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ORIGINAL

HER2 is Rarely Expressed in Endometrial Carcinoma in Sudanese Population

HER2 rara vez se expresa en el carcinoma endometrial en la población sudanesa

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ABSTRACT

Introduction: endometrial cancer is the most common gynecologic cancer in high-income countries, and its incidence is increasing in low-and middle-income nations. Although differentiating between high-grade and low-grade tumors is mandatory for the survival of the patients, histomorphology alone has limited reproducibility owing to the overlapping of the morphologic features by routine H&E stain. Human Epidermal Growth Factor Receptor 2 (HER2) expression has been observed in various cancers with a potential role in prognosis and targeted therapy for endometrial carcinoma.
Objective: the study aimed to assess the HER2 expression pattern and its potential role as a natural history predictor and target therapy in endometrial carcinoma among Sudanese women.
Method: a cross sectional descriptive institutional based study was done where all Sudanese female patients diagnosed with endometrial carcinoma from January 2013 to October 2016 were included. Fifty-four cases were evaluated for HER2 expression through immunohistochemistry using the Hercep Test (Dako, Glostrup, Denmark).
Results: the results showed that 92,59 % of the cases were negative (0 or 1+), 5,56 % were equivocal (2+), and only 1,85 % were positive (3+). correlation of statistical significance was identified between HER2 expression and histological subtypes (P value = 0,01). However, the association between HER2 expression and tumor grade and between HER2 expression and lymphovascular invasion within the tumor was insignificant (P value = 0,06 and 0,49 respectively).
Conclusions: HER2 expression is infrequently observed in Sudanese patients with endometrial carcinoma, with the sole positive instance occurring in carcinosarcoma. This indicates that the biological characteristics of endometrial carcinoma in this region of the world is different from their counterpart in European nations while similar in some Asian countries. Thus, its potential as target in treatment is questionable.

Keywords: Endometrial Carcinoma; HER2; Immunohistochemistry.

RESUMEN

Introducción: el cáncer de endometrio es el cáncer ginecológico más común en países de altos ingresos

y su incidencia está aumentando en los países de ingresos bajos y medios. Si bien la diferenciación entre tumores de alto y bajo grado es fundamental para la supervivencia de las pacientes, la histomorfología por sí sola presenta una reproducibilidad limitada debido a la superposición de las características morfológicas en la tinción de rutina con hematoxilina y eosina (H&E). La expresión del receptor del factor de crecimiento epidérmico humano tipo 2 (HER2) se ha observado en diversos tipos de cáncer, con un posible papel en el pronóstico y la terapia dirigida para el carcinoma de endometrio.
Objetivo: el estudio tuvo como objetivo evaluar el patrón de expresión de HER2 y su posible papel como predictor de la evolución natural y terapia dirigida para el carcinoma de endometrio en mujeres sudanesas.
Método: se realizó un estudio transversal, descriptivo, de base institucional, en el que se incluyeron todas las pacientes sudanesas diagnosticadas con carcinoma de endometrio entre enero de 2013 y octubre de 2016. Se evaluaron cincuenta y cuatro casos para la expresión de HER2 mediante inmunohistoquímica con la prueba Hercep (Dako, Glostrup, Dinamarca).
Resultados: los resultados mostraron que el 92,59 % de los casos fueron negativos (0 o 1+), el 5,56 % fueron equívocos (2+) y solo el 1,85 % fueron positivos (3+). Se identificó una correlación estadísticamente significativa entre la expresión de HER2 y los subtipos histológicos (p = 0,01). Sin embargo, la asociación entre la expresión de HER2 y el grado tumoral, así como entre la expresión de HER2 y la invasión linfovascular dentro del tumor, fue insignificante (p = 0,06 y 0,49, respectivamente).
Conclusiones: la expresión de HER2 se observa con poca frecuencia en pacientes sudanesas con carcinoma endometrial, y el único caso positivo se presentó en el carcinosarcoma. Esto indica que las características biológicas del carcinoma endometrial en esta región del mundo difieren de las de sus contrapartes en países europeos, mientras que son similares en algunos países asiáticos. Por lo tanto, su potencial como objetivo de tratamiento es cuestionable.

Palabras clave: Carcinoma Endometrial; HER2; Inmunohistoquímica.

INTRODUCTION

An estimated 1,28 million new cancer case and 9 700 000 cancer death is predicted to occur in Africa by the year 2030. Cancer care in Sudan continues to be neglected although the numbers are growing reflecting the general trend in that part of the world. Unfortunately women are affected disproportionately more by this neglect.[1]

Endometrial cancer is the most common tumor of the female reproductive tract. It is the sixth most common malignancy among women across various populations.[2]

Endometrial carcinoma (EC) encompasses a wide variety of histologic subtypes, which are categorized into type I and type II. Type I endometrial tumors are characterized by endometrioid histology, while the type II spectrum includes various histologies such as uterine serous carcinoma, carcinosarcoma, and clear cell carcinoma.[3] Incidence of EC is increasing necessitating parallel efforts to elucidate the biology of the tumor in order to identify possible potential therapy.[4]

The human epidermal growth factor receptor type II (HER2), also known as c-erbB-2, is a pivotal protein involved in regulating cell growth and differentiation. The HER2 gene is situated on the long arm of chromosome 17 and encodes a transmembrane tyrosine kinase receptor with a molecular weight of 185 kDa.[5] HER2 plays role in cell regulation and differentiation (Iqbal and Iqbal). In typical cellular genetics, organisms possess two copies of the HER2 gene. However, additional copies may arise upon amplification, which is evident at the transcriptional level as an increased concentration of HER2 messenger RNA and at the phenotypic level as an elevated expression of HER2 protein,[6] thereby affecting cell survival, proliferation, differentiation, angiogenesis, and invasion in a variety of malignancies.[7]

HER2 overexpression has been associated with heightened tumor aggressiveness, an increased propensity for metastasis, and a diminished prognosis.[8] Various variants of HER2 have been delineated, including the alternative splicing variant referred to as the Delta16 isoform.[9] HER2-targeting monoclonal antibodies, exemplified by trastuzumab (Herceptin), have demonstrated efficacy in inducing regression of tumors characterized by HER2 overexpression EC may function as a valuable prognostic indicator while also offering significant therapeutic avenues by administering anti-HER2 antibodies. Thus, if significant positive results are obtained, it can justify incorporating HER2 immunohistochemistry test as routine practice similar to breast cancer.

The current study seeks to assess the levels of HER2 expression in EC among Sudanese women, its effects on tumor biological behavior and the potential to influence the management strategies for patients presenting with EC and HER2 overexpression.

METHOD

This is an observational cross-sectional descriptive institutional study that covered all Sudanese female patients diagnosed with EC at the National Public Health Laboratory and Soba University Hospital laboratory from January 2013 to October 2016. Fifty-four cases were included. All cases had archived paraffin-embedded tissue blocks from hysterectomies or endometrial curettages in the aforementioned two laboratories.

H &E microscopic diagnosis

Tissue sections were prepared for hematoxylin and eosin staining and examined by the microscope to confirm the diagnoses and stratify the histologic variants according to the WHO diagnostic criteria.

Immunohistochemistry

Following a detailed microscopic analysis, slides stained with hematoxylin and eosin were designated for tumor location. Paraffin-embedded blocks that exemplified the typical morphological features for each case were chosen. Tissue sections were created from these blocks onto adhesive microscopic slides, and the Hercep Test (Dako, Glostrup, Denmark) was conducted. Specifically, the tissue sections underwent deparaffinization in xylene twice for 10 minutes each, were rehydrated in graded alcohols, and rinsed in tap water. Antigen retrieval was achieved through heat; the slides were microwaved at 92°C for 15 minutes in buffered EDTA (pH 8) and then allowed to cool for 20 minutes at room temperature. A polyclonal anti-HER2 antibody (DAKO) was applied at a dilution of 1:1100. To prepare the DAB solution, 0,1 ml of DAB chromogen was mixed with 1,9 ml of DAB buffer and vortexed briefly. The sections were then incubated with this substrate-chromogen mixture for 10 minutes. Finally, the slides were counterstained with hematoxylin and mounted. A HER2-positive breast carcinoma served as the positive control, while negative controls for all immunostaining were obtained by replacing the primary antibody with normal rabbit serum.

Visualization under light microscopy was performed to assess tumor cells. The positive tumor cells were graded and scored on a scale ranging from 0 to 3+, in accordance with the ASCO-CAP HER2 test guideline recommendations from 2013 for breast carcinoma. Grade 0 indicates tumors with no staining or only incomplete, faint/barely perceptible membranous staining observed in 10 % or fewer of invasive tumor cells. Grade 1 is assigned to tumors exhibiting incomplete, faint/barely perceptible membranous staining in more than 10 % of invasive tumor cells. Grade 2 corresponds to tumors with circumferential incomplete and/or weak to moderate membranous staining in more than 10 % of invasive carcinoma cells, or those with circumferential complete intense membranous staining in fewer than 10 % of invasive tumor cells. Lastly, Grade 3 is designated for tumors demonstrating circumferential, complete, and intense membranous staining in more than 10 % of invasive carcinoma cells. The final scores report for tumors with 0 and 1+ as HER2 negative, 2 + was deemed equivocal, which necessitates further analysis using in situ hybridization and 3+ was identified as HER2 overexpression.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 23 and Excel sheets. Pearson's chi-squared test was used to assess the goodness of fit, homogeneity, and independence. The linear-by-linear test was used to test the association among variables. A P-value of 0,05 or less was considered significant.

Ethical consideration

The ethical approval for the present study was obtained from the Ethical Committee at Assafa College. The data were anonymized, and written consent was obtained from all patients prior to enrolment in the study.

RESULTS

62,3 % (33) of EC cases in Sudanese women occured in the age group 50-69 years constituting the majority of the population under study while 26,22 % (14) occured in above 70 years, 8,2 % (5) happened in 30-49 years and the rest were (2) unspecified.

Histologic results

The results showed that conventional adenocarcinoma was the most common histologic subtype of EC, accounting for 74,1 % of cases, followed by papillary serous carcinoma, carcinosarcoma, and clear cell carcinoma, seen in 13 %, 9,2 %, and 3,7 %, respectively (figure 1).

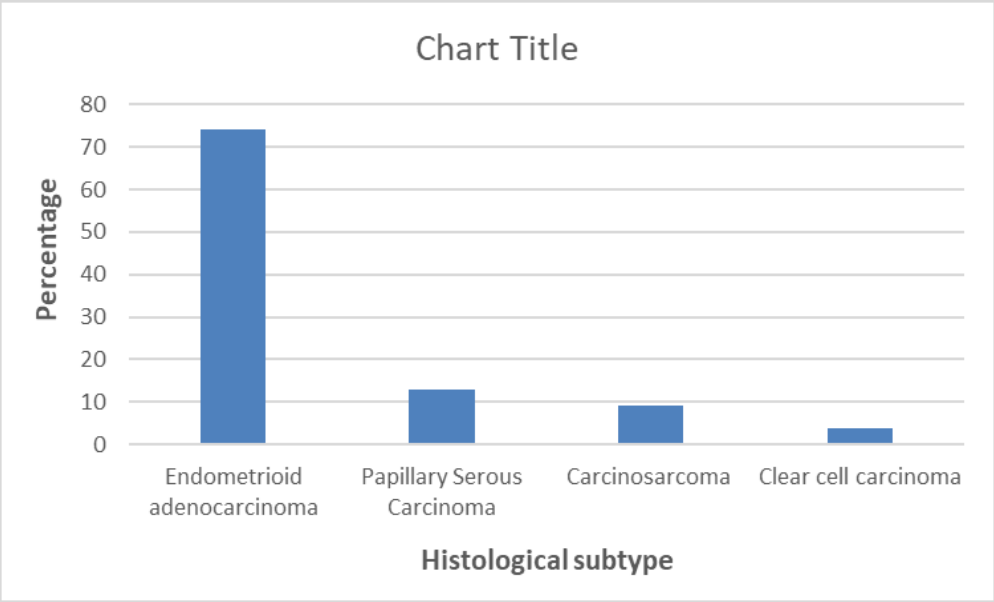

Figure 1. Distribution of cases of EC in Sudanese women according to histological subtypes (n=54)

Of the 54 cases, 22,2 % were grade I, 31,5 % were grade II, and 46,3 % were grade III.

Immunohistochemistry findings

Concerning HER2 expression, 92,59 % of the cases were negative (0 or 1+), 5,56 % were equivocal (2+), and only 1,85 % were positive (3+) (figures 2-4).

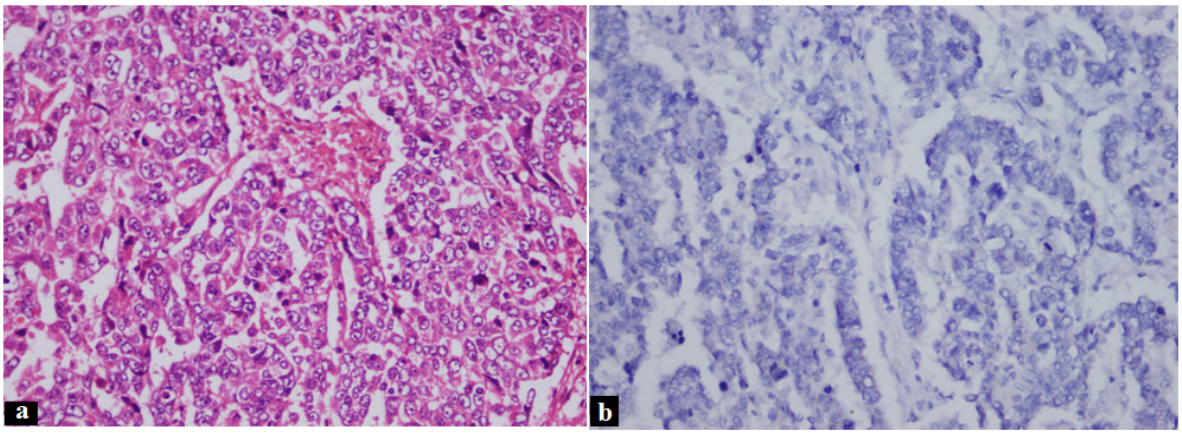

Figure 2. Endometrioid adenocarcinoma with negative (0) HER2 expression in one of the Sudanese patients with EC: (a) H and E, (x40). (b) HER2, (x40)

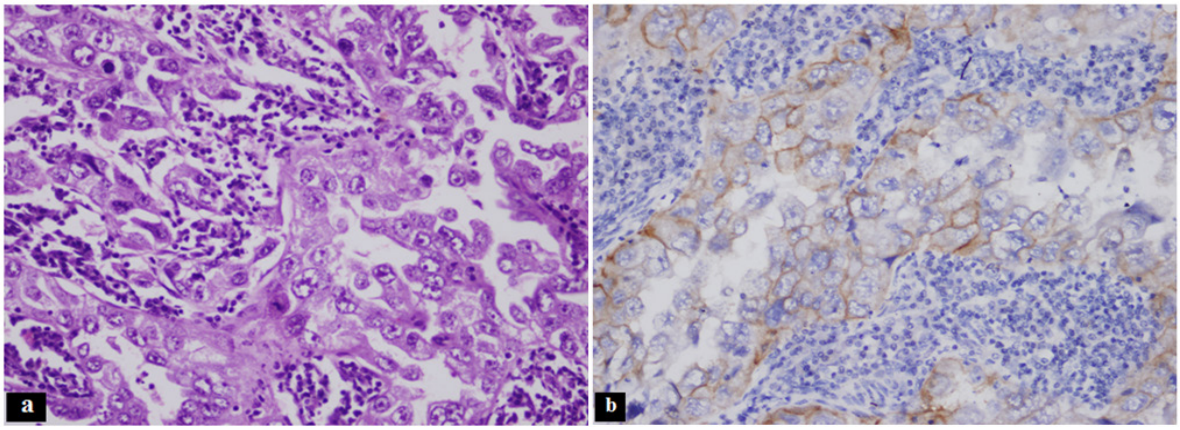

Figure 3. Serous papillary carcinoma with equivocal (2+) HER2 expression in one of the Sudanese patients with EC: (a) H and E, (x40) (b) HER2, (x40)

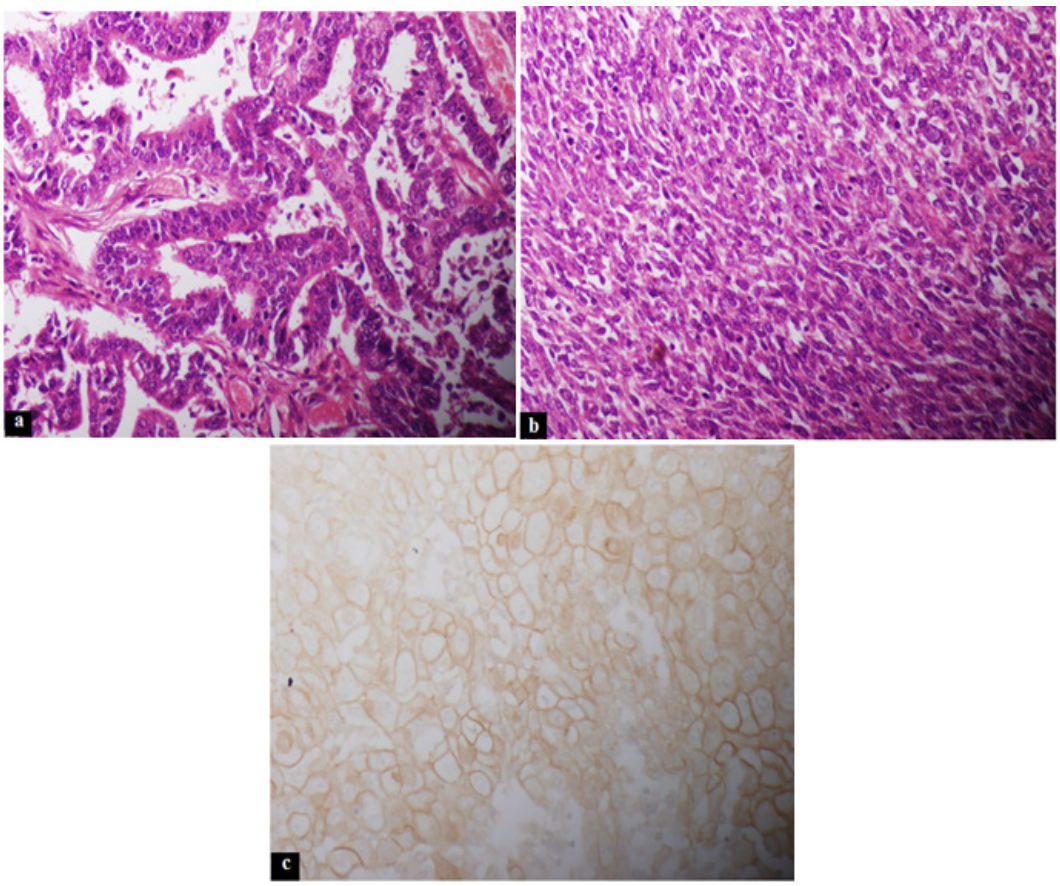

Figure 4. Carcinosarcoma with positive HER2 expression in one of the Sudanese patients with EC: (a) carcinomatous part H and E, (x40). (b) sarcomatous part (c) HER2, (x40)

HER2 Expression and Lymphovascular Invasion

The investigation into the relationship between HER2 expression and the histological subtypes of EC revealed that out of 40 cases of endometrial endometrioid adenocarcinoma, 39 cases exhibited negative HER2 expression (scores of zero and 1+).Only one case demonstrated positive HER2 expression (3+), identified as carcinosarcoma, with a significant P value of 0,01 (table 1).

Table 1. Relationship between HER2 expression and histological subtypes of EC in Sudanese women (n=54)

		HER2 Expression			
		Negative (0/1+)	**Equi-vocal (2+)**	**Positive (3+)**	
Histologic Variant	Endometrioid Adenocarcinoma	39	1	0	40
	Papillary Serous Carcinoma	6	1	0	7
	Clear Cell Carcinoma	1	1	0	2
	Carcinosarcoma	4	0	1	5
Total		50	3	1	54

Note: P value = 0,01 (Significant)

Furthermore, the correlation between HER2 expression and the histologic grade of EC indicated that all tumors classified as grade I (12 tumors) and grade II (17 tumors) were negative for HER2 expression (scores of zero and 1+). Among the 25 tumors graded as grade III, three displayed equivocal HER2 expression, while only one exhibited positive expression (3+) with an insignificant P value of 0,06 (table 2).

Of the 20 cases of EC characterized by lymphovascular invasion, 19 cases exhibited negative HER2 expression (scores of 0 and 1+), while one case showed equivocal results (score of 2+). Conversely, among the 34 cases lacking lymphovascular invasion, 31 were HER2 negative (scores of 0 and 1+), two cases were equivocal (2+), and one case was positive (3+). The statistical analysis yielded a p-value of 0,49, indicating no significant correlation between HER2 expression and lymphovascular invasion (figure 5).

Table 2. Relationship between HER2 expression and histologic grade of EC in Sudanese women (n=54)

		HER2 Expression			Total
		Negative (0/ 1+)	Equivocal (2+)	Positive (3+)	
Histologic Grade	I	12	0	0	12
	II	17	0	0	17
	III	21	3	1	25
Total		50	3	1	54

Note: P value = 0,06 (Not significant)

Total	HER2 Expression			Lymphovascular Invasion
	Positive (3+)	Equivocal (2+)	Negative (0/ 1+)	
20	0	1	19	Yes
34	1	2	31	No
54	1	3	50	Total

Figure 5. Relationship between HER2 expression in EC in Sudanese women and lymphovascular invasion (n=54)
Note: P value = 0,49 (Not significant)

DISCUSSION

The study indicates that the most common subtype of EC in the Sudanese population is conventional (endometrioid) carcinoma, which is observed in 74,1 % of cases. This is followed by non-endometrioid types, which account for a total of 26,0 % (14/54), including papillary serous (13 %; 7/54), carcinosarcoma (9,2 %; 5/54), and clear cell carcinoma (3,7 %; 2/54). The distribution of histological subtypes observed in this study aligns with the findings reported by Watkins et al.[10] which indicated that the most prevalent subtype was endometrioid adenocarcinoma, constituting 87,2 % of cases. In contrast, the prevalence of serous, clear cell, and carcinosarcomas was recorded at 5,6 %, 1,7 %, and 3,9 %, respectively.

Furthermore, Huang et al.[11] identified an increased incidence of endometrioid carcinoma at 91,2 %, which was accompanied by lower rates of other carcinoma types compared to our findings. In Huang et al. study, the percentages for papillary carcinoma, clear cell carcinoma, and carcinosarcoma were reported as 2,9 %, 1,9 %, and 3,9 %, respectively. These initial epidemiological findings are not surprising as they match the global trend.

In the context of HER2 expression, it was observed that 92,59 % (50 out of 54) of the cases exhibited negative results (0 or 1+). Moreover, 5,56 % (3 out of 54) presented equivocal results (2+), while only 1,85 % (1 out of 54) demonstrated positive expression (3+). The rarity of positive expression suggests a low prevalence within the studied population. This finding is in concordance with the results of an American study where HER2 overexpression was observed in 12,6 % of EC.[12]

Earlier studies carried out in India by Mohapatra et al.[13] and two another studies conducted in Thailand by Suthipintawong et al.[14] and Srijaipracharoen et al.[15] reported positive detection rates of 2,8 % in a cohort of 35 cases, 1,8 % in a cohort of 65 cases, and 2,8 % in a larger cohort of 108 cases, respectively. In contrast, the findings from the current study differ from those of Łapińska-Szumczyk et al.[16] in Poland and Peiró et al.[17] in Germany where higher rates of positive cases (22 % and 36,8 %) were observed respectively. The ethnic background appears to have impacted the outcomes within the different racial groups. As far as we know this is the first kind of such a study to be conducted in an African population.

The results of this study cannot be attributed to the sample sizes, as analogous sample sizes have previously yielded significant HER2 expression. This includes investigations by Peiró et al.[18] conducted in Germany, which reported a prevalence of 22 % among 60 cases, as well as the study by Saeed et al. in Iraq, which found a prevalence of 58,8 % among 51 cases.

Recent studies have focused in assessing HER2 expression on specific pure subtype of EC. None of the papillary serous carcinoma in our study showed HER2 Positivity, this is in contrast to the works of Erickson cohort in 2020

testing women with stage 1 uterine serous carcinoma and finding that 26 % were HER2 positive,[19] and the work of Shao et al.[20] who detected 3 + positivity in 10 cases of uterine papillary serous carcinoma representing 13 % of their cases. In 2023 HER2 expression in endometrial clear cell carcinoma was explored and showed that 4 % of cases exhibited 3+ expression.[21]

In our study, a statistically significant result concerning the correlation between HER2 expression and histological subtypes (P = 0,01) was identified. Among carcinosarcomas, 20 % (1 out of 5) exhibited HER2 positivity. Conversely, none of the endometrioid, papillary, or clear cell carcinomas demonstrated HER2 expression. Furthermore, no endometrioid-type carcinomas presented 3+ positivity in this current investigation, which stands in contrast to the findings of Peiró et al.[17] who reported that 18 % of endometrioid carcinomas were positive for HER2 expression.

None of the seven papillary serous carcinomas in this study exhibited HER2 positivity. This finding contrasts significantly with the results from four independent studies conducted in the United States by Grushko et al.[22], Morrison et al.[23], Santin et al.[24], and Villella et al.[25], which reported HER2 expression rates of 40,7 %, 26 %, 43 %, and 61 %, respectively.

The latter findings can be attributed to the difference in tumor biology across different races.

This study examined the relationship between HER2 expression and the FIGO grade in EC. Notably, 100 % (1/1) of the HER2 3+ cases and 100 % (3/3) of the equivocal (2+) cases were classified as FIGO grade III, with a P value of 0,06. These findings align with those reported by Morrison et al.[23] who concluded that HER2 expression significantly correlates with both the grade and stage of EC.

In contrast, Peiró et al.[17] observed that 28 % of FIGO grade III cases exhibited HER2 expression. In the current investigation, only 4 % (1/25) of FIGO grade III cases tested positive for HER2, whereas 12 % (3/25) were classified as equivocal (2+).

1,4 % of FIGO 3 endometrioid EC showed 3+ positivity in a study conducted in United States of America by Abada et al.[26] this is in agreement with our observed results were none of the FIGO 3 endometroid subtype had HER2 overexpression.

Regarding the correlation between HER2 expression and lymphovascular invasion in this study, none of the HER2-expressing cases displayed lymphovascular invasion. Among the equivocal cases, two of three (66,67 %) showed no lymphovascular invasion, while one case (33,33 %) exhibited lymphovascular invasion (P value = 0,49). This finding contradicts the conclusions drawn by Peiró et al.[17] in Germany, who reported lymphovascular invasion in 26 % of cases with HER2-positive overexpression. The difference can be justified by possible genetic characters that may define the nature of the tumor among different ethnicities.

The low prevalence of HER2 expression in the present cohort raises important considerations for further research and clinical implications. The low detection rate of HER2 overexpression may accurately reflect the biological characteristics of tumors within the studied population. Nonetheless, it is imperative to acknowledge potential issues related to quality control.

Fixation methods and durations influence HER2 protein antigenicity. Delays in the initiation of fixation and instances of over-fixation and under-fixation are plausible in this region, especially given the high temperatures.

Considering the existence of various HER2 variants, it remains feasible that some forms of HER2 could evade detection by available antibodies designed to identify HER2 expression.

Limitations of the study

The limitations of this study encompass the potential mishandling of specimens and the presence of crushed artifacts, which contributed to the exclusion of specific cases.

CONCLUSIONS

HER2 expression is infrequently observed in Sudanese patients with EC, with the sole positive instance occurring in carcinosarcoma. This indicates that the biological characteristics of EC in this region of the world is different from their counterpart in European while similar in some Asian countries. Thus, its potential as target in treatment is questionable. In cases where results are equivocal, in situ hybridization is recommended. In brief HER2 expression continues to represent a vital area for further research.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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