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Immunohistochemical Markers of Endometrial Carcinoma

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Abstract: ***Endometrial carcinoma (EC) is the most common gynaecologic malignancy among women worldwide with 287, 000 new casesand 74, 000 mortalities per year. EC is the fourth most common type of cancer in females. Traditionally, ECs have been classified into two types. The more common is type I, mostly endometrioid carcinomas, which are estrogen - dependent cancers with a relatively good prognosis. On the other hand, type II tumours are not estrogen - driven and affect older age groups. These tumours have a poor prognosis and demonstrate more common extrauterine spread. The prototype for this group is serous carcinoma. In order to improve the efficacy of EC treatment, identification of high - risk prognostic factors is a high research priority. Early assessment could enable conservative therapy in patients with favorable prognosis as well as reserve effective and more radical therapy for patients with aggressive forms of the tumor.***

Keywords: endometrial carcinoma, immunohistochemical markers

1. Introduction

Endometrial carcinoma (EC) is the most common gynaecologic malignancy among women worldwide with 287, 000 new casesand 74, 000 mortalities per year [1]. EC is the fourth most common type of cancer in females [2, 3]. Traditionally, ECs have been classified into two types. The more common is type I, mostly endometrioid carcinomas, which are estrogen - dependent cancers with a relatively good prognosis. On the other hand, type II tumours are not estrogen - driven and affect older age groups. These tumours have a poor prognosis and demonstrate more common extrauterine spread. The prototype for this group is serous carcinoma [1, 4, 5]. In order to improve the efficacy of EC treatment, identification of high - risk prognostic factors is a high research priority. Early assessment could enable conservative therapy in patients with favorable prognosis as well as reserve effective and more radical therapy for patients with aggressive forms of the tumor [6]. The use of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki - 67 have been routinely used in breast cancer cases for molecular subtyping and guiding treatment. However, unlike breast cancer, there is no molecular classification for EC based on such markers [7]. Recently, integrated genomic characterization of EC revealed four genomic classes; however, receptor status is not involved in this molecular classification [8]. Numerous studies showed that the EC prognosis is closely related to patient age, tumour grade, depth of invasion and/or cervical involvement, and the occurrence of lymph node metastases [9]. Some potential biological markers including hormone receptors, oncogenes, and tumour suppressor genes are also involved. However, no single marker was found to be indicative of ECoftenenough to allow routine use in the sub - classification of EC [10]. Therefore, in the current study, a panel of immunohistochemical markers (ER, PR, Her - 2, and Ki - 67) was tested to ascertain their relationships with the histopathological prognostic parameters of EC. The aim was to identify suitable markers to guide treatment and assess prognosis of EC patients.

2. Materials and Methods

This is a retrospective study including 109 hysterectomy specimens of EC at university hospital "Queen Geraldine", Tirana during 2015 - 2019. These cases were diagnosed in the period between 2015 and 2019. The histological types were endometrioid (89 cases), serous (12 cases), undifferentiated (one case), dedifferentiated (one case), and carcinosarcoma (three cases). The remaining three cases showed mixed patterns. The major component in two was endometrioid; the other was serous carcinoma. Hematoxylin and eosin (H&E) stained slides for every case were reviewed by two independent pathologists. International Federation of Gynecology and Obstetrics (FIGO) revised criteria in 2009 were used for grading and staging of cases [11].

Tissue microarray construction: The tissue microarray (TMA) was constructed as previously published [12]. Briefly, a representative slide for each tumor was selected and an area of the tumor was circled. Using the manual tissue arrayer (MTA - 1, Estigen, Tartu, Estonia), the areas of interest of a donor block were cored using tissue punches of 0.6 mm diameter. The cores were then transferred into the recipient block. Three cores were taken from each tumour. In carcinosarcoma cases, only the epithelial component was assessed. Sections from these microarrays were then H&E stained and tested for spot adequacy. Immunohistochemistry

3. Results and Discussion

Clinicopathological features of the studied cases Patient ages ranged from 37 to 79 years with a mean age of 59.8 ± 8.2 years. Most of the cases (88 patients, 80.7%) in this study were postmenopausal. Tumors ranged from 1 to 14 cm in largest dimension with a median value of 3 cm. There were 36 cases of grade 1 (33%), 43 cases of grade 2 (39.4%), and 30 cases were high grade carcinomas (27.5%) including

grade 3 endometrioid, serous, mixed, undifferentiated and dedifferentiated carcinomas, and carcinosarcomas.

In three cases (2.7%) the tumour was limited to the endometrium, 69 (63.3%) cases showed infiltration of the inner myometrial half, the tumour infiltrated the outer half in 26 cases (24%), and the serosa was infiltrated in three cases (2%). Cervical involvement was found in 20 cases (18%), 71 cases (65%) were free from cervical infiltration and in 14 cases (12.8%) cervical involvement was not determined due to suboptimal surgery. Adnexal metastases were found in 11 cases (10%), 83 cases (76%) were free from adnexal infiltration, and in 15 cases (13.7%) adnexal infiltration was unknown due to suboptimal surgery. There were 71 cases (65.1%) in stage I (56 stage IA and 15 stage IB), 15 cases in stage II (13.8%), 10 cases (9%) in stage IIIA, only two cases were stage IIIB, and one case was stage IVA. Lymphovascular emboli were found in 29 cases (26.6%). ER and PR scores were statistically associated (p <.001). There were significant relationships between low ER scores and nonendometrioid histology (p =.007) and higher grade of endometrial cancer (p =.007). The ER score tended to decrease with advanced stage (p =.057). Low ER score was associated with ovarian involvement (p =.025), lymphovascular space invasion (LVSI) (p =.006), and higher Ki - 67 values (p =.024). Low PR expression score was associated with non - endometrioid histology (p <.001), higher tumour grade (p <.001), advanced stage (p =.009), and ovarian involvement (p <.007). The PR score decreased with LVSI (p =.06), and lower score was associated with lymph node metastasis (p =.026). Ki - 67 values were higher with low PR score (p =.025). HER2 expression was significantly associated with advanced tumour stages (p =.04), increased depth of myometrial infiltration (p =.02), greater incidence of LVSI (p =.017), ovarian involvement (p =.038), and lymph node metastasis (p =.038). There was a notable relationship between HER2 expression and cervical involvement (p =.009). A positive correlation was found between tumour size and Ki - 67 index (p =.02). Higher Ki - 67 index was linked to more aggressive features such as non - endometrioid histotype (p <.001) and poor differentiation grade (p <.001). There was a strong relationship between higher Ki - 67 values and lymph node involvement (p =.012). Median Ki - 67 index value was higher in HER2 - neu–positive cases than that of negative cases (p =.482, Mann - Whitney test). EC is the most common gynaecologic cancer worldwide and the incidence is increasing [14 - 16]. EC may not always fit into the dual model of type I and type II cancers: those can be vague clinicopathological designations rather than firm diagnostic entities. Tumours display varying degrees of conformity with both types and have different behaviours and prognoses [17 - 19]. According to the National Cancer Comprehensive Network guidelines for management of EC, the treatment strategy depends on surgical staging, depth of infiltration and the presence of adverse risk factors such as age, tumour size, LVSI and lower uterine involvement. Adjuvant therapy determinations are made on the basis of pathologic findings in the postoperative specimen. Superficially invasive, low grade (G 1–2) carcinomas in the absence of adverse risk factors can be treated by surgery with post - operative observation. However, in the presence of adverse risk factors, patients need adjuvant radiotherapy. High grade carcinomas with no adverse risk factors may be spared from adjuvant chemotherapy [20] cancers in females, and both are largely considered to be hormonedependent tumours. In breast cancer, a simple immunohistochemical panel of ER, PR, HER2, and Ki - 67 is routinely performed on preoperative or postoperative specimens yielding valuable therapeutic and prognostic information. Similar to breast cancer, this panel may be of value when assessing EC specimens. The information attained may be helpful in guiding patient management and in providing prognostic information about tumour behaviour [7]. In the current work, we assessed the immunohistochemical expression of the same panel of biological markers (ER, PR, HER2, and Ki - 67) on 109 cases of EC and their association with histopathological prognostic characteristics. The presence of hormone receptors in ECs correlates with the clinical disease stage, histological grade, and overall survival. The absence of hormone receptors is considered to indicate aggressive tumour behaviour and poor prognosis [21, 22]. A recent systematic review and meta - analysis revealed that higher levels of ER and PR were associated with favourable prognosis and longer overall survival [23]. This study showed close associations between low ER and PR scores, nonendometrioid histology and high grade endometrial cancer. Moreover, low PR score was significantly associated with advanced tumour stage. These findings agree with previous studies [21, 24, 25]. While not statistically significant, the ER score tended to be lower with advanced stage. Some studies failed to show associations between ER and PR expression and tumour stage [26, 27]. Our data revealed significant associations between ovarian involvement and low ER and PR scores, an observation in contrast to previous observations [6, 28]. This discrepancy may be due to differences in sample size, primary antibody used, and the method of scoring the immunohistochemical results. ER and PR did not show significant association with the depth of myometrial invasion or cervical infiltration as previously reported [25, 26]. Low ER score was significantly associated with LVSI; low PR score tended to be associated with LVSI as well, but the strength of the low PR association did not match that of low ER. This agrees with the findings of a previous study [24]. Low PR scores were significantly associated with lymph node metastasis as reported earlier [26]. Consistent with previous studies, high ER and PR scores were highly associated while lower scores were associated with higher Ki - 67 values [24, 27, 29]. The increased expression of HER2 correlates with worse prognosis in various malignant tumours. In their extensive study (483 cases), Morrison et al. [30] demonstrated that the over - expression of HER2 was an independent prognostic factor that correlated with worse survival. Our work confirms a close relationship between HER2 overexpression and some of the traditional prognostic factors of endometrial cancer. In partial agreement with previous studies, we found HER2 expression to be associated with advanced tumour stages and increased depth of myometrial invasion [31 - 33]. We have not observed, however, any substantial relationship between HER2 overexpression and the grading of ECs. Some previous studies did not show a significant association between HER2 expression and the prognostic parameters [6, 33]. In contrast to this, our study revealed that HER2 overexpression was significantly associated with a greater incidence of ovarian and cervical involvement,

lymphovascular emboli and LN metastasis, findings in line with a previous observation [4]. We did not find HER2 over - expression to be significantly associated with ER, PR, or Ki - 67 expression, a finding inconsistent with that of a study showing significant correlation between HER2 over - expression and high Ki - 67 index.4 Increased Ki - 67 expression indicates higher mitotic activity and greater tumour cell proliferation. Some studies revealed that Ki - 67 could be an independent prognostic marker of survival in EC [34, 35]. On the other hand, Pansare et al.36 did not find correlations between Ki - 67, histological type, grading, and tumour clinical staging. An elevated Ki - 67 expression in this study was strongly related to non - endometrioid histotype and poor differentiation. Higher Ki - 67 index was also found to be associated with lymph node involvement but not tumour stage, depth of myometrial invasion, cervical infiltration, or ovarian involvement. Our proposed immunohistochemical panel (ER, PR, HER2, and Ki - 67) may be of value for preoperative biopsies. Results may indicate tumour behaviour characteristics, presence of adverse risk factors such as lymphovascular emboli and cervical involvement, and the necessity for more radical surgery with pelvic and para - aortic lymph node dissection [37]. Moreover, the panel may also be performed on postoperative specimens. The panel may be included routinely as an adjunct consideration in the postoperative treatment decision making process. Low risk patients with low grade, superficially invasive tumours may be spared the morbidity of lymphadenectomy as well as the cost and morbidity of radiotherapy. The panel results can also assist in identifying high risk patients requiring more radical surgery, post - operative radiotherapy, and/or chemotherapy [38].

4. Conclusion

In conclusion, low ER and PR expression scores (category I), together with HER2 overexpression (score + 3) and Ki - 67 indices of more than 20%, were associated with more malignant behavior of ECs. Further studies involving larger numbers of patients are needed to investigate the correlation between this immunohistochemical panel's results and the recent molecular classification of EC.

References

[1] Le Gallo M, Bell DW. The emerging genomic landscape of endometrial cancer. Clin Chem 2014; 60: 98 - 110.
[2] Llaurado M, Ruiz A, Majem B, et al. Molecular bases of endometrial cancer: new roles for new actors in the diagnosis and the therapy of the disease. Mol Cell Endocrinol 2012; 358: 244 - 55.
[3] Backes FJ, Walker CJ, Goodfellow PJ, et al. Estrogen receptor - alpha as a predictive biomarker in endometrioid endometrial cancer. Gynecol Oncol 2016; 141: 312 - 7.
[4] Yu CG, Jiang XY, Li B, Gan L, Huang JF. Expression of ER, PR, CerbB - 2 and Ki - 67 in nendometrial carcinoma and their relationships with the clinicopathological features. Asian Pac J Cancer Prev 2015; 16: 6789 - 94.
[5] Arafa M, Somja J, Dehan P, et al. Current concepts in the pathology and epigenetics of endometrial carcinoma. Pathology 2010; 42: 613 - 7.
[6] Markova I, Duskova M, Lubusky M, et al. Selected immunohistochemical prognostic factors in endometrial cancer. Int J Gynecol Cancer 2010; 20: 576 - 82.
[7] Lapinska - Szumczyk S, Supernat A, Majewska H, et al. HER2 - positive endometrial cancer subtype carries poor prognosis. Clin Transl Sci 2014; 7: 482 - 8.
[8] Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497: 67 - 73.
[9] Faria SC, Sagebiel T, Balachandran A, Devine C, Lal C, Bhosale PR. Imaging in endometrial carcinoma. Indian J Radiol Imaging 2015; 25: 137 - 47.
[10] Li M, Zhao L, Qi W, et al. Clinical implications and prognostic value of five biomarkers in endometrial carcinoma. Chin Ger J Clin Oncol 2013; 12: 586 - 91.
[11] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009; 105: 103 - 4.
[12] Arafa M, Boniver J, Delvenne P. Progression model tissue microarray (TMA) for the study of uterine carcinomas. Dis Markers 2010; 28: 267 - 72.
[13] Zannoni GF, Vellone VG, Arena V, et al. Does high - grade endometrioid carcinoma (grade 3 FIGO) belong to type I or type II endometrial cancer? A clinical - pathological and immunohistochemical study. Virchows Arch 2010; 457: 27 - 34.
[14] Kounelis S, Kapranos N, Kouri E, Coppola D, Papadaki H, Jones MW. Immunohistochemical profile of endometrial adenocarcinoma: a study of 61 cases and review of the literature. Mod Pathol 2000; 13: 379 - 88.
[15] Brunelli M, Manfrin E, Martignoni G, et al. HER - 2/neu assessment in breast cancer using the original FDA and new ASCO/CAP guideline recommendations: impact on selecting patients for herceptin therapy. Am J Clin Pathol 2008; 129: 907 - 11.
[16] Binder PS, Mutch DG. Update on prognostic markers for endometrial cancer. Womens Health (Lond) 2014; 10: 277 - 88.
[17] Rutgers JK. Update on pathology, staging and molecular pathology of endometrial (uterine corpus) adenocarcinoma. Future Oncol 2015; 11: 3207 - 18.
[18] Maiques O, Cuevas D, Garcia Dios DA, et al. FISH analysis of PTEN in endometrial carcinoma. Comparison with SNP arrays and MLPA. Histopathology 2014; 65: 371 - 88.
[19] Garg K, Soslow RA. Strategies for distinguishing low - grade endometrioid and serous carcinomas of endometrium. Adv Anat Pathol 2012; 19: 1 - 10.
[20] Koh WJ, Greer BE, Abu - Rustum NR, et al. Uterine neoplasms, version 1.2014. J Natl Compr Canc Netw 2014; 12: 248 - 80.
[21] Ferrandina G, Ranelletti FO, Gallotta V, et al. Expression of cyclooxygenase - 2 (COX - 2), receptors for estrogen (ER), and progesterone (PR), p53, ki67, and neu protein in endometrial cancer. Gynecol Oncol 2005; 98: 383 - 9.

[22] Jazaeri AA, Nunes KJ, Dalton MS, Xu M, Shupnik MA, Rice LW. Well - differentiated endometrial adenocarcinomas and poorly differentiated mixed mullerian tumors have altered ER and PR isoform expression. Oncogene 2001; 20: 6965 - 9.
[23] Zhang Y, Zhao D, Gong C, et al. Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta - analysis. World J Surg Oncol 2015; 13: 208.
[24] Engelsen IB, Stefansson IM, Akslen LA, Salvesen HB. GATA3 expression in estrogen receptor alpha - negative endometrial carcinomas identifies aggressive tumors with high proliferation and poor patient survival. Am J Obstet Gynecol 2008; 199: 543. e1 - 7.
[25] Tomica D, Ramic S, Danolic D, et al. A correlation between the expression of estrogen receptors and progesterone receptors in cancer cells and in the myometrium and prognostic factors in endometrial cancer. Coll Antropol 2014; 38: 129 - 34.
[26] Srijaipracharoen S, Tangjitgamol S, Tanvanich S, et al. Expression of ER, PR, and Her - 2/neu in endometrial cancer: a clinicopathological study. Asian Pac J Cancer Prev 2010; 11: 215 - 20.
[27] Sivridis E, Giatromanolaki A, Koukourakis M, Anastasiadis P. Endometrial carcinoma: association of steroid hormone receptor expression with low angiogenesis and bcl - 2 expression. Virchows Arch 2001; 438: 470 - 7.
[28] Kobel M, Atenafu EG, Rambau PF, et al. Progesterone receptor expression is associated with longer overall survival within highgrade histotypes of endometrial carcinoma: a Canadian high risk endometrial cancer consortium (CHREC) study. Gynecol Oncol 2016; 141: 559 - 63.
[29] Stoian SC, Simionescu C, Margaritescu C, Stepan A, Nurciu M. Endometrial carcinomas: correlation between ER, PR, Ki67 status and histopathological prognostic parameters. Rom J Morphol Embryol 2011; 52: 631 - 6.
[30] Morrison C, Zanagnolo V, Ramirez N, et al. HER - 2 is an independent prognostic factor in endometrial cancer: association with outcome in a large cohort of surgically staged patients. J Clin Oncol 2006; 24: 2376 - 85.
[31] Ioffe OB, Papadimitriou JC, Drachenberg CB. Correlation of proliferation indices, apoptosis, and related oncogene expression (bcl - 2 and c - erbB - 2) and p53 in proliferative, hyperplastic, and malignant endometrium. Hum Pathol 1998; 29: 1150 - 9.
[32] Williams JA Jr, Wang ZR, Parrish RS, Hazlett LJ, Smith ST, Young SR. Fluorescence in situ hybridization analysis of HER - 2/neu, cmyc, and p53 in endometrial cancer. Exp Mol Pathol 1999; 67: 135 - 43.
[33] Gul AE, Keser SH, Barisik NO, et al. The relationship of cerb B 2 expression with estrogen receptor and progesterone receptor and prognostic parameters in endometrial carcinomas. Diagn Pathol 2010; 5: 13.
[34] Salvesen HB, Iversen OE, Akslen LA. Prognostic significance of angiogenesis and Ki - 67, p53, and p21 expression: a populationbased endometrial carcinoma study. J Clin Oncol 1999; 17: 1382 - 90.
[35] Geisler JP, Geisler HE, Miller GA, Wiemann MC, Zhou Z, Crabtree W. MIB - 1 in endometrial carcinoma: prognostic significance with 5 - year follow - up. Gynecol Oncol 1999; 75: 432 - 6.
[36] Pansare V, Munkarah AR, Schimp V, et al. Increased expression of hypoxia - inducible factor 1alpha in type I and type II endometrial carcinomas. Mod Pathol 2007; 20: 35 - 43.
[37] Goebel EA, Vidal A, Matias - Guiu X, Blake Gilks C. The evolution of endometrial carcinoma classification through application of immunohistochemistry and molecular diagnostics: past, present and future. Virchows Arch 2018; 472: 885 - 96.
[38] Sundar S, Balega J, Crosbie E, et al. BGCS uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol 2017; 213: 71 - 97.