Expression of Her-2/neu oncogene in endometrial carcinoma in OMTH

1Mohamed Rafea Ebrahim, 2 Dr Mohammed A Abdallah ,3 Mohammed A. Hammad.

Abstract: Objective: This retrospective descriptive study to, assess the expression of Her-2 in endometrial carcinoma & to correlate the results with other known clinic pathologic features in Sudanese patients .
Material and Methods: Twenty three (23) paraffin-embedded formalin-fixed tissue blocks of endometrial carcinoma were stained by immunoperoxidase stains for Her-2/neu (DAKO, Denmark), collected with their clinical data from archives of Omdurman Military Teaching Hospital in Khartoum-Sudan ,from January to December 2015. The result was correlated with clinical data.
Results: Majority of the endometrial carcinoma were in the (57%) most of them lie between (61-70 years) . Her-2/ neu expressed in (8patients) 34.7% of cases. The most frequent association was with non-endometroid carcinoma 2 cases (100%).
Conclusion: HER-2/neu appears it to be expressed in endometrial carcinoma(endometroid & non endometroid especially papillary-serous type).

Key words: EC- Endometrial carcinoma , HER2/neu , OMTH.

1 INTRODUCTION

Endometrial cancer (EC) is the most common malignancy of the female genital tract in the developed countries; it accounts for about 7% of all malignancies occurring in women [1&2]. In USA there were about 39.080 new cases of EC for the year 2007 representing the fourth most common cancer in women and ranks the first one, in cancers of the female genital tract[3]. Endometrial carcinoma (EMC) in Sudan is is 3rd type of gynecological cancer in Sudan ,in study done at Gezira state incidence it represent 14,7% representing the7th type of cancer in females, Most of the Sudanese patient presented at stages II and stage III. Dafalla Omer Abuidris [4]

It is represent the 4th cause of death after breast, colon and pulmonary cancer and the 7th cause of death due to women's cancer [5].

Most risk factors of endometrial cancer are associated with long stimulation by estrogen action not antagonized by progesterone, such factors being nuliparity (50% of cancers), late menopauses , obesity by converting adrenal androstendion in estrone in adipose tissue , polycystic ovary syndrome or functional ovarian tumors and estrogen substitution in postmenopausal treatment.[6]

Histological types of endometrial carcinoma is grouped into 2 different types: 1- endometroid and it is variants, such as ciliated cell adenocarcinoma, secretory adenocarcinoma, villoglandular, and adenocarcinoma with squamous differentiation, accounting for(75-80%). This type is believed to be hormone-related and to be significantly associated with both unopposed estrogen therapy and obesity. Type 2 endometrial cancer, which is less common (20% of all cases), consists of less common histological subtypes such as papillary serous <10%; clear cell carcinoma 4%, mucinous 1%, squamous cell accounting for <1%, and carcinosarcoma. This second group is usually not associated with excess estrogen exposure. [7,8]

Endometrial cancers are most frequently diagnosed in the perimenopausal/ postmenopausal age group. However, up to 10% to 15% of cancers can occur in premenopausal patients, of whom up to 2% to 5% will be under the age of 40.[9] In these young patients, up to one third will also have either a synchronous ovarian primary or metastasis at the time of diagnosis.[9]

Most endometrial cancers nearly (90%) still are sporadic and less than 10% thatare hereditary [10] and usually associated with hereditary non-polyposis colonic cancer [11]

The Her-2/neu (c-erb B-2) gene is protooncogen localized to chromosome 17q that encodes a 185 kd transmembrane glycoprotein with tyrosine kinase activity and structural homology to the human epidermal growth factor receptor. Tyrosine kinase receptor family involved in cell-cell and cell-stromal interaction [10].

Overexpression of Her-2 oncogene occurs in range between4% to 69% of endometrial arcinomas[9,10]. However; HER-2 amplification or overexpression has been reported in 4% to 69% of endometrial carcinomas, and some series note that, overexpression are more often in tumors of serous histology [10].

In breast,endometrial, and ovarian cancer, several studies have reported that over expression of this gene is associated

.MSC, Histopathology &cytology, Neelen University
2-MDHistopatho logy and Cytology, College of Medicine, Karary University, Khartoum, Sudan.
3-PHD Microbiology, College of Medical laboratory Science, Karary University, Sudan.
*Corresponding author: Mohammed Rafea Ebbrahim . 1-Department of Histopathology and Cytology, Military Hospital, Omdurman, Khartoum, Sudan . Tel: 009249122008731
E-mail: Mohammedrafea5@gmail.com

with resistance to treatment and poor survival, which suggests that tumors that over express HER2/neu may manifest a more aggressive biologic behavior. Our study aimed to assess the expression of
immunohistochemistry in endometrial carcinoma in Sudanese patients.

2 Materials And Methods:

This was a retrospective descriptive study conducted during the period between January and December 2015, 23 paraffin-embedded formalin-fixed tissue blocks of endometrial carcinoma were included in this study. These tissue blocks were obtained from the archives of Omdurman Military Teaching Hospital (OMTH), after taking the numbers of blocks from the hospital records of the years 2015.

Two 3-4 μ m-thick tissue sections were cut from each block using a rotary microtome. One section was put on a frosted-end glass slide and stained by Hematoxylin and Eosin stain reviewed for histological type, grade and depth of invasion of the myometrium. Clinical data were obtained from archival histopathological reports.

2.1 Immunohistochemistry

Immunoperoxidase stain for HER2 /neu monoclonal antibodies have been used (DAKO, Denmark was performed on representative formalin-fixed paraffin embedded blocks.

2.1.1 Description Of The Procedure

We used the Ultra Vision (LabVision) system on formalin fixed tissue samples embedded in paraffin. For immunohistochemistry, the sections have been dewaxed, incubated at 100°C in citrate solution at pH 6, and were washed in distilled water. After blocking the endogenous peroxidase the primary antibodies were applied for 60 minutes, then, following a washing cycle with TBS, the biotinylatedbiotinylated antibody has been applied (Biotinylated Goat Anti - Polyvalent Solution) for 5 minutes. After another TBS wash, the sections were incubated with streptavidineperoxidase for another 5 minutes. The reactions were visualized using a DAB (3,3' Diaminobenzidine Dihydrocloride) solution. The nuclei have been stained with Mayer hematoxylin

2.2 Interpretation of IHC Reactions

I t was scored from 0 to 3 score according to the resent criteria set by ASCO/CAP, in which the cut-off positivity is changed from the previous 10% membrane staining cells to 30%. In final analysis score 0 and 1+ were considered negative, score 2+ was considered weakly positive and score 3+ was considered as strongly positive[12,13]

Statistical Package for Social sciences (SPSS) software version 16 was used for data entry and analysis. Results were tabulated and presented in percentage form. Parameters analyzed were age, sex, and IHC results.

3 Results

The total number of the obtained tissue blocks was 23 blocks with all their records studied and analyzed. Age of patients ranged between 50 and 80 year , most of them lie in the age between 61&70 years 57% age of (Table No 1). Endometroid carcinoma (with its variants) was the predominant type encountered in 21 out of 23 cases (91.3%) , while the non endometroid carcinoma was diagnosed in 2 (8.7%) cases,(papillary serous carcinoma were 1 (50%) cases and clear cell carcinoma 1 (50%) cases.

3.1 Her-2/ neu status:

Overexpression of Her-2 was identified in 6 (28.9%) cases of endomtroid type out of 21 cases. All of these scored 2+ and Scored 1+ (21.56%). While the remaining (non endometroid type, shows positivity in 2 out of 2 (100%) cases. (Table No 2).

Table (1)

Age group	No.of patients	Frequency
50 -60	6	26%
61 – 70	13	57%
71 -80	4	17%

Table(2)

Histological type	Her2 +ve	Her2 –ve	Total No.	Percentage of positivity
Endometriod	6	15	21	28.9%
Papillary	1	0	1	100 %
Clear type	1	0	1	100%

4 Discussion:

The HER2/neu growth factor has an important role in the regulation of cell proliferation and differentiation [14]. I t is one of a member of the human epidermal growth factor receptors. They are (EGFR) family of transmembrane tyrosine kinases including EGFR (HER1, ErbB1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4).

Many studies have shown that increased HER2/neu expression in ovarian and breast cancer is an independent factor predicting a poor prognosis. It is found that overexpression of Her-2/neu oncogene occurs in about 20-40% of endometrial carcinomas[10,14,15,16]. To our knowledge, this is the first study in Sudan that investigated the expression of HER2/neu in endometrial carcinoma ,this expression of Her-2 was observed in endometrial carcinoma in(34,7)% in all cases ,but a relatively lower

percentage(28.9%) seen endometroid type of endometrial carcinoma. On the other side the non endometroid type (Papillary and Clear type) of the endometrial carcinoma, shows great positivity (100%), this likely due to lower number. Grushko et al treport a that 44% positivity of Her-2/neu among the endometroid carcinoma[10] ,which is higher than our study,this most likely due to lower number of patients in our study . Khalifa and *Mohammed* and found that 59% ,(58.8%) positivity of Her-2/neu expression respectively[17,18]). I n the majority of studies of non endometroid type, found positivity ranging between 40-80% [19]. Santin et al, found that 80% of uterine papillary-serous carcinoma overexpressed Her-2/neu, and Prat et al, evaluated 10 cases of papillary-serous carcinoma and found protein overexpression in 40% of the tumors [20,21].

5 Conclusion:

Her-2/neu appears to play an important role in the biologic behavior of an endometrial cancers, HER-2 over expression was more common in non-endometroid carcinoma, especially (papillary-serous type, clear type), this relative to other histologic types, (100% versus 28.9%) .

Further studieswith larger number of patients are recommended, to get more valuable results.

6 References

[1] Creasman WT, Sims JM. Endometrial carcinoma. E Med Obst Gyncol July 2007.

[2] Horn LC, Meinel A, Handzel R. Histopathology of endometrial hyperplasia and endometrial carcinoma. An update. Ann Diagn Pathol 2007; 11:297-311 .

[3] Jemal A, Siegel R, Ward E, Murray T, Xu J , Thun MJ, Smigal C. Cancer statistics. CA Cancer J Clin 2007; 57:43-66

[4] Dafalla Omer Abuidris 1, Rehab Sid-Ahmed Mohammed Ibnoof 2, Mohamed Elsanousi Mohamed Elsanousi 3, Elgaylani Abdalla Eltayeb 4, Elgaili Mohamed El Gaili, Gynecological Malignancies Managed in The Institute of Nuclear Medicine and Oncology, Wadmedani-Sudan During 1999-2005 Gezira Journal of Health SciencesVol4 No2.

[5] Stolnicu S, Rădulescu R, Mocanu S, Puşcaşiu L – Patologia colului şi a corpului uterin. Polirom 2003.

[6] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium [published erratum in Int J Gynaecol Obstet 2010;108(2):176]. Int J Gynaecol Obstet 2009;105(2):103–4.

[7] Baekelandt MM, Castiglione M. Endometrial carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19(Suppl 2):ii19-ii20. Available at: http://annonc.oxfordjournals.org/ content/19/suppl_2/ii19.10ng. Accessed January 30, 2013

[8] Munstedt K, Grant P, Woenckhaus J, Roth G, Tinneberg HR. Cancer of the endometrium: current aspects of diagnostics and treatment. World J Surg Oncol 2004; 2:24. Available at: http://www.wjso.com/content/2/1/24. Accessed January 30, 2013.

[9] Renaud MC, Plante M. Medical treatment of endometrial carcinoma for the premenopausal woman wanting to preserve her ability to have children. J Obstet Gynaecol Can 2001;23(3):213–9.

[10] Grushko TA, Filiaci VL, Mundt AJ, Ridderstrale K, Olopade OI, Pleming GF. An exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: A gynecologic oncology group study. Gynecol Oncol 2008; 108:3-9.

[11] Ryan A, Susil B, Jobling T & Oehler M. Endometrial cancer. Cell Tissue Research 2005; 322: 53–61. Bansal N, Yendluri V & Wenham RM. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. Cancer Control 2009; 16:8–13 .

[12] DAKO HercepTest™. A Manual for Interpretation, ttp://pri.dako.com/28630_herceptest_interpretation _manual.pdf.

[13] Rosai J. Breast. In: Rosai J. Rosai and Ackerman's Surgical Pathology. 10th edition. China. Mosby Elsevier Inc 2011; Vol (2):1659-1770

[14] Uharcek P: Prognostic factors in endometrial carcinoma. J Obstet Gynaecol Res 2008; 34(5):776-83.

[15] Creasman WT, Sims JM. Endometrial carcinoma. E Med Obst Gyncol July 2007.

[16] Munsted k, Grant P, Lans JW, et al. Cancer of endometrium, current aspect of diagnostic and treatment. Wor J Sur Oncol 2004; 2:2-24.

[17] Khalifa MA, Mannel RS, Haraway SD, Walker J and Min KW. Expression of EGFR, HER-2/*neu*, P53, and PCNA in Endometrioid, Serous Papillary, and Clear Cell Endometrial Adenocarcinomas. Gynecol Oncol 1994; 53 (1):84-92. Available online 24 April 2002.

[18] *Mohammed S. Saeed,1* Abeer H. Ahmad,2 Bashar AJ Hassawi3* Overexpression of Her-2/neu oncogene in 51 cases of endometrial carcinoma*J Med J 2013; September Vol. 47 (3) http://dar.ju.edu.jo/jmj* 212.

[19] Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM, Berek JS, Chapman JA, DiSilvestro PA, Horowitz IR, Fiorica JV. Phase II

trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2010 116 (1):15-20. Epub 2009 .

[20] Santin AD, Bellone S, Gokden M , et al: Overexpression of HER-2/neu in uterine papillary serous carcinoma. Clin Cancer Res 2002; 8:1271-1279.

[21] Prate J, Oliva E, Lerma E, et al: Uterine papillary serous adenocarcinoma: A 10-case study of p53 and c-erbB-2 expression and DNA content. Cancer 1994; 74:1778-1783.