2], Esraa Mohamed Youssef [1], Rasha Mohamed Samir Sayed[1]

[1] Pathology
Department, Faculty of Medicine, Aswan University, Aswan, Egypt
[2]Pathology Department, Faculty of Medicine, Sohag University, Sohag, Egypt

Corresponding author*
Shaimaa Mohamed Mouneer Bebars

Email:
bebars34@gmail.com,
shaimaa_monir@aswu.edu.eg

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ABSTRACT

Background: Ovarian cancer (OC) is the most fatal gynecologic malignancy in women due to its silent growth and late diagnosis.The FOX A1 protein plays important roles in the development of tumors depending on its complex actions.Limited data are available regarding the expression of FOX A1 in OC, and to our knowledge, no previous study has demonstrated FOXA1 about p53 and CEA expression in OC.The objective of the present work was to evaluate FOX A1 immunohistochemical expression in association with p53 status and CEA expression and clinicopathological data in invasive serous and mucinous ovarian carcinomas to determine its predictive value. **Methods**: This retrospective study was carried out on paraffin-embedded blocks of 46 and 21 invasive serous and mucinous ovarian carcinomas respectively. Sectioning and immunohistochemical staining were conducted using anti-FOX A1, anti-p53, and anti-CEA antibodies. **Results:** FOX A1 showed high expression (80.6%) in studied cases and significant association with old age (p=0.048), stage (p=0.001), high grade, capsular rupture, and ascites (p<0.001). p53 expression was detected in approximately two-thirds of cases (65.7%), and only significant association could be detected with serous type. CEA expression was detected in (22.4%) cases, and significant association was found with age and mucinous type. 82.6% of negative p53 cases and 80.8% of negative CEA cases showed positivity for FOX A1. All positive CEA cases were p53 negative and this relation was significant. **Conclusions:** FOX A1 is highly expressed and has a poor prognostic indication in invasive serous and mucinous ovarian carcinomas regarding its considerable association with bad prognostic parameters. p53 & CEA could help to differentiate high-grade serous and mucinous ovarian carcinomas. FOX A1 overexpression in ovarian carcinomas could be used as a biomarker that is also helpful in prognosis contribution, particularly in cases of negative p53 and CEA.

Keywords: CEA; FOX A1; immunohistochemistry; mucinous ovarian carcinoma; p53; serous ovarian carcinoma.

INTRODUCTION

Ovarian cancer (OC), which is mostly epithelial derivative, represents a major concern worldwide since it is the most fatal gynecologic malignancy in women [1]. The estimated global new cases of cancer ovary were 3.4% of all new cancer cases in females. However, there is a considerable geographical variance in the drain of cancer ovary as the rates differ from Africa to Europe [2, 3]. The elevated cancer ovary death rate is endorsed to silent growth of such tumor, and absence of appropriate screening test, that cause late diagnosis after disease progression into advanced stages [4].

Depending on clinical, pathological and molecular criteria, ovarian carcinomas are classified into two types (1&2), the 1st type includes serous carcinoma of low-grade, clear cell, endometrioid, mucinous, and transitional cell carcinomas, the 2nd type includes high-grade serous carcinoma (HGSC), carcinosarcoma, and undifferentiated carcinoma [5]. Whereas HGSC is the most common type seen histologically, mucinous type is a distinct entity that has different clinical history, prognosis, genetic profile and response to chemotherapy [6]. Moreover, Serous carcinoma type II (HGSC) is linked to a worse clinical sequence than type I [7].

The gene FOX or forkhead box family is derived from winged helix transcription factors family [8]. In mammalians, transcription factors of FOX are classified into A to S sub-classes depending on similar sequence not only inside but also outside of FOX [9]. As other members of FOX family, FOX A1 regulates the transcription of gene by direct engagement to its consensus sequence, the forkhead motif. Furthermore, FOX A1 is able to open nearby chromatin, and consequently letting other factors transcription, such as androgen receptor, to be in approximation to their targets site, hence employing transcriptional regulation of gene expression [10]. The FOX A1 protein plays important roles in development of tumors depending on its complex actions, mostly in instability of genes and genomic mutation, stimulation of invasion and metastasis, and continuous signaling of proliferation. In cancer ovary, FOX A1 is proposed to act as an oncogene by prompting expression of numerous proteins [11].

The mainstream of HGSC type originated from the epithelium of fallopian tube through a sequence of precursor lesions that aim the secretory type of cells. HGSCs are originating from serous tubal intraepithelial carcinoma and presenting in late stage with elevated incidence of *TP53* mutations [12]. Studies have been dedicated to inspecting if mutations and protein expression of p53 are related to invasiveness and its resistance to chemotherapy mainly because *TP53* gene mutations are the commonest alteration in genes in ovarian type of cancers [13].

Carcinoembryonic antigen (CEA) is an oncofetal glycoprotein that has attachment to epithelial cells through its glycosylphosphatidylinositol c-terminal anchor, one of the superfamily of immunoglobulin cell adhesion molecules. CEA could realize adhesion between the tumor cells and extracellular collagen, which plays an essential role not only in cancer development but also in metastasis. Researches showed that CEA can affect either epithelial or stromal cells and immunity to adjust associated signaling sequence including phosphoinositide 3-kinases (PI3K), transforming growth factor receptor 1 (TGF-R1), apoptosis controlling, and protein kinase B (AKT) actions to help metastatic

dissemination [14-17].

Limited data are available in the literature regarding the expression of FOX A1 in invasive serous and mucinous carcinoma of the ovary, and to our knowledge no previous study demonstrated FOXA1 in relation to p53 and CEA expression in such cases. In this work we aimed to study FOX A1 in cases of invasive ovarian serous and mucinous carcinoma in association with p53 and CEA immunohistochemical expression and to explore the relation with clinicopathological data to reveal association with tumor prognosis.

METHODS

This retrospective study was performed on 67 cases of invasive ovarian carcinoma cases (46 serous and 21 mucinous). The cases were collected as paraffin embedded blocks from the archives of pathology department since January 2016- December 2019 according to inclusion and exclusion criteria. Approval from the ethical committee of the Faculty of Medicine was acquired (#408/9/19) and all cases were anonymous and handled according to legal, and ethical standards. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria

All received primary invasive serous and mucinous ovarian carcinoma specimens with confident histopathological diagnoses fulfilling clinical information on each patient were included.

Exclusion criteria

The following cases were not eligible for this study; inadequate material or missing tissue blocks, other types of carcinoma. Patients who received treatment, cases with missing clinical data, or unfit for immunohistochemistry (excessive fibrosis or necrosis) were also excluded.

Clinical data and pathological examination

Clinical data were obtained and serial sections from each paraffin-embedded block were cut at 4 microns thickness to be used for H&E and immunohistochemical staining. Histological grade was done according to the scoring system endorsed by Shimizu et al. (1998), where the atypia of the nucleus was either mild, moderate or severe with scores 1, 2, 3 respectively, mitoses 0–9, 10–24, and >25 were scored 1, 2, 3 respectively, and architecture was regarded as glandular, papillary, and solid scored 1, 2, 3 respectively with a calculation of their sum as total score where grade 1 when scored 3–5, grade 2 when scored 6–7, and grade 3 when scored 8–9 [18]. Tumors of grade 1 were considered as low-grade, while tumors of grades 2 and 3 were regarded as high-grade according to the WHO grading system [19].

Immunohistochemistryof FOX A1, p53 and CEAwas conducted using Rabbit monoclonal antibody against FOX A1, A9793, against p53, A11232, 1ml concentration and FLEX monoclonal mouse Anti-Human CEA Clone II-7 Dako Ready-to-Use according to manufacture guide.Omission of 1ry antibody was used asnegative control. Breast tissue was used as positive control for FOX A1 and colonic carcinoma was used for p53 and CEA.

Immunohistochemical evaluation

Immune reactivity of FOX A1 in tumor cells:

Scoring of FOX A1 nuclear expression was as follow: negative = 0; 1 to 50% = 1; > 50 to 75% = 2; and > 75% = 3 and staining intensity was scaled from 1 to 3 (weak; intermediate; and strong). Both, percentage and intensity grades were multiplied to acquire a concluding score: 0 = negative ; 1–

2 = +1; 3–4 = +2; 6–9 = +3 [20].

Immune reactivity of p53 in tumor cells:

The evaluation of p53 was according to nuclear staining intensity and was scored depending on the percentage of positive cells. Intensity of staining was recorded as a scale from 0 to 3 according to negative, weak, moderate, and strong, and the proportion of positive tumor cells was recorded as follow; 0=10%, 1= >10–25%, 2= >25–50%, 3= >50–75% and 4= >75% [21].

Immune reactivity of CEA in tumor cells:

The cytoplasmic expression of CEA was scored depending on the percentage of positive cells. Proportion of positive tumor cells was as follow; 0= 5%, 1= >5–25%, 2= >25–50%, 3= >50–75% and 4= >75% [22].

STATISTICAL ANALYSIS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Comparisons between groups for categorical variables were assessed using the Chi-square test (Fisher or Monte Carlo). Sensitivity;The capacity of the test to correctly identify diseased individuals in a population TRUE POSITIVES The greater the sensitivity the smaller the number of unidentified case false negatives. Specificity; The capacity of the test to correctly exclude individuals who are free of the disease TRUE NEGATIVES. The greater the specificity, the fewer "false positives" will be included. PPV the probability of the disease being present among those with positive diagnostic test results. NPV the probability that the disease was absent among those whose diagnostic test results were negative. Accuracy Rate of Agreement = (True positives + True negatives) / Total tested x 100. The significance of the obtained results was judged at the 5% level.

RESULTS

In this work, we studied 67 cases of invasive ovarian carcinoma (46 serous types and 21 mucinous types). All clinicopathological data were recorded in Table (1). Cases with positive p53 represented 65.7% of all cases, of which score 4 represented 52.2%. FOX A1 positivity was observed in 80.6% of studied cases, while, CEA expression was detected in 22.4% of studied cases (table 1) (Figure 1).

FOXA1 showed a significant association with age, 61.1% of positive cases were older than 50 years with significant difference. A highly significant association was detected with stage (p=0.001), grade, capsular rupture, and ascites (p<0.001) (table 2). In the studied cases only a significant association could be detected between the expression of p53 and histologic type (serous type) (table 3). The expression of CEA showed a significant association with age and mucinous carcinoma cases (table 4). No agreement could be detected between FOX A1 expression neither with p53 nor with CEA. However, 82.6% of negative p53 cases showed positivity for FOX A1 and 80.8% of negative CEA cases showed positivity for FOX A1. The expression of CEA with the other two markers was only significant in relation to p53 as all positive CEA cases were p53 negative (Table 5).

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Table 1: Distribution of the studied cases according to different parameters (n= 67)

	No. (%)
Age (years)	
≤50	30(44.8%)
>50	37(55.2%)
Mean ± SD.	52.1 ± 11.5
Median (Min. – Max.)	53(31 – 71)
Site	
Unilateral	26(38.8%)
Bilateral	41(61.2%)
Stage	
I	29(43.3%)
II	11(16.4%)
III	16(23.9%)
IV	11(16.4%)
Histologic type	
Serous	46(68.7%)
Mucinous	21(31.3%)
Grade	
I	18(26.9%)
II	22(32.8%)
III	27(40.3%)
Capsule rupture	39(58.2%)
Ascites	39(58.2%)
FOX A1 expression	
Negative	13(19.4%)
Positive	54(80.6%)
FOX A1 score	
0	13(19.4%)
1	4(6%)
2	26(38.8%)
3	24(35.8%)
P53 Expression	
Negative	23(34.3%)
Positive	44(65.7%)
P53 Score	
0	23(34.3%)
1	2(3%)
2	4(6%)
3	3(4.5%)
4	35(52.2%)
CEA expression	
Negative	52(77.6%)
Positive	15(22.4%)
CEA score	
0	52(77.6%)
3	8(12.0%)
4	7(10.4%)

Table 2: Relation between FOX A1 expression and different clinicopathological parameters (n = 67)

	FOX A1 expression		Test of sig.	P
	Negative (n= 13)	Positive (n= 54)		
Age (years)				
≤50	9 (69.2%)	21 (38.9%)	χ^2= 3.901*	0.048*
>50	4 (30.8%)	33 (61.1%)		
Mean ± SD.	45.3 ± 10.94	53.8 ± 11.1	t=2.475*	0.016*
Median (Min. – Max.)	39(31 – 63)	54(33 – 71)		
Laterality				
Unilateral	4 (30.8%)	22 (40.7%)	χ^2= 0.439	0.508
Bilateral	9 (69.2%)	32 (59.3%)		
Stage				
I	12 (92.3%)	17 (31.5%)		
II	0 (0.0%)	11 (20.4%)	χ^2= 14.726*	MCp= 0.001*
III	0 (0.0%)	16 (29.6%)		
IV	1 (7.7%)	10 (18.5%)		
Histologic type				
Serous	10 (76.9%)	36 (66.7%)	χ^2= 0.512	MCp= 0.740
Mucinous	3 (23.1%)	18 (33.3%)		
Grade				
I	12 (92.3%)	6 (11.1%)	χ^2= 30.442*	MCp <0.001*
II	0 (0.0%)	22 (40.7%)		
III	1 (7.7%)	26 (48.1%)		
Capsule rupture				
No	12 (92.3%)	16 (29.6%)	χ^2= 16.921	<0.001*
Yes	1 (7.7%)	38 (70.4%)		
Ascites				
No	12 (92.3%)	16 (29.6%)	χ^2= 16.921	<0.001*
Yes	1 (7.7%)	38 (70.4%)		

χ^2: **Chi-square test** FE: **Fisher Exact** MC: **Monte Carlo** t: **Student t-test**
p: p-value for an association between different categories *: Statistically significant at $p \leq 0.05$

Table 3: Relation between P53 expression with stage, grade, and histologic type (n = 67)

	P53 Expression		□²	P
	Negative (n= 23)	Positive (n= 44)		
Stage				
I	12 (52.2%)	17 (38.6%)		
II	3 (13.0%)	8 (18.2%)	□□□□□	MCp= 0.092
III	2 (8.7%)	14 (31.8%)		
IV	6 (26.1%)	5 (11.4%)		
Grade				
I	8 (34.8%)	10 (22.7%)	□□□□□	0.224
II	9 (39.1%)	13 (29.5%)		
III	6 (26.1%)	21 (47.7%)		
Histologic type				
Serous	2(8.7%)	44(100%)	58.514*	<0.001*
Mucinous	21(91.3%)	0(0%)		

χ^2: **Chi square test** MC: **Monte Carlo** p: p value for association between different categories
*: Statistically significant at $p \leq 0.05$

Table (4): Relation between CEA score expression and different clinicopathological parameters (n = 67)

	CEA score Negative (n= 52)	Positive (n= 15)	Test of sig.	P
Age (years)				
≤50	20 (38.5%)	10 (66.7%)	χ^2= 3.745	0.053
>50	32 (61.5%)	5 (33.3%)		
Mean ± SD.	53.6 ± 10.9	47 ± 12.3	t=2.006*	0.049*
Median (Min. – Max.)	54.5(31 – 70)	43(33 – 71)		
Site				
Unilateral	20 (38.5%)	6 (40.0%)	χ^2= 0.012	0.914
Bilateral	32 (61.5%)	9 (60.0%)		
Stage				
I	22 (42.3%)	7 (46.7%)		
II	9 (17.3%)	2 (13.3%)	χ^2= 2.250	MCp= 0.526
III	14 (26.9%)	2 (13.3%)		
IV	7 (13.5%)	4 (26.7%)		
Histologic type				
Serous	46 (88.5%)	0 (0.0%)	χ^2= 42.335	FEp <0.001*
Mucinous	6 (11.5%)	15 (100.0%)		
Grade				
I	12 (23.1%)	6 (40.0%)	χ^2= 1.654	MCp= 0.469
II	18 (34.6%)	4 (26.7%)		
III	22 (42.3%)	5 (33.3%)		
Capsule rupture				
No	24 (46.2%)	4 (26.7%)	χ^2= 1.817	0.178
Yes	28 (53.8%)	11 (73.3%)		
Ascites				
No	24 (46.2%)	4 (26.7%)	χ^2= 1.817	0.178
Yes	28 (53.8%)	11 (73.3%)		

χ^2: **Chi-square test** FE: **Fisher Exact** MC: **Monte Carlo** t: **Student t-test**
p: p-value for association between different categories *: Statistically significant at $p \leq 0.05$

Table 5: Relation between CEA expression and expression of FOX A1 and P53 in studied cases

	CEA expression Negative (n= 52)	Positive (n= 15)	□²	P
FOX A1 expression				
Negative	10(19.2%)	3(20%)	□□□□	FEp= 1.000
Positive	42(80.8%)	12(80%)	□	
P53 expression				
Negative	8(15.4%)	15(100%)	□□□□	<0.001*
Positive	44(84.6%)	0(0%)	□□*	

χ^2: **Chi-square test** FE: **Fisher Exact** p: p-value for association between different categories
*: Statistically significant at $p \leq 0.05$

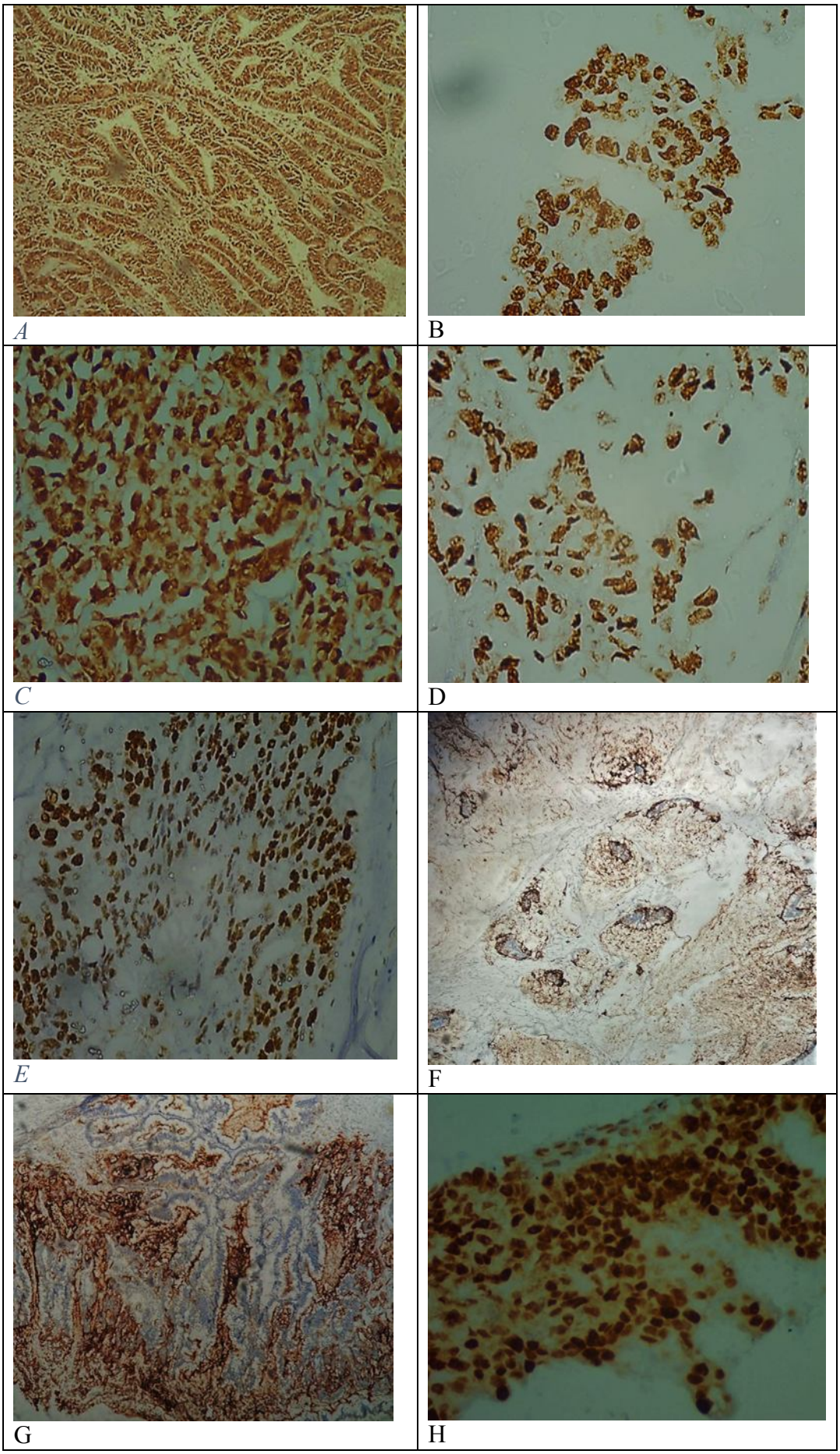

Figure 1:

A. Serous ovarian cystadenocarcinoma, grade II, strong nuclear FOX A1 expression in tumor cells (IHC X 100)
B. Serous ovarian cystadenocarcinoma, grade II, strong nuclear p53 expression in tumor cells (IHC X 400)
C. Serous ovarian cystadenocarcinoma, grade III, strong nuclear FOX A1 expression in tumor cells (IHC X 400)
D. Serous ovarian cystadenocarcinoma, grade III, strong nuclear p53 expression in tumor cells (IHC X 400).
E. Mucinous ovarian cystadenocarcinoma, gradeII, strong FOX A1 expression in tumor cells (IHC X 400)
F. Mucinous ovarian cystadenocarcinoma, gradeII, moderate cytoplasmic & membranous CEA expression in tumor cells (IHC X 100)
G. Mucinous ovarian cystadenocarcinoma, gradeII, strong cytoplasmic & membranous CEA expression in tumor cells (IHC X 200)
H. Mucinous ovarian cystadenocarcinoma, grade III, strong nuclear FOX A1 expression in tumor cells (IHC X400)

DISCUSSION

Since ovarian carcinomas are likewise hormone-dependent, this provoked the evaluation of FOX A1 expression in such tumors since FOX A1 is suggested to play a major role in controlling steroid receptor action in the nucleus (androgen and estrogen receptors) contributing to tumorigenic promotion [11]. The present work evaluated FOX A1 about p53 and CEA expression and other clinicopathological data in invasive serous and mucinous carcinomas to determine prognostic value. FOX A1 showed high expression in invasive serous and mucinous cases with significant association with old age, and highly significant association with staging, grading, capsular rupture, and ascites ($p=0.001$ and <0.001 respectively), whereas, no significant association could be detected between FOX A1 and laterality of the tumor nor its type. These results indicate the contribution of FOX A1 to bad prognostic parameters in ovarian carcinoma. The bad prognostic indicators in OC such as older age, staging, grading and tumor rupture were previously pointed out by other authors [23]. p53 expression was detected using immunohistochemistry in approximately two third of the studied cases (65.7%), and score 4 was the most frequent score (52.2%). In the studied cases only significant association could be detected between expression of p53 and histologic type as all positive cases were of serous type. CEA expression was detected in 22.4% of studied cases all were of mucinous carcinoma type and their significant association with age and mucinous carcinoma cases was proved.

Limited data are available in the literature regarding the expression of FOX A1 in OC, and to our knowledge, no previous study has explored FOXA1 in relation to p53 and CEA expression in OC. This research showed that FOX A1 overexpression in OC particularly in cases of negative p53 and CEA could be used as a biomarker which is also helpful in prognosis and the three markers could be used as a panel in OC cases. However, there are some limitations to the current work since this was a retrospective study conducted with a sample size of 67 cases of invasive ovarian carcinoma (46 serous type and 21 mucinous type) and limited access to clinical data. Hence, further prospective researches with larger number of cases and inclusion of other clinico-pathological criteria such as survival and response in chemo-resistant cases are required to confirm the prognostic value of

FOX A1 immunohistochemical expression in such patients.

FOX A1 showed high expression (80.6%) of invasive serous and mucinous cases, and score 2 & 3 represented 38.8% and 35.8% respectively. This high expression of FOX A1 is in concordance with the study conducted byWang et al., (2018)whoreported that FOX A1 over expression was detected in about 73.6% of variable types of OC [11]. In contrast, Wang et al., (2017) stated that FOX A1 expression in epithelial OC was about 32.03% [20]. The later authors did not specify the exact types of ovarian carcinoma used in their research, while we specified serous and mucinous types only.

We found that FOX A1 showed significant association with older age, and highly significant association with stage, grade, capsular rupture, and ascites (p=0.001 and <0.001 respectively), whereas, no significant association could be detected between FOX A1 and laterality of the tumor nor its type.

In this study, 61.1% of FOX A1 positive cases were older than 50 years, and 69.2% of negative cases were 50 years or younger with significant difference. This result is in line with the study of Wang et al., (2018),sincethey reported that FOX A1 expression was more in patients older than 55 years, however, their study showed no significant difference [11].

On exploration of FOX A1 expression in relation to tumor staging; 48.1% of positive FOX A1 cases were of advanced stage (III & IV) while 92.3% of FOX A1 negative tumors were of stage (I). This result agrees with Wang et al., (2018), who reported significant expression of FOX A1 in 41.8% of cases at stage III & IV tumors. Furthermore, this study goes hand in hand with theirresults regarding significant association of high expression with increased grading as we found that 88.8% of FOX A1 positively expressed tumors were of high grade. They also reported no significant association with laterality and subtype, which is in line with our results [11].

The present results indicate the contribution of FOX A1 to bad prognostic parameters including advanced age, high grade, advanced stages, tumors with ruptured capsules and ascites regardless of laterality and type. Furthermore, these results support the suggestion of Wang et al., (2018) that FOX A1 functions in epithelial OC as a prognostic marker, and their proposal of being a targeted therapy [11], likewise, Wang et al., (2017) provided evidence that FOX A1 plays a role as an oncogene in OC pathogenesis and progression [20].

Moreover, with the use of therapeutic lines, the work of Rutten provided evidence that FOX A1 expression in previously treated OC tissues was significantly associated with chemotherapy response since it was highly expressed in OC tissue with no response to chemotherapy in comparison to chemo-sensitive ones [24].

FOX A1 increased activity and expression as a transcriptional factor has been evidenced in other advanced tumors such as breast, lung, esophagus, thyroid, and prostate with potential role in cancer progression. The high expression of FOX A1 suggests its implication in treatment of chemo-resistant OC cases in relation to estrogen receptor expression which requires further investigation to provide more evidence on targeted therapy likewise the recent work on role of FOX A1 in treatment resistance of breast cancer [25, 26].

Immunohistochemical staining for p53 has been regarded as a crucial biomarker for clinical research trials targeting mutant *TP53*

and utilized in the diagnostic & prognostic examination of variable types of cancer, including ovarian ones [27].In the current study, p53 expression was detected using immunohistochemistry in approximately two third of the studied cases (65.7%), and score 4 was the most frequent score (52.2%). In the studied cases, only significant association could be detected between expression of p53 and histologic type as all positive cases were of serous type. Immunohistochemical expression of p53 in OC is a reflect of *TP53* mutation with good indication as previously evident by many authors [13, 28]. The expression of p53 in this study is in concordance with the study conducted by RazakAmanullah and coworkers (2020), who reported p53 expression in 65.2% of epithelial OC samples, and all their positive cases were of serous type, which was also previously reported by Sylvia et al., (2012) [29, 30]. p53 positivity in this work was comparable to that reported by Ndukwe et al. (2018) in 58% of epithelial OC [31]. Furthermore, a previous meta-analysis stated that the expression of p53 in epithelial OC ranged from 13.7 to 82.0% [32]. Moreover, strong expression was reported in 55% of cases studied by Havrilesky et al. [33].

In the present study, all p53 positive tumors were serous malignancies. p53 positivity was seen in 95.65% of serous carcinomas. This pattern of p53 expression in serous carcinoma and negativity in mucinous carcinoma was also reported in previous studies [20, 26]. Some authors well-thought-out that p53 expression is a substitute marker for the differentiation of HGSC from other OC [34]. It is worth mentioning that we found more expression of p53 in HGSC than low grade type, although, no statistical significance could be detected. Psyrri et al. (2007) found that p53 immunohistochemical expression in OC had no statistically significant association with clinicopathological criteria including grade, stage, and histologic type [35]. On the contrary, Missaoui et al. (2018) and RazakAmanullah et al. (2020) showed a significant association of p53 expression with stage and other clinical parameters [30]. While, Ndukwe et al. (2018) reported significant association with grade, and with histologic type [31]. The variation in these results may be related to the geographical distribution of the different studied groups. Larger scales of investigation may give a clear idea about p53 expression as a marker for OC risk, prognosis, response to therapy, and targeted treatment.

In this work, CEA expression was detected in 22.4% of studied cases all were of mucinous carcinoma type, showing significant association with age and mucinous carcinoma cases. When comparing the expression of CEA with the other two markers, it was only significant in relation to p53 as all positive CEA cases were p53 negative which was previously reported by other authors [22, 36].

In this work, no agreement could be detected between FOX A1 expression neither with p53 nor CEA, however, 82.6% of negative p53 cases and 80.8% of negative CEA cases showed positivity for FOX A1. This could indicate the implication of FOX A1 as a marker in cases of OC, particularly with negative p53 and CEA. FOX A1 is suggested to be targeted as a new line of treatment in such cases which requires further investigation.

CONCLUSION

FOX A1 has a poor prognostic indication in invasive serous and mucinous ovarian carcinomas as it is highly expressed in a majority of such cases, and significantly

associated with advanced age, high-grade, advanced-stage, tumors with ruptured capsule, and ascites. p53 is highly expressed, and significantly associated with serous ovarian carcinoma, while, CEA showed significant association with age and mucinous ovarian carcinoma. This indicates that p53 and CEA could be helpful in differentiating serous type (particularly HGSC) and mucinous type. FOX A1 overexpression in both invasive serous and mucinous OC could be used as a biomarker which is also helpful in prognosis particularly in cases of negative p53 and CEA.

CONFLICT OF INTEREST

The authors report no conflicts of interest that are directly relevant to the content of this study.

FINANIAL DISCLOSURE

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