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Expression of MTA1 and nm23-H1 protein in ovarian carcinomas in relation to lymph node metastasis

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Objective : Cancer metastasis is a complex process involving a sequential series of multi-step genetic events, which produces an imbalance between stimulatory and inhibitory genes for metastasis. Presently, we examined the expression of metastatic tumor antigen 1 (MTA1) and nonmetastatic protein 23 homologue H1 (nm23-H1) proteins in metastasized epithelial ovarian cancer cells.
Methods : Fifty-one primary epithelial ovarian tumors and corresponding lymph nodes (LNs) were examined immunohistochemically for expression of MTA1 and nm23-H1. Expression of these proteins was statistically evaluated.
Results : The frequency of MTA1 expression was 30.3% (10/33) in stage III/IV LNs but was absent (0/18) in stage I/II LNs (p=0.01). MTA1 expression was observed in 50% (6/12) of metastasizing LNs but in only 10.3% (4/39) of non-metastasizing LNs (p=0.01). In contrast with MTA1, nm23-H1 expression was evident in 16 of 18 (88.9%) stage I/II ovarian cancer tissue samples but only in 20 of 33 (60.6%) stage III/IV tissues (p=0.05), and nm23-H1 production was also observed in 75.6% (34/45) of ovarian cancer tissue with residual tumors under 2 cm in diameter, but in 2/6 (33.3%) of cancer tissue with residual tumors exceeding 2 cm in diameter (p=0.03).
Conclusion : The degree of expression and imbalance of MTA1 and nm23H1 are correlated with ovarian cancer LN metastasis.

Key Words : Ovarian neoplasms, Lymphatic metastasis, MTA1, nm23-H1

INTRODUCTION

According to statistics reported by the Cancer Committee of the Korean Obstetrics and Gynecology Association, advanced stage cancer is more common in patients with ovarian cancer at diagnosis than with cervical or endometrial cancer.[1] Cancer-related morbidity and mortality are predominantly the result of tumor invasion and metastasis.[2] Because distant metastasis is also one of the most important factors affecting prognosis in the patients with ovarian cancer, extensive efforts have been made to predict metastasis. However, metastasis is a complex process involving the expression of several genes including those important in the detachment of cancer cells from the primary tumor, penetration into the local vessels and lymphatics, arrest at distant sites by adhesion to endothelial cells and underlying matrix, extravasations, the induction of angiogenesis, escape from anti-tumor immune responses, and growth at metastatic sites.[3]

Metastatic tumor antigen 1 (MTA1) is the human homologue of the *mta1* gene cloned by differential cDNA library screening using a rat carcinoma metastatic model.[4-6] Expression of MTA1 It correlates with metastatic potential in several human cancers including gastric and colorectal carcinomas[7] and esophageal cancer.[8] Expression of the MTA1

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gene is related to degree of invasion and lymphatic metastasis. On the contrary, the nonmetastatic protein 23 homologue H1 (nm23-H1) gene was initially cloned as a metastasis suppressor gene, with reduced nm23 mRNA levels correlating with higher metastatic potential *in vitro*.[9] Transfection of human nm23-H1 cDNA into human MDA-MB-435 breast cancer cell lines significantly reduces the metastatic potential *in vivo*.[10] In breast, gastric, and hepatocellular cancers, and in melamona, nm23 expression has been inversely correlated with metastatic potential and/or survival.[11] However, high nm23 expression is associated with more aggressive disease progression in pancreatic cancer and neuroblastoma.[12] Studies on ovarian cancer are few, and so the association between nm23 expression and prognosis is unclear and contentious.[13-15]

Here, we examined MTA1 and nm23-H1 expression in primary ovarian cancer and metastatic lymph nodes (LNs) to determine whether the expression of MTA1 and nm23-H1 are significant predictors of metastasis.

MATERIALS AND METHODS

1. Patients

We studied 51 epithelial ovarian cancer samples that were over FIGO stage Ic obtained from 51 patients treated at Kyung-hee University Hospital between January 1993 and April 2004. Clinical and pathologic data were retrieved retrospectively from a database. The variables included patient age, disease stage, histologic type and differentiation, postoperative residual tumor size, LN status, and response to chemotherapeutic agents.

2. Immunohistochemistry

For MTA1 and nm23-H1 immunohistochemical staining, the CAP-Plus Detection Kit (Zymed Laboratories, San Francisco, CA) was used. Sections of 5 m thickness were cut from 10% formalin-fixed, paraffin-embedded tissue blocks. Deparaffinized sections were treated with methanol with 1.5% hydrogen peroxide (H_2O_2) for 20 min to block endogenous peroxidase. Cross reactivity was blocked with 2% nonimmune rabbit serum and 0.1% bovine serum albumin in phosphate buffered saline. Sections were then incubated with MTA1 specific monoclonal antibody A11 (1 μg IgG_1/ml) and nm23-H1 specific monoclonal antibody clone NM301 (5 μg IgG_1/ml) for 1 h at room temperature. The sections were then incubated with secondary anti-mouse IgG antibody and streptavidin-peroxidase for 20 min each. Tissue was stained for five min with 3'3'-diaminobenzidine. The primary cancer specimen and ovarian cancer LN tissue were used as positive controls for MTA1 and nm23-H1, respectively. For negative controls, sections were treated the same way, except they were incubated with buffered saline instead of the primary antibody. The intensity of cell staining was graded 1-4, corresponding to absence of stain, intensity $<5\%$, intensity of 5-70%, and intensity $>70\%$, respectively (Fig. 1, 2).

3. Statistical analyses

Statistical analyses were conducted using SPSS version 11.0 (SPSS, Chicago, IL). Relations between the expression of MTA1 and nm23-H1 and the clinicopathological parameters were evaluated via Chi-square tests. For all statistical tests, the level of significance was set at a p-value <0.05.

RESULTS

The median age at diagnosis of the 51 patients was 51 years (range 21-73 years). The pathological characteristics of the patients are shown in Table 1. There were 14 stage I cases (27.5%), 4 stage II cases (7.8%), 29 stage III cases (56.9%), and 4 stage IV cases (7.8%). Adenocarcinomas included serous (n=26, 51%), mucinous (n=14, 17.6%), and endometrioid (n=9, 17.6%). Forty-five (88.2%) patients had postoperative residual masses <2 cm in diameter and 6 patients (11.8%) had a residual mass ≥ 2 cm in diameter. Twelve (23.6%) cases were LN metastasis positive and 39 (76.4%) were LN metastasis negative. MTA1 expression was positive in 37 (72.5%) cases of primary cancer tissue and 10 (19.6%) cases of LN. Thirty-six (70.5%) cases showed positive staining for nm23-H1 in ovarian cancer tissue and 4 (7.8%) cases were LN positive. LNs for both MTA1 and nm23-H1

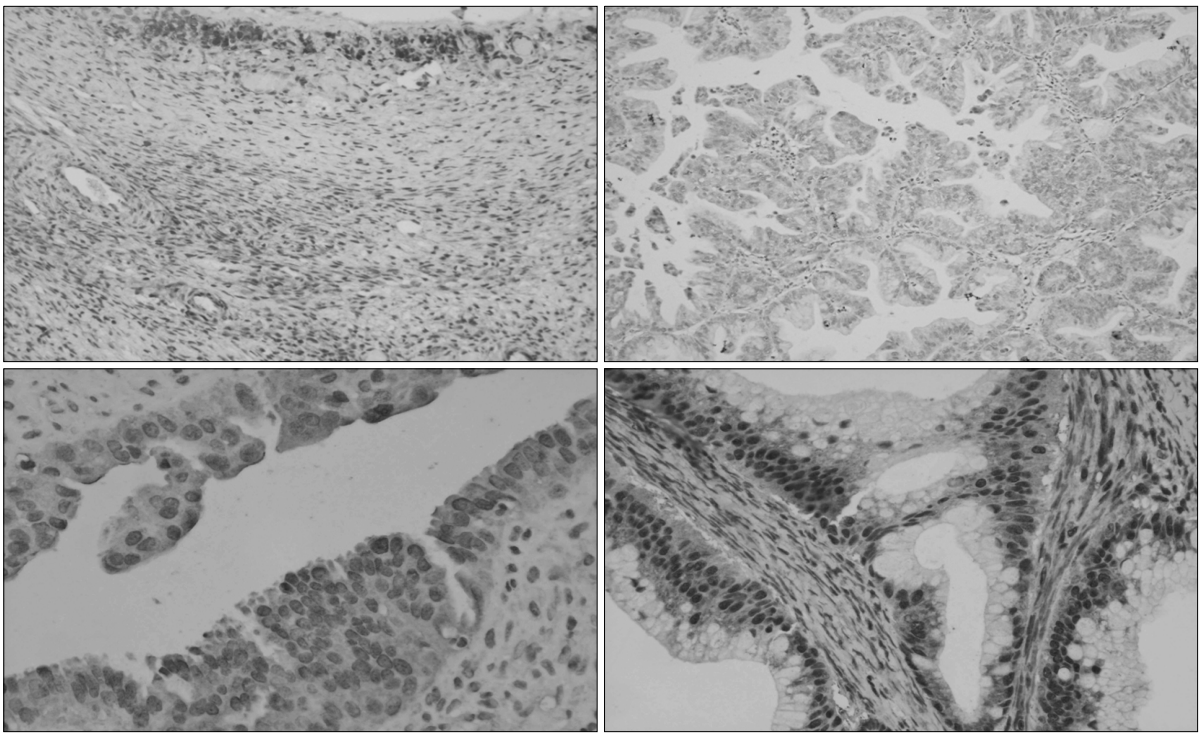

Fig. 1. Representative images of tissue microarray samples staining absent, weak, moderate, and strong for MTA1 expression. MTA1 expression was confined to the nuclei of cells as demonstrated by immunohistochemistry (×200 magnification).

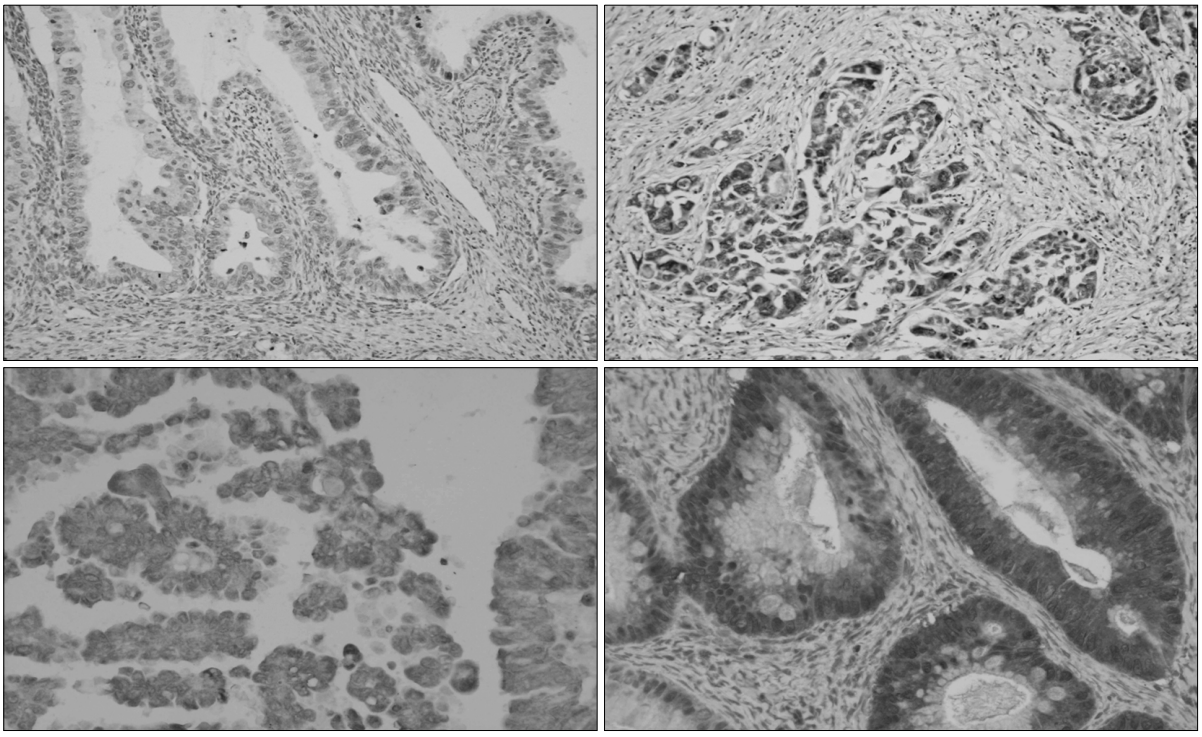

Fig. 2. Representative images of tissue microarray samples staining absent, weak, moderate, and strong for nm23-H1 expression. nm23-H1 expression was confined to the nuclei of cells as demonstrated by immunohistochemistry (×200 magnification).

Table 1. Characteristics of the 51 patients

Clinicopathological parameters	Number	%
Stage		
I	14	27.5
II	4	7.8
III	29	56.9
IV	4	7.8
Histologic type		
Serous	26	51.0
Mucinous	14	27.6
Endometrioid	9	17.6
Clear cell	1	1.9
Unclassified	1	1.9
Histologic grade		
Well	17	33.3
Moderate	7	13.8
Poor	24	47.0
Unknown	3	5.9
Residual tumor		
<2 cm	45	88.2
≥ 2 cm	6	11.8
LN metastasis		
Present	12	23.6
Absent	39	76.4
MTA1 expression (Primary tumor/LN)		
Negative	14/41	27.5/80.4
Positive	37/10	72.5/19.6
nm23-H1 expression (Primary tumor/LN)		
Negative	15/47	29.5/92.2
Positive	36/4	70.5/7.8

displayed expression that was below that of primary ovarian cancer tissue.

The relationship between the frequency of MTA1 expression and the clinicopathological parameters is shown in Table 2. For primary ovarian cancer tissue, MTA1 expression did not correlate with any of the clinicopathological parameters such as stage, histologic type and grade, residual tumor size, and lymph node metastasis. However, for LN staining, the absence of MTA1 expression in stage I/II LNs was significantly lower than the 30.3% level in stage III/IV LNs. MTA1 expression in metastasized LNs (50%) was significantly higher that non-metastasized LNs (10.3%).

The clinicopathological correlation between the expression level of the nm23-H1 protein and several parameters is shown in Table 3. In primary ovarian cancer tissue, the frequency of nm23-H1 expression in stage I/II (88.9%) was significantly higher than the frequency in stage III/IV (60.6%) ($p=0.05$). Patients whose residual tumor size was <2 cm (75.6%) were significantly more inclined to be nm23-H1 positive than patients with a residual tumor ≥ 2 cm (33.3%). No significant association was evident between nm23-H1 expression and the examined clinicopathological factors in LNs.

DISCUSSION

In the present study, we demonstrate that the expression of MTA1 in LNs is significantly associated with advanced stage (stage III/IV) and lymphatic metastasis. In contrast, expression of nm23-H1 is significantly associated with stage I/II tumor and small (<2 cm) residual tumor size.

MTA1 is normally expressed only at low levels in various tissues.[5] However, in several human metastatic cancers, expression levels of MTA1 correlate with metastatic potential and degree of invasion.[5,7,8,16-18] The relationship between MTA1 protein overexpression and the invasion/metastasis of cancer cells has also been also demonstrated *in vitro*. Increasing MTA1 expression enhances migration, invasion and anchorage-independent survival of immortalized human keratinocytes[19] and in epithelial ovarian cancer cells.[20] The latter study also showed that increased expression of MTA1 significantly correlates with the histological grade and stage of ovarian cancer. Our findings agree with these previous studies.

The nm23 gene is a metastasis-associated gene that maps to human chromosome band 17q22.[21] The nm23 gene family consists of eight genes, of which nm23-H1 and H2 are the most studied members.[22] These two genes encode nucleoside diphosphate kinases (NDPK) A and NDPK B, respectively. The nm23 protein seems to play an important, but as yet unclear, role in human cancer. Potential suggested roles for the nm23 protein include regulating cell signals by NDPK, GDP/GTP exchange,[23] tumor

Table 2. Relationship between MTA1 expression and clinicopathological parameters in epithelial ovarian cancer

	Positive expression by immunohistochemistry (%)			
	Primary tumor		LN	
	n (%)	p-value	n (%)	p-value
Stage				
I/II	12/18 (66.7)	0.53	0/18 (0)	0.01*
III/IV	25/33 (75.8)		10/33 (30.3)	
Histologic type				
Serous	22/26 (84.6)		8/26 (30.8)	
Mucinous	9/14 (64.3)		1/14 (7.1)	
Endometrioid	6/9 (66.7)	0.22	1/9 (11.1)	0.14
Clear cell	0/1 (0)		0/1 (0)	
Unclassified	0/1 (0)		0/1 (0)	
Histological grade				
Well	11/17 (64.7)		0/17 (0)	
Moderate	5/7 (71.4)	0.09	2/7 (28.6)	0.34
Poor	21/24 (87.5)		8/24 (33.3)	
Unknown	1/3 (33.3)		0/3 (0)	
Residual tumor				
<2 cm	31/45 (68.9)	0.13	8/45 (17.8)	0.38
≥ 2 cm	6/6 (100.0)		2/6 (33.3)	
LNs metastasis				
Absent	28/39 (71.8)	0.71	4/39 (10.3)	0.01*
Present	10/12 (83.3)		6/12 (50.0)	

*statistically significant

Table 3. Relationship between nm23-H1 expression and clinicopathological parameters in epithelial ovarian cancer

	Positive expression by immunohistochemistry (%)			
	Primary tumor		LN	
	n (%)	p-value	n (%)	p-value
Stage				
I/II	16/18 (88.9)	0.05	1/18 (5.6)	1.00
III/IV	20/33 (60.6)		3/33 (9.1)	
Histologic type				
Serous	16/26 (61.5)		4/26 (15.4)	
Mucinous	10/14 (71.4)		0/14 (0)	
Endometrioid	7/9 (77.8)	0.29	0/9 (0)	0.11
Clear cell	1/1 (100)		0/1 (0)	
Unclassified	1/1 (100)		0/1 (0)	
Histological grade				
Well	17 (33.3)		1/17 (5.9)	
Moderate	7 (13.8)	0.09	0/7 (0)	0.34
Poor	24 (47.0)		3/24 (12.5)	
Unknown	3 (5.9)		0/3 (0)	
Residual tumor				
<2 cm	34/45 (75.6)	0.03*	3/45 (6.7)	0.40
≥ 2 cm	2/6 (33.3)		1/6 (16.7)	
LNs metastasis				
Absent	30/39 (76.9)	0.14	1/39 (2.6)	0.06
Present	6/12 (50.0)		3/12 (25.0)	

*statistically significant

differentiation,[24] and cell proliferation.[25]

In epithelial ovarian cancer, high levels of nm23 expression have been linked to the increased metastatic spread of the cancer.[13,14] In childhood neuroblastomas, mutations and/or genetic alterations of the nm23-H1 gene, together with overexpression associated with a more malignant phenotype, have also been reported.[26] As well, association between nm23-H1 and the clinical significance of gastric cancer[27] and breast cancer[28] has been reported. However, our results demonstrate that the expression of nm23-H1 is decreased in advanced stage (III/IV) and when residual tumors are ≥2 cm in size. The present results, together with those of a previous study[15] indicate that nm23-H1 overexpression might be a good prognostic factor for epithelial ovarian cancer. Indeed, nm23-H1 overexpression has been associated with both a survival advantage and greater response to chemotherapy in patients with advanced ovarian cancer, with the percentage of nm23-H1 positivity being higher in LN negative (70%) than in LN positive cases (40%), and the survival rate of nm23-H1 positive patients being higher than nm23-H1 negative patients.[29]

In conclusion, our results demonstrate the positive correlation between MTA1 expression and LN metastasis, and implicate nm23-H1 expression as a good prognostic factor in epithelial ovarian cancer. The expression of MTA1 and nm23-H1 might be of considerable importance as biologic predictive markers of LN metastasis of epithelial ovarian cancer. However, the exact mechanism of the pathogenesis of the two genes that gives rise to the metastasis is unknown and in need of further study.

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=초록=

상피성 난소암에서 림프절 전이 유무에 따른 MTA1 및 nm23-H1 단백 발현

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목적 : 암전이는 전이를 자극하는 유전자와 이를 억제하는 유전자간의 불균형의 과정 및 일련의 유전적인 복잡한 과정을 통해서 일어나게 된다. 난소암에서 치료 실패 및 사망하게 되는 가장 큰 원인은 전이라 할 수 있다. 본 연구는 상피성 난소암에서 암전이와 관련된 유전자인 MTA1과 전이억제 유전자로 알려진 nm23-H1의 발현 정도를 확인하여 림프절 전이와의 상관관계를 알아보고자 한다.

연구 방법 : 연구 대상은 1993년 1월부터 2004년 4월까지 상피성 난소암으로 수술을 시행한 51예에서 MTA1과 nm23-H1 단백의 발현을 면역조직화학염색을 통해 확인하였다.

결과 : 면역조직화학염색 결과 MTA1 유전자 발현은 원발 종양에서 37예(72.5%)에서 양성이었고 림프절의 경우 10예(19.6%)였으며, nm23-H1 유전자 발현은 원발 종양에서 36예(70.5%)였고 림프절에서는 4예(7.8%)에서 양성이었다. MTA1은 병기 III/IV의 진행된 병기의 림프절과, 전이가 있는 림프절에서 발현 빈도가 유의하게 증가되었고, nm23-H1은 병기 I/II의 낮은 병기와 잔류종양의 크기가 2 cm 미만인 종양에서 통계적으로 유의하게 발현이 증가되는 것을 관찰할 수 있었다.

결론 : MTA1의 발현이 림프절 전이에 있어서 양의 상관관계를 나타내며, nm23-H1의 발현은 난소암의 좋은 예후인자와 관련이 있는 것을 알 수 있었다. 이는 MTA1과 nm23-H1의 발현정도와 두 유전자의 불균형이 난소암의 림프절전이와 연관이 있음을 추측할 수 있으나 두 유전자가 난소암 전이에 관여하는 정확한 기전에 대해서는 아직 알려져 있지 않으며, 향후 이에 관한 추가적인 연구가 필요할 것으로 생각된다.

중심단어 : 난소암, 전이, MTA1, nm23-H1

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