

Original Article

Loss of c-met expression in malignant endometrial tumors: an immunohistochemistry study

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Abstract: Introduction: Many studies described c-Met involvement in cancer development and progression by its multiple biological responses, which stimulate proliferation, differentiation, survival, motility, migration, angiogenesis and invasion. This study portrays the immunostaining of c-Met in endometrial neoplasms, and assesses its value as diagnostic and prognostic marker. Methods: This study retrospectively recruited 102 cases that include 72 and 30 cases of malignant and benign endometrial tissues respectively. These cases were retrieved from the archives of Pathology Department at King Abdulaziz University, Jeddah, Saudi Arabia. Tissue microarrays and immunostaining were used to show the phenotype of c-met. Results: A total number of 13 (18.05%) tumor cases were positive for c-met immunostaining. Yellow to brown cytoplasmic and/or membranous expression of c-met was detected in 2/9 (22.2%) of papillary serous endometrial carcinomas, 9/53 (17%) of endometrioid adenocarcinomas, and one case of each endometrial stromal sarcoma and malignant mixed Mullerian tumor. Twenty three (76.6%) control cases showed positive immunostaining. c-Met immunostaining was common in the cytoplasm more than membranes in malignant tumors while it was cytoplasmic and membranous in benign tissues. Significant different c-Met immunostaining distribution was observed between tumor cases and control group (P -Value = 0.0000). Furthermore, inverse odds ratio shows that tumor cases are 14.92 times less likely of having positive c-Met immunostaining (odds ratio 0.067 with 95% confidence interval 0.024-0.189). This study did not find relation between c-Met expression and disease recurrence, survival or any of the other clinicopathological parameters in endometrial tumors. Conclusion: This study in favor of c-Met expression is not a valuable factor for tumor development, recurrence, and survival in endometrial tumors. Greater c-Met staining was seen in normal and benign endometrial tissue compared to endometrial carcinomas. Loss of c-Met expression gives an indication for endometrial tumors.

Keywords: c-Met, endometrial tumors, immunohistochemistry

Introduction

c-Met is a 190 kDa glycoprotein that belongs to a subfamily of receptor tyrosine kinases, predetermined by a proto-oncogene named MET, that is found in band 21-31 of the arm q of chromosome 7 [1]. Hepatocyte growth factor is the only recognized natural ligand of the c-Met [2]. On binding to c-Met, both molecules exert a variety of effects on epithelial and surrounding tissues, which stimulate proliferation, differentiation, survival (prevention of apoptosis), motility, branching morphogenesis, migration, angio-

genesis, invasion, and epithelial-mesenchymal transition [3-9]. Furthermore, c-Met has critical cytoprotective role when a response to injuries is required [10, 11].

The advantage conferred by the activation of c-Met pathway to neoplastic cells during tumor progression has been linked mainly to their increased capability to disaggregate from surrounding tumor cells, destroy the basement membranes, and enhance cell motility and metastatic potential [6, 12, 13]. Many recent reviews have documented that the c-Met can

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be overexpressed, potentially mutated, and/or amplified in a large number of human malignancies and conduct a critical role in epithelial mesenchymal transition. Changes in c-Met expression levels, and/or mutation/amplification of the receptor, and/or changes in kinase activity can occur in tumors of liver, lung, colon, breast, brain, head and neck, esophagus, stomach, thyroid, pancreas, ovary, cervix, in addition to mesothelioma and sarcomas [6, 12-17].

To our knowledge, only four studies (one of it in Chinese language) have assessed c-Met expression in endometrial tumors and benign conditions of endometrium [18-21]. Endometrial carcinomas are the commonest aggressive malignant neoplasm of the female reproductive organs in developed countries [22]. In Saudi Arabia, two hundred and twenty cancer cases of the corpus uteri have been reported among women representing about 4.1% of all newly confirmed cancer cases in 2010. This type of malignant neoplasm rated sixth amongst female population. The average age was sixty years (28-85). Morphologically, the most common type is endometrial (endometrioid) adenocarcinoma accounts for more than 70%, and less frequently, serous cystadenocarcinoma, clear cell adenocarcinoma, endometrial stromal sarcoma, adenocarcinoma with mixed subtypes, and Others [23].

There are considerable variations between the major histologic types of endometrial carcinoma concerning a range of factors that may influence the treatment of patient, including prognosis, recurrence pattern, chemotherapeutic response, and possibility of thromboembolic complications [24-29]. Such factors require accurate distinction between histologic tumor types of endometrium. Nonetheless, substantial interobserver inconstancy persists among qualified pathologists in the identification of subtypes of endometrial carcinomas [30, 31]. Therefore, a vigorous immunohistochemical diagnostic marker for differentiating histological types of endometrial carcinomas is probably to be valuable.

The current study describes the immunohistochemical phenotype of c-Met in endometrial tumors, investigates its association with clinicopathological factors and follows up data, and tests its reliability as prognostic marker.

Material and methods

Study subjects

This study retrospectively recruited 102 cases that include 72 and 30 cases of malignant and non-malignant endometrial tissues respectively. These cases were retrieved from the archives of Pathology Department at King Abdulaziz University, Jeddah, Saudi Arabia.

Thirty benign cases of endometrial tissue were recruited as a control group. These control cases were chosen from individuals who were curetted for non-cancerous conditions comprising 16 proliferative endometrium, 10 secretory endometrium and 4 benign endometrial polyps. The average age of this control group is 35.6 years.

These cases (both malignant and benign) covered the period from January 2001 to December 2012. Four micron thickness sections were sliced from paraffin blocks, then stained with hematoxylin and eosin for tumors histopathological characteristics evaluations, grading and staging. Patient's clinical data (age, type of tumor, size, grade and stage of carcinoma) were extracted from the patient's medical records. All recruited tissue blocks of both benign and malignant conditions were used for tissue microarray construction in the present study. Biomedical Ethical Committee at King Abdulaziz University has approved the present study.

Tissue microarray construction

Seventy two primary endometrial carcinomas and 30 non-cancerous endometrial tissue samples were used for tissue microarray construction (TMA) as previously described [32]. Blocks of TMA were cut into 4-micron thickness sections and placed on aminosilane coated slides to be used later in immunohistochemistry.

Immunohistochemistry staining protocol

Immunohistochemical staining of endometrial tumor samples, using anti-c-Met monoclonal antibody (Spring Bioscience, CA, USA), was performed by Multimer technology: *ultra View*TM DAB procedure following manufacturer's kit instructions. Immunohistochemistry procedure was conducted using Ventana BenchMark ULTRA automatic immunostainer (Ventana

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Table 1. C-met immunostaining in endometrial tumors and controls cases

Characteristics	Total no	%	C-met Immunostaining		P-Value ^a
			Negative	Positive	
72 Endometrial Tumors					
Endometrioid adenocarcinoma	53	73.6	44	9	0.0000
Endometrioid adenocarcinoma with squamous differentiation	6	8.3	6	0	
Serous adenocarcinoma	9	12.5	7	2	
Clear cell adenocarcinoma	1	1.38	1	0	
Malignant mixed mullerian tumor	2	2.77	1	1	
Endometrial stromal sarcoma	1	1.38	0	1	
Total	72	100	59	13	
30 Non-cancerious control cases					
Proliferative endometrium	16	53.33	4	12	
Secretory endometrium	10	33.33	1	9	
Endometrial polyp	4	13.33	2	2	
Total	30	100	7	23	

a: Fisher's Exact Test Exact Sig. (2-sided).

Table 2. Clinicopathological characteristics of endometrial tumor patients

Characteristics	Total No (72)	%	C-met Immunostaining		P-Value ^a
			Negative	Positive	
Tumor differentiation					
Well differentiated	41	56.9	33	8	0.1123
Moderately differentiated	20	27.7	17	3	
Poorly differentiated	8	11.1	8	0	
Ungraded	3	4.16	1	2	
FIGO grades					
I	40	55.6	32	8	0.148
II	23	31.9	20	3	
III	6	8.33	6	0	
Ungraded	3	4.16	1	2	
FIGO stages					
IA	22	30.55	16	6	0.2033
IB	11	15.27	9	2	
IC	1	1.38	0	1	
II	1	1.38	0	1	
IIA	1	1.38	1	0	
IIB	3	4.16	2	1	
IIIB	1	1.38	1	0	
IIIC	8	11.11	8	0	
IV	1	1.38	1	0	
IVA	1	1.38	1	0	
IVB	1	1.38	1	0	
Unstaged	21	29.16	19	2	
Recurrent					
Yes	15	20.83	13	2	0.4574
No	57	79.17	46	11	
Mortalities					
Yes	17	23.61	16	1	0.1256
No	55	76.39	43	12	

a: Fisher's Exact Test Exact Sig. (2-sided).

Medical Systems Inc., Arizona, USA). Colorectal adenocarcinoma tissue sample previously shown to be stained with this antibody was utilized as positive control. Tris-buffered saline replaced the primary antibody in a negative control slide. Slides were considered positive when granular yellow or brown staining was revealed in the membranes or cytoplasm of cells. c-Met positivity was scored by two pathologists using scoring system of Al-Maghrabi et al. [32]. The approximated grade of immunostaining intensity mirrored positive staining in transformed cells that make more than 5% of tumor cells.

Statistical analysis

Data was statistically analysed using IBM-SPSS version 21. Relation between categorical variables was established by Chi-Square and Fisher's exact test analysis. P-value < 0.05 is the statistical significance level.

Results

Seventy two endometrial neoplastic cases were re-

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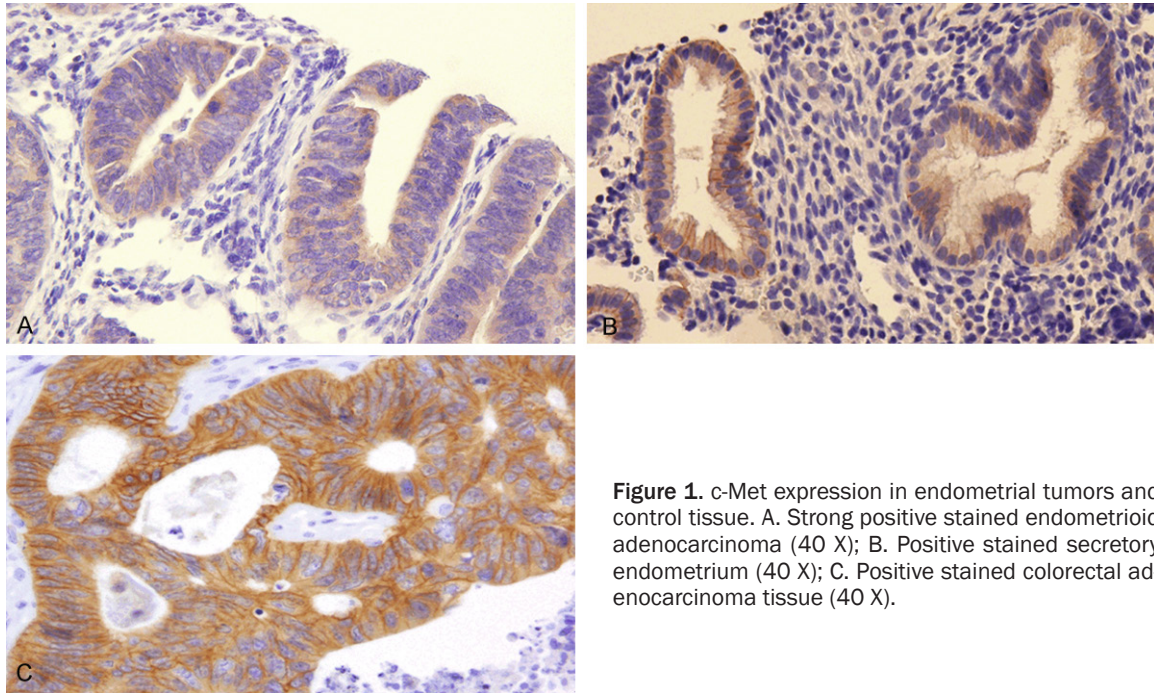


Figure 1. c-Met expression in endometrial tumors and control tissue. A. Strong positive stained endometrioid adenocarcinoma (40 X); B. Positive stained secretory endometrium (40 X); C. Positive stained colorectal adenocarcinoma tissue (40 X).

sed. Morphologically, the most common type was endometrioid adenocarcinoma accounted for 73.6%, and less frequently, 12.5% papillary serous adenocarcinoma, 8.3% endometrioid endometrial adenocarcinoma with squamous differentiation, 1.38% clear cell carcinoma, 2.77% malignant mixed Mullerian tumor (MMMT), and 1.38% endometrial stromal sarcoma (**Table 1**). The median age of these cases was 54 years (ranging 26-86 yrs.). More than a half (56.9%) of tumors were well differentiated, 27.7% moderately differentiated, 11.1% were poorly differentiated and three cases were not described (**Table 2**). FIGO histologic classification was used for grading endometrial tumors, the grades of tumor cases were I, I/II, I/III, II, II/III, and III accounting for 35 (48.6%), 1 (1.38%), 4 (5.55%), 20 (27.77%), 3 (4.16%), and 6 (8.33%), respectively (**Table 2**). Three cases were not graded. Only 51 endometrial tumors were staged using FIGO staging system; the most frequent stage was I accounted for 34 (47.22%) including 22 (30.55%) IA, 11 (15.27%) IB, and 1 (1.38%) IC. Next in descending frequency was stage III including 8 (11.11%) IIIC and 1 (1.38%) IIIB, followed by five cases and three cases of stages II and IV respectively (**Table 2**). The whole number of mortalities in the full panel of cases was 17 (23.61%). Tumor recurrences were seen in 15 (20.83%) cases

(**Table 2**), 10 of these patients are deceased because of their tumor, and the remaining 5 patients were still alive at the latest follow up.

Positive cytoplasmic and less frequently membranous expression of c-Met were detected in 13 (18.05%) cases of endometrial tumors which include 9 endometrioid adenocarcinomas, 2 papillary serous carcinomas, one malignant mixed Mullerian tumor and one endometrial stromal sarcoma (**Figure 1**). Three endometrioid adenocarcinoma exhibited moderate to strong immunostaining in more than 75% of tumor cells, and 6 cases were of weak staining in more than 50% of transformed cells. Two cases of papillary serous adenocarcinoma were of weak focal immunostaining in approximately 25% of tumor cells. In respect of the two cases, MMMT case and stromal sarcoma case, immunoreactivity was moderate to strong and observed in a range of 10-60% of tumor cells.

Twenty three benign control cases were positive for c-Met immunostaining, include 12 proliferative endometrium, 9 secretory endometrium, and 2 endometrial polyps. The majority of control cases revealed membranous and cytoplasmic staining. All nine positive secretory endometrium cases showed moderate to strong c-Met expression. Positive proliferative endometrium cases varied in staining intensity

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Table 3. C-met expression in endometrial tumors and benign conditions in studies from the literature

	Endometrial carcinoma	Serous carcinoma	Clear cell carcinoma	Endometrial polyp	Normal endometrium	Proliferative	Secretory	Atrophic tissue
Wagatsuma et al. 1998	59 (63.4)				2 (14.3)	2 (40.0)	0 (0.0)	0 (0.0)
Bishop et al. 2011	21 (81%)	27 (71%)						7 (58.3%)
Felix et al. 2012	Low grade 12 (19) High grade 11 (35)	25 (37%)	8 (26%)					
Current study	9 (17%)	2 (22.2%)	0 (0.0)	2 (50%)		12 (75%)	9 (90%)	

with weak stain in 50% of it. In respect of the two polyp cases, one case was of moderate staining and the other one was of weak staining. Significant different c-Met immunostaining distribution was observed between malignant cases and benign control groups (P -Value = 0.0000), furthermore, inverse odds ratio shows that tumor cases are 14.92 times less likely of having positive c-Met immunostaining (odds ratio 0.067 with 95% confidence interval 0.024-0.189). Statistical analysis did not find significant association between c-Met immunostaining, clinical and histopathological characteristics of the endometrial tumors such as differentiation, grade, stage, recurrence and mortality status (**Table 2**).

Discussion

Recently, many attentions have been brought to c-Met as a promising biomarker in tumor pathogenesis, and possible therapeutic agent in several human tumors, making MET gene and its protein an important subject in cancer research. Many papers have reported c-Met overexpression in many human malignancies [6-17]. However, few studies have assessed c-Met expression in endometrial tumors and benign conditions of endometrium [18-21]. The results of these studies were inconsistent and positivity of c-Met expression ranged from 19% to 81% of tumor cases, and from 0.0% to 58.3% of benign endometrial tissues (**Table 3**).

Although the current study recruited a small sample size, our results regarding the incidence of the positive immunostaining of c-Met in the 30 controls were higher than the results of other studies (**Table 3**) [18, 19]. In respect of endometrial endometrioid adenocarcinoma, the results of this study are in agreement with those of Felix et al. [20] which showed positive immunoreactivity in only 19% of the low grade tumor cases, and contradict the results of Wagatsuma et al., and Bishop et al. who found remarkable percentage of cases with positive c-Met expression 63.4% and 81% respectively [18, 19]. Regardless of the small number of serous carcinomas in the current study, our findings are three times less than those of Bishop et al. [19] who reported positive immunostaining in 71% of the cases. They concluded that total c-Met staining was significantly different between the tissue types and greater staining for total c-Met was seen in tumors as com-

pared to atrophic endometrium, which contradicts our findings of greater expression of c-Met in benign than malignant tissues. Regarding the clinicopathological parameters such as grade, stage, recurrence, and survival, our findings are in same orientation of those of Felix et al. [20], who reported "no significant associations were observed between c-Met expression and any of the clinicopathological factors".

However, the differences between the current study and the other studies could be explained by procedures sensitivity, populations' diversity and variances in sample size. Our study and some other similar studies which attempted to evaluate the diagnostic and prognostic value of c-Met immunostaining in malignant and benign endometrial tissues had some limitations. First, the relative small sample size of tumor cases included in these studies. Second, interpretation of immunohistochemical staining is semi-quantitative [33]. However, greater inclusive researches are important for evaluating the diagnostic and prognostic capacities of c-Met immunostaining in malignant and benign endometrial tissues.

In conclusion, this study reveals that c-Met expression is not a critical factor for tumor progression, recurrence, and survival in endometrial tumors. Greater c-Met staining was seen in normal and benign endometrial tissue compared to endometrial carcinomas. Loss of c-Met expression gives an indication for endometrial tumors.

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Disclosure of conflict of interest

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