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Pathology

Prognostic Value of HER2 Protein Expression in Endometrial Cancer: A Study of 98 Cases in the "Souss-Massa Region"

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Abstract **Case Report**

***Background*:** Endometrial cancer is the most common gynecological malignancy in industrialized countries. Among its subtypes, type II tumors (mainly serous and clear cell carcinomas) are associated with poor prognosis. HER2 (ERBB2) overexpression and amplification have been reported as markers of tumor aggressiveness and may represent potential therapeutic targets. ***Objective*:** To evaluate the expression of HER2 in endometrial carcinomas and to analyze its association with conventional histopathological prognostic factors. ***Methods*:** We conducted a retrospective study including 98 cases of endometrial carcinoma collected in the Souss Massa region (Morocco) between January 2017 and June 2025. Histological type, tumor grade, vascular emboli, myometrial invasion, and parametrial invasion were assessed. HER2 expression was evaluated by immunohistochemistry (IHC) and classified according to a semi-quantitative scoring system (0–3+). Equivocal cases (2+) underwent in situ hybridization (ISH) to assess ERBB2 amplification. ***Results*:** The mean age of the patients was 64 ± 6.5 years. Histologically, the cohort included 43 low-grade endometrioid adenocarcinomas, 30 high-grade endometrioid adenocarcinomas, 18 serous carcinomas, 4 carcinosarcomas, and 3 clear cell carcinomas. HER2 overexpression (score 3) was observed in 19 cases (19.4%), mainly in serous carcinomas (78.9%), with smaller proportions in high-grade endometrioid adenocarcinomas (15.8%) and clear cell carcinoma (5.3%). All HER2-positive cases were of high grade, with vascular emboli in 63%, universal myometrial invasion (100%), and parametrial invasion in 37%. In contrast, HER2-negative tumors (80.6%) were predominantly low-grade endometrioid carcinomas, with lower rates of myometrial (31.6%) and parametrial (2.5%) invasion. ***Conclusion*:** HER2 overexpression in endometrial carcinoma is strongly associated with aggressive histological subtypes and adverse prognostic features. These findings reinforce the prognostic value of HER2 and support its potential role as a therapeutic target, particularly in serous carcinoma. Routine assessment of HER2 status should be considered in high-grade endometrial carcinomas to guide prognosis and personalized treatment strategies.

Keywords: Endometrium, Cancer, HER2, Prognostic, Immunohistochemistry.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in industrialized countries, with an incidence that is steadily increasing [1]. It predominantly affects postmenopausal women but may also occur earlier, particularly in the context of genetic predisposition syndromes such as Lynch syndrome [2].

From a histopathological perspective, two main tumor groups are distinguished: type I endometrioid carcinomas, which are hormone-dependent and generally associated with a better prognosis, and type II non-endometrioid carcinomas (primarily serous and clear cell carcinomas), which are less frequent but considerably more aggressive [3, 4]. The latter group is often diagnosed at an advanced stage and carries a high risk of recurrence despite appropriate surgical and adjuvant management [5].

HER2 (Human Epidermal Growth Factor Receptor 2), also known as ERBB2, is a transmembrane receptor with tyrosine kinase activity belonging to the ErbB receptor family. When overexpressed or amplified, HER2 activates signaling pathways such as PI3K/AKT and MAPK, thereby promoting cell proliferation, survival, and tumor aggressiveness [6].

The objective of our study was to highlight a statistically proven association between HER2

amplification and conventional histopathological prognostic factors in endometrial carcinoma, namely histological type, tumor grade, lymphovascular invasion, myometrial invasion, and parametrial invasion.

We did not include the lymph node status, as not all of our patients underwent lymphadenectomy.

MATERIEL ET METHODES

Tumor Samples

We collected 98 cases of endometrial tumors from the Souss Massa region in Morocco over a period of 7.5 years (102 months), from January 2017 to June 2025. These samples corresponded to total hysterectomy specimens, which were fixed in formalin for 48 hours after gross opening.

Histological Analysis

The histological examination of the surgical specimens allowed us to gather the following data: histological type, tumor grade, presence or absence of vascular emboli, and the presence or absence of myometrial and/or parametrial invasion.

This analysis also ensured the selection of tissues with adequate fixation quality for subsequent immunohistochemical evaluation.

Immunohistochemical Analysis

The selected samples underwent immunohistochemical (IHC) analysis. The technique was based on the use of a specific monoclonal antibody applied to formalin-fixed, paraffin-embedded (FFPE) tissue sections. Interpretation was performed using a semi-quantitative scoring system, based on both the intensity and extent of membranous staining. The scoring scale ranged from 0 to 3+: scores 0 and 1+ were considered negative, score 3+ was considered positive, and score 2+ was defined as equivocal.

Molecular Analysis

For equivocal cases (IHC score 2+), in situ hybridization (ISH) was performed to assess ERBB2 gene amplification on chromosome 17. This method relied on the use of labeled probes to compare the number of HER2 gene copies to that of the chromosome 17 centromere (CEP17). Amplification was defined either by a HER2/CEP17 ratio ≥ 2, or by an average HER2 copy number ≥ 6 per nucleus, even when the ratio was < 2.

Data Collection

Based on these results, we established a standardized data sheet including: histological type, tumor grade, presence or absence of vascular tumor emboli, myometrial and parametrial invasion, and HER2 amplification status.

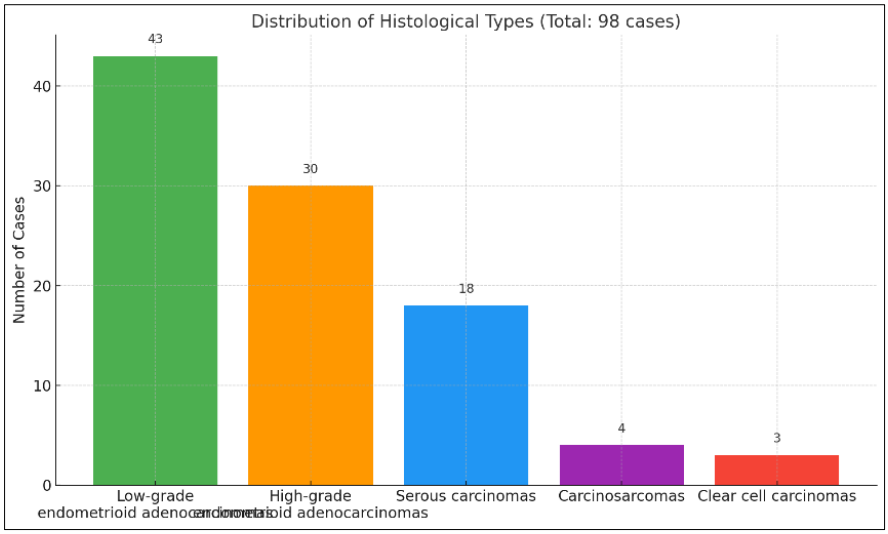
RESULTATS

During the study period, we collected 98 cases of endometrial carcinoma. The mean age of the patients at the time of diagnosis was 64 years with a standard deviation of ±6.5 years.

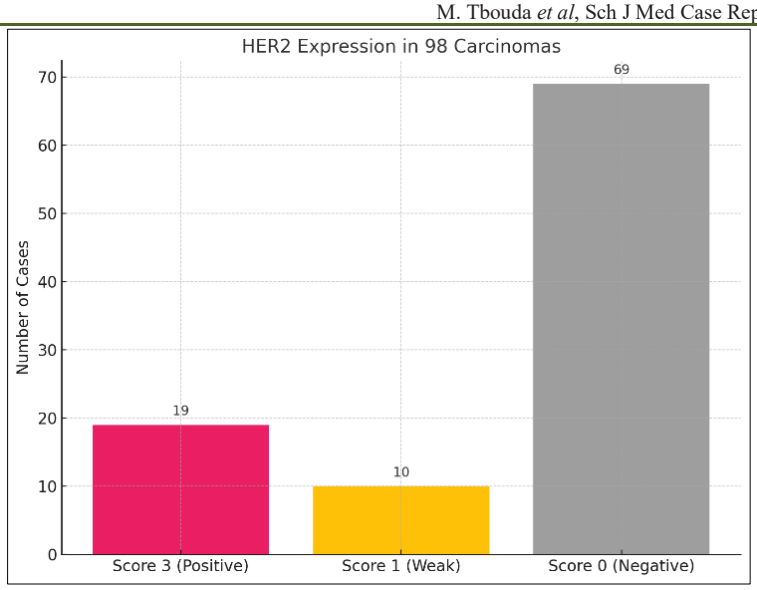
Regarding the histological type:

- 43 cases were low-grade endometrioid adenocarcinomas,
- 30 cases were high-grade endometrioid adenocarcinomas,
- 18 cases were serous carcinomas,
- 4 cases were carcinosarcomas, and
- 3 cases were clear cell carcinomas (Diagram 1).

Among the 98 analyzed carcinomas, 19 cases showed complete and strong membranous staining with the anti-HER2 antibody (score 3), 10 cases showed weak and incomplete staining (score 1), while the remaining cases were negative (score 0) (Diagram 2).



"Figure 1: Distribution of Histological Types of Endometrial Carcinomas in Our Study."



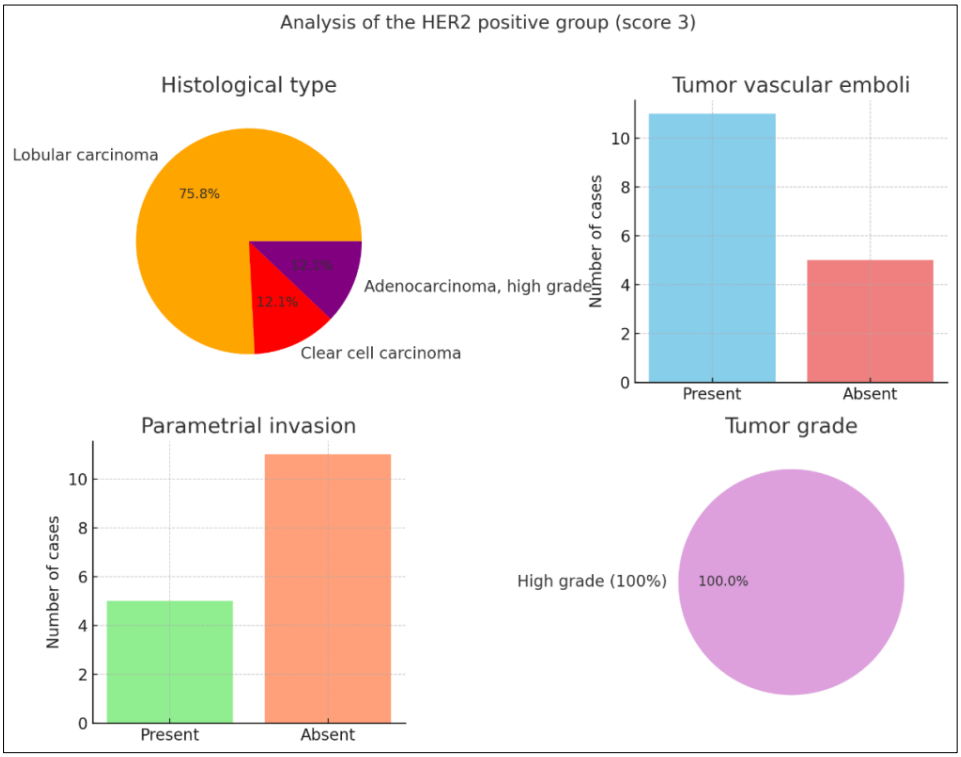
"Figure 2: HER2 Expression in the Endometrial Carcinomas Studied."

In the HER2-positive group (score 3), which included 19 cases (Table 1):

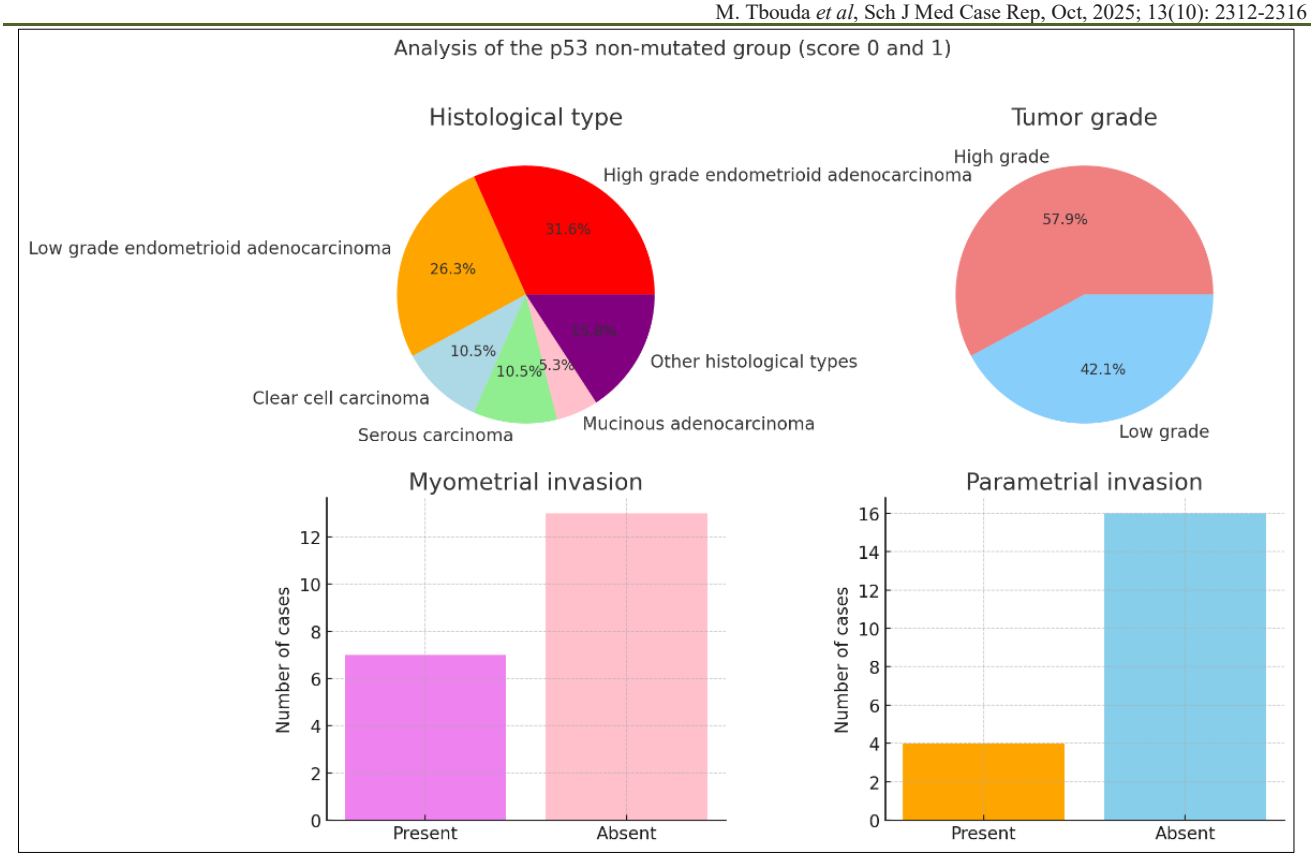
- Histological type: 15 cases of serous carcinoma, 3 cases of high-grade endometrioid adenocarcinoma, and 1 case of clear cell carcinoma.
- Tumor grade: All cases were high grade (19 cases).
- Tumor vascular emboli: Present in 12 cases.
- Myometrial invasion: Present in all cases (19/19).
- Parametrial invasion: Present in 7 cases.

In the p53 wild-type (non-mutated) group (score 0 and 1), which included 79 cases (Table 2) :

- Histological type: 3 cases of serous carcinoma, 27 cases of high-grade endometrioid adenocarcinoma, 43 cases of low-grade endometrioid adenocarcinoma, 2 cases of clear cell carcinoma, and 4 cases of carcinosarcoma.
- Tumor grade: 36 cases were high grade, and 43 cases were low grade.
- Tumor vascular emboli: Present in 12 cases.
- Myometrial invasion: Present in 25 cases.
- Parametrial invasion: Present in 2 cases.



"Figure 3: Distribution of Histoprognostic Factors in the HER2-Positive Group."



"Figure 4: Distribution of Histoprognostic Factors in the HER2-Positive Group."

DISCUSSION

Nous avons observés que 79 (80.61 %) des patientes appartiennent au groupe HER2 négatif et 19 appartiennent au groupe HER2 positif (19.39). Ces données se concordent avec plusieurs études dans la littérature [7].

In this study, we demonstrate that HER2 positivity is prevalent in 19.38% and arises in various histological subtypes including endometrioid (15.78%), serous (78.94%), and clear cell (5.26%) EC.

In our series, HER2 overexpression (score 3) was identified in 19 out of 98 endometrial carcinoma cases (19.4%). This finding is in line with previous studies reporting variable HER2 expression in endometrial cancer, particularly enriched in aggressive histological subtypes.

The majority of HER2-positive tumors were serous carcinomas (78.9%), followed by a smaller proportion of high-grade endometrioid adenocarcinomas (15.8%) and clear cell carcinoma (5.3%). These results are consistent with the literature, which shows that HER2 amplification and overexpression are most frequently observed in uterine serous carcinoma, a subtype known for its aggressive behavior and poor prognosis.

Importantly, all HER2-positive tumors in our study were of high histological grade, further supporting the association between HER2 expression and adverse pathological features. Additionally, we observed a high frequency of tumor vascular emboli (63%), universal myometrial invasion (100%), and a notable proportion of parametrial invasion (37%) in the HER2-positive group. These findings suggest that HER2 overexpression may be associated with an increased risk of local invasion and metastatic spread.

In contrast, the p53 wild-type (non-mutated) group (scores 0 and 1), which included the majority of our cohort (79 cases), showed a predominance of low-grade endometrioid adenocarcinomas with a lower frequency of aggressive histological subtypes. This group had a more balanced distribution between high-grade and low-grade tumors and demonstrated a lower incidence of parametrial invasion (2.5%) and myometrial invasion (31.6%) compared with the HER2-positive group.

From a clinical perspective, these results highlight the potential prognostic and therapeutic implications of HER2 expression in endometrial carcinoma. HER2-positive endometrial cancers, particularly of the serous subtype, may benefit from targeted anti-HER2 therapies (such as trastuzumab), which have shown promising results in recent clinical trials. Therefore, routine assessment of HER2 status in endometrial carcinoma, especially in high-grade non-endometrioid subtypes, could provide valuable

information for risk stratification and personalized treatment.

CONCLUSION

HER2 overexpression in endometrial carcinoma is predominantly observed in high-grade and aggressive histological subtypes, especially serous carcinomas. It is strongly associated with adverse prognostic features, including high tumor grade, vascular emboli, deep myometrial invasion, and parametrial involvement. These findings highlight the significant prognostic value of HER2 and underscore its potential as a therapeutic target. Routine evaluation of HER2 status in high-grade endometrial carcinomas may help identify patients who could benefit from targeted therapies and support more personalized management strategies.

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