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HER2 and Ovarian Cancer: A Retrospective Study Investigating Clinico-Pathological Correlations

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Abstract—Background*: Ovarian cancer is the deadliest type of gynecologic malignancy. While it ranks third after cervical and uterine cancers, its prognosis is the gloomiest.* ***Aim****: To assess the relationship between the expression of HER2/neu marker in ovarian cancer subtypes and its implications for the prognosis of ovarian cancer.* ***Methods****: a cross-sectional study involving a total of 50 formalin-fixed and paraffin-embedded samples of surface epithelium ovarian cancer were collected with associated patients clinicopathological information including age, laterality, size, types, grades. HER2/neu protein was evaluated by immunohistochemistry and scored using a semiquantitative method.* ***Results****: Patients age ranged between 25 to 74 years, with a mean of 50.2 (± 4.8) years. 11.4% of serous cases, 16.6% of mucinous cases, 13.5% of unilateral cases, 12.5% of tumors greater than or equal to 10 centimeters, and 14.8% of cases with metastasis exhibited HER2/NEU overexpression. Nonetheless, no statistical significance was found in these observations. HER2/neu expression was absent in all endometroid carcinomas.* ***Conclusions****: Although HER2 expression is comparatively higher in ovarian mucinous and serous carcinomas, its impact on epithelial ovarian malignancies may not be substantial when all histological subtypes and clinicopathological variables are considered.*

Keywords— *Ovarian surface epithelial carcinoma, HER2/neu, ovarian serous carcinoma, ovarian mucinous carcinoma, ovarian endometrioid carcinoma.*

I. INTRODUCTION

Ovarian cancer stands as the eighth most common cause of death from cancer impacting women globally. Despite its lower prevalence compared to breast cancer, it proves three times more lethal, and projections indicate a substantial increase in mortality rates by 2040 [1, 2]. In 2020, Iraq reported 914 new cases of ovarian cancer, with an annual death toll of approximately 678, expected to escalate to 1,482 by 2040, according to the Global Cancer Observatory (GLOBOCAN) [3].

Epithelial ovarian cancer comprises a diverse range of tumors originating from the epithelial cells of the ovaries. Often diagnosed at advanced stages due to vague symptoms and the absence of reliable screening methods, it leads to suboptimal overall survival rates [4].

While the precise causes of ovarian cancer remain incompletely understood, several risk factors have been identified. These encompass advanced age, a family history of ovarian or breast cancer, inherited genetic mutations (such as BRCA1 and BRCA2), a personal history of breast or endometrial cancer, specific reproductive factors (like early menarche, late menopause, nulliparity), hormone replacement therapy, obesity, and exposure to talcum powder. Additionally, emerging evidence suggests that chronic inflammation, oxidative stress, and hormonal imbalances may contribute to the initiation of ovarian cancer [4-6].

HER2/neu (human epidermal growth factor receptor-2), a member of the EGFR tyrosine kinase receptor family, functions as a proto-oncogene by encoding a specific protein. Overexpression of HER2/neu triggers internal signaling pathways, influencing cellular processes such as differentiation, proliferation, migration, and apoptosis. Approximately 20-30% of ovarian epithelial cancers exhibit overexpression of HER2/neu [7]. In various cancers, increased HER2/neu expression is linked to reduced patient survival, and it is frequently observed in epithelial ovarian cancers. This overexpression is associated with a grim prognosis and resistance to chemotherapy [8].

Recognizing the background, epidemiology, causes, risk factors, diagnosis, and screening programs for ovarian cancer is essential for effective prevention, early detection, and enhanced outcomes for affected individuals. The objective of this study was to assess the HER2/neu expression status in primary ovarian epithelial carcinomas and explore its correlation with clinicopathological parameters.

II. METHODS

This is a cross-sectional study conducted in the Unit for Cancer Research/ Alkufa University-Faculty of Medicine from (2019-2023) involving patients diagnosed with primary ovarian carcinoma. The study protocol was approved by The Iraqi Ministry of Higher Education and Scientific Research Ethics Committee (Medical Ethics Committee) and followed the tenets of the Helsinki Declaration.

The power of the study was estimated using Daniel's sample size formula [9]: with an expected prevalence of 21% depending on a previous Iraqi study [10], statistical power of 80%, and precision of 0.05-0.1. The calculated sample size was 63.

A total of 50 formalin-fixed and paraffin-embedded (FFPE) samples of surface epithelium ovarian cancer were collected from the archive of private laboratories and pathology department of Al-Sader Teaching Hospital with associated patients clinicopathological information including age, laterality, size, types, grades. Ten cases with incomplete clinicopathological information were excluded. The final included cases were 50.

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All included tumors were reexamined microscopically by two pathologists to confirm the diagnosis by hematoxylin and eosin-stained sections. The cases were classified according to the WHO classification of ovarian tumors.

Immunohistochemistry procedure and interpretation: Sections were prepared following the manufacturer's instruction and as previously described in [11]. Briefly, 4 μm FFPE sections underwent initial deparaffinization followed by rehydration using graded alcohol. Antigen retrieval was achieved in citrate for 20 minutes before applying the primary polyclonal rabbit anti-human c-erbB-2 oncoprotein (Agilent Technologies Singapore international, Denmark) at a dilution of 1:1000. Subsequently, samples were incubated in a humidified chamber for 18 hours at 4°C. Visualization was carried out using the EnVision complex (Dako) and counterstained with Myers hematoxylin. Finally, the samples were dehydrated and mounted.

Her2/Neu expression was evaluated following the guidelines proposed by Eills and Wolff [12]: A score of 0 signifies a negative outcome, indicating the absence of HER2/Neu protein staining in less than 10% of cells. A score of 1+ indicates weak and incomplete membranous staining in more than 10% of cells. A score of 2+ signifies complete membranous staining with either non-uniform or weak intensity in at least 10% of tumor cells. A score of 3+ indicates uniform, intense, and complete membranous staining in at least 10% of cells.

III. Results

The average age of the patients was 50.2 years, with a standard deviation of 4.8 years, ranging between 25 to 74 years. Nearly half of the patients, 48%, were aged 65 years or older. The most common type of tumor was serous, accounting for 70% of the cases, followed by mucinous at 24%, as detailed in Table. The average tumor size was 9.4 cm, with a standard deviation of 3.9 cm, and sizes varied from 2 to 26 cm. More than half of the tumors, 52%, were larger than 10 cm. Most of the tumors, 74%, were unilateral. In terms of tumor differentiation, 40% of the cases were low grade, while 45% were high grade with distant metastasis.

Characteristics		frequency	Percentage
Age	25-44	8	16%
	45-64	18	36%
	≥65	24	48%
Type of tumor	Serous	35	70.0
	Mucinous	12	24.0
	Endometrioid	3	6.0
Laterality	Unilateral	37	74
	Bilateral	13	26
Size	≥10	26	52
	<10	24	48
Grade	Low	20	40.0
	Moderate	3	6.0
	High	27	54.0
Metastasis	No	23	46.0
	Yes	27	54.0

The semiquantitative HER2/NEU scores are summarized in Table.

SCOR Her2/ result	Frequency	Percentage
Negative (0)	35	70%
Weak and incomplete membranous staining (+1)	9	18%
Strong and complete membranous staining (+3)	6	12%
Equivocal (+2)	0	0%

The overexpression of HER2/NEU was observed in 11.4% of serous cases, 16.6 of mucinous, 13.5% of unilateral cases, and 12.5% of tumors larger than or equal to 10 cm, as well as in 14.8% of cases with metastasis. However, these observations did not show any statistical significance, as elaborated further in Table.

Characteristics		HER2/neu expression				
		Negative	%	Positive	%	P value
Age	Mean	55	-	59	-	0.752
Type of tumor	Serous	31	88.6	4	11.4	0.605
	Mucinous	10	83.4	2	16.6	
	Endometrioid	3	100	0	0	
Laterality	Unilateral	31	86.5	5	13.5	0.162
	Bilateral	13	92.4	1	7.6	
Size	≥10 cm	23	88.5	3	11.5	0.539
	<10 cm	21	87.5	3	12.5	
Grade	Low	17	85	3	15	0.580
	Intermediate	3	100	0	0	
	High	24	88.9	3	11.1	
Metastasis	Absent	21	91.3	2	8.7	0.777
	Present	23	85.2	4	14.8	

IV. Discussion

Ovarian cancer is the deadliest type of gynecologic malignancy. While it ranks third after cervical and uterine cancers, its prognosis is the gloomiest [6]. The results of the current study provide the relationship between the expression of HER2/neu marker in ovarian cancer subtypes (serous, mucinous, and endometrioid) and its potential implications for the prognosis of ovarian cancer.

The variability in sample sizes across studies highlights the diverse research methodologies and the difficulties encountered in collecting comprehensive data in the intricate field of ovarian cancer research. In our study, we initially identified 60 cases. However, due to various limitations such as incomplete data and sample issues, our analysis was ultimately conducted on 50 cases, with a Her2 expression rate of 12%.

This finding was consistent with several studies that reported rates around 10%, including Hogdall et al. in 2003 at 13.3%, Bookman et al. in 2003 [13] at 11.4%, and Tuefferd et al. in 2007 at 12.8% [14]. Some studies reported higher rates, notably Verma N et al. in 2018, which found a significant rate of 62.8% [14]. On the other hand, lower rates were reported by Lee CH et al. in 2005 with 4.9%, and Pathak et al. with 6% of cases [14].

We have shown higher expression of HER2/neu in unilateral, large tumors with metastasis but differences did not reach statistical significance. Similarly, a previous local study

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conducted on Iraqi patients in 2013, which had a smaller sample size limited to 38 cases, concluded that 21% of early-stage ovarian cancer were Her2 positive with no significant correlation with tumor grade or subtype [10]. Further Grover and colleagues found no significant correlation between HER2/neu expression and histological type, histological grade, extent of tumor (stage), and distant metastasis of ovarian surface epithelial tumors apart from nodal metastasis [15].

Mucinous and serous adenocarcinoma were the subtypes that overexpressed Her2 in the current study with a rate of 16.6% and 11.1% respectively, while endometrioid cases were consistently negative. Woo et al 2016 conducted a study on the overexpression and amplification of HER2/neu in gynecologic malignancies. By the current results, they concluded that 11.1% of serous adenocarcinomas were positive for HER2/neu, with 2.2% originating from the ovary. However, no endometrioid adenocarcinomas tested positive for HER2/neu [16]. McAlpine et al. reported for the first time that the frequency of HER2 overexpression/amplification in ovarian mucinous carcinoma was up to 18% [17], while earlier studies that explored the prognostic implications of HER2 overexpression or HER2 targeted therapy in EOC often included few or no cases of mucinous histology [13, 16, 18].

V. CONCLUSION

While HER2 amplification may not be a significant factor in epithelial ovarian cancers when evaluated across all histological subtypes and clinicopathological variables, our findings indicate that it is relatively more in ovarian mucinous and serous carcinomas. The evaluation of HER2/NEU could aid in identifying patients with different risk profiles and assist in tailoring treatment strategies to individual needs.

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