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ORIGINAL RESEARCH

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Evaluation of tissue expressions of kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in ovarian neoplasms

Sevil Sayhan[1,*], Gulden Diniz[2], Dudu Solakoglu Kahraman[1], Duygu Ayaz[1], Pinar Ayvat[3], Ilker Cakir[4], Sefa Kurt[5], Ibrahim Gulhan[6]

[1]Pathology Laboratory, SBU İzmir Tepecik Education and Research Hospital, 35180 Izmir, Turkey
[2]Pathology Department, İzmir Democracy University, 35390 Izmir, Turkey
[3]Anesthesiology and Reanimation Department, Izmir Democracy University, 35390 Izmir, Turkey
[4]Gynecology Department, Buca Seyfi Demirsoy Hospital, 35390 Izmir, Turkey
[5]Gynecology Department, Dokuz Eylul University, 35340 Izmir, Turkey
[6]Gynecology Department, SBU İzmir Tepecik Education and Research Hospital, 35180 Izmir, Turkey

***Correspondence**
sevil.sayhan@saglik.gov.tr
(Sevil Sayhan)

Abstract

Background: Even the slightest bit of evidencehave demonstrated that elevated expressions of kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) play critical roles in tumor progression in many malignant diseases. But still a little is known about their effects on ovarian carcinogenesis. In this retrospective study, we havetargeted to investigate the positivity of KIM-1 and NGAL (if any) in a spectrum of ovarian surface epithelial neoplasms. **Methods**: Herein we have assessed the prognostic values of KIM-1 and NGAL tissue expressions and their relations with some clinicopathologic parameters of 128 cases with ovarian neoplasms. **Results**: This study group consists of cases of 34 (26.6%) benign, and 10 (7.8%) borderline serous tumors, 29 (22.7%) serous, 38 (29.7%) endometrioid and 17 (13.3%) mucinous carcinomas. KIM-1 expression was found in both tumor and inflammatory cells, but NGAL expression was detected only in inflammatory cells. Although it is known that KIM-1 biomarker is expressed at a higher rate in carcinoma cases compared to benign tumors, due to the limited number of cases any statistically significant intergroup difference could not be observed (p = 0.217). Besides, NGAL-positive inflammatory cells were detected at a statistically significantly higher rate in cases with borderline serous tumors and carcinomas (p = 0.003). **Conclusions**: Herein we have shown the presence of a correlation between infiltrationof NGAL—positive inflammatory cells and malignant behavior of ovarian neoplasms. In addition, we have detected the strong cytoplasmic expression of KIM-1 (or its synonym T-cell immunoglobulin and mucin domain/TIM-1), in more than one-third of the malignant ovarian neoplasms which provides supportive evidence favoringthe use of anti-TIM1 immunotherapies in the treatment of patients with KIM-1 positive ovarian neoplasms.

Keywords

Ovarian tumors; KIM-1; TIM-1; anti-TIM1 drugs; NGAL

1. Introduction

Kidney Injury Molecule (KIM-1) was initially found to be a serum biomarker of proximal tubular damage [1]. KIM-1 shares structural similarities with the monkey hepatitis A virus-cell receptor-1 and belongs to the immunoglobulin gene superfamily [1–3]. Currently T cell immunoglobulin and mucin domain 1 (TIM-1) are preferred terms. Expression of TIM-1 is detected not only in ischemic conditions but also in normal kidneys. While it is released in very limited quantities in healthy kidneys, its serum level increases dramatically in some malignant diseases. Therefore, KIM-1 is thought to be a promising target for immune-mediated therapy [1–4]. Currently, a specific antibody (CDX-O14) has been developed against TIM-1. This agent is demonstrated to bind with the TIM-1 protein found in several cell lines, including the IGROV-1 human ovarian cancer cell line which is a well-known model for drug-resistant ovarian carcinoma. However, it has not been incorporated into the standard treatment plan up to now [4–6].

The 25 kDa glycoprotein known as neutrophil gelatinase-associated lipocalin (NGAL) is covalently bound to neutrophil matrix metalloproteinase 9 [7–9]. During inflammation and tissue damage, neutrophils and a number of other cells quickly release this acute-phase protein [9]. In response to a number of harmful stimuli, such as infection, ischemia and toxicity, renal tubular epithelial cells also release NGAL [8, 9]. Several renal lesions have been associated with elevated serum and urine NGAL levels [7–10]. Recently, it has also been determined that NGAL is involved in several processes of development, growth and tumorigenesis [10–12].

Ovarian carcinoma is the most fatal neoplasm among gy-

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necological tumors. Most cases have disseminated diseases, and respond to multi-disciplinary therapies at first, but later on they recur and eventually become resistant to therapy [12–14]. Therefore, in addition to traditional medications, novel therapeutic agents are needed for the management of advanced stage disease [6, 15]. Up to now, KIM-1 and NGAL expressions have been studied both to assess the proliferative activity of neoplasm in several cancers and to predict clinical response in nontumoral kidney diseases [1–3, 10, 11]. However, their tissue manifestations and prognostic value in ovarian cancer patients are still contentious topics that have not been thoroughly investigated and clarified so far. The purpose of this work is to examine the relationship between the immunohistochemical expressions of KIM-1 and NGAL in ovarian epithelial tumors and their correlations with clinicopathological characteristics.

2. Material and methods

A total of 128 patients diagnosed with benign, borderline or malign serous tumors, endometrioid carcinomas and mucinous carcinomas, and treated accordingly at the Izmir Tepecik Education and Research Hospital, between 2002 and 2013 were evaluated. The Local Ethics Committee of the hospital approved this study. The International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie Obstétrique: FIGO) grading system for ovarian cancers was used to evaluate the stages of these tumors.

The paraffin blocks most suitable for immunohistochemical (IHC) analysis were selected via evaluating the archival slides stained with hematoxylin-eosin. The 4-μm thick sections were cut from these selected paraffin blocks. IHC tests were manually performed using streptavidin-biotin peroxidase staining technique (Invitrogen, Camarillo, 85-9043, USA) following the manufacturer's instructions. The pretreatment procedure was applied using10 mM/L citrate buffer. Then the specimens were treated with monoclonal antibodies against KIM-1 (bs-20474R, Bioss, Philadelphia, PA, USA, HAVCRI), and NGAL (Novus Biologicals, Littleton, CO, USA, NDP1-90331) at a dilution of 1:300 for an hour. Pathologists who were blind to the patients' clinical characteristics assessed each slide. Cytoplasmic staining intensity similar to that observed with renal proximal tubules in control tissues was considered KIM-1 positive. KIM-1 negative was defined as focal or relatively faint staining. Tumor cells did not exhibit NGAL expressions. On a few occasions, we found very weak NGAL expressions in tumor cells, which we regarded as erroneous background staining when contrasted to that of the inflammatory cells [2, 3]. We counted the NGAL-positive neutrophils that invaded the tumors in each high-power field (HPF) in order to measure the expression of NGAL.

Statistical analysis: The SPSS 25.0 statistical package (IBM, New York, NY, USA) was used to conduct the statistical analysis. The chi-square test was employed to compare the quantitative data. The Kruskal-Wallis or Mann-Whitney U tests were used to compare non-parametric data. Statistical significance was defined as a p value of less than 0.05.

3. Results

In this study, 34 (26.6%) benign serous, 10 (7.8%) borderline serous tumor, 29 (22.7%) serous, 38 (29.7%) endometrioid and 17 (13.3%) mucinous carcinoma specimens were analyzed (Table 1). The mean (±Standard Deviation (SD)) age of allpatients was46.2 ± 14.1 years (range: 17–78 years). When compared in terms of mean (±SD) ages and respectiveage ranges ofthe cases, the patientswith borderline (37.3 ± 14.4 and 23–72 years) and benign serous tumors (37.7 ± 14.8 and 17–62 years) were statistically significantly younger than those with serous carcinoma (53.5 ± 8.6 and 33–70 years) ($p < 0.001$). On the other hand, the mean ages of the cancer patients did not differ significantly ($p = 0.127$). Patients with endometrioid and mucinous carcinomas had mean ages of 51.2 ± 11.3 years (34–77 years) and 46.1 ± 15 years (18–78 years), respectively. While 15 cases of cancer have exited, all 44 cases with benign and borderline serous tumors survived. Serous carcinoma cases had the greatest mortality rate (31%, n = 9), which was statistically significantly higher than those with other malignancies ($p = 0.022$). Additionally, one patient (5.9%) with mucinous carcinoma and five cases (13.2%) with endometrioid cancer had passed away. In addition, four cases with mucinous carcinoma and ten cases with endometrioid carcinoma were lost to follow-up. Mean (±SD) survival times and corresponding time ranges of serous, endometrioid and mucinous carcinoma cases were 16.3 ± 12.1 (0–45), 79 ± 63.1 (0–176) and 97 ± 64.7 (23–203) months, respectively. The mean survival time was statistically significantly shorter in patients with serous carcinoma than patients with endometrioid and especially with mucinous carcinoma ($p < 0.001$).

Cytoplasmic KIM1 expression was also detected in cases with benign or borderline serous tumors (n: 11; 25%), serous carcinoma (n: 11; 37.9%), endometrioid carcinoma (n: 11; 36.8%), mucinous carcinoma (n: 5; 29.4%) (Fig. 1). It was determined that the positivity rates of KIM-1 expression were slightly higher in the carcinomas when compared with benign and borderline tumors without any statistical significant intergroup difference ($p = 0.217$) which may be related to the scarcity of our cases.

NGAL-positive inflammatory cells were determined in indicated number of cases with benign serous tumor (58.8%: n = 20), borderline serous tumors (70%: n = 7), serous carcinoma (82.8%: n = 24), endometrioid carcinoma (92.1%; n = 35) and mucinous carcinoma (94.1%: n = 16). The average NGAL-positive inflammatory cell countsin each HPF were calculated for serous tumors (n: 25), borderline serous tumors (n: 5.5), serous carcinomas (n: 3.7), 8 in endometrioid carcinomas (n: 8) and mucinous carcinomas (n: 11.4) (Fig. 2). The number of NGAL-positive inflammatory cells was statistically significantly higher in borderline serous tumors and carcinomas when compared with benign tumors ($p = 0.003$).

In short, it was found that the rates of KIM-1 expressions and the number of NGAL expressing inflammatory cells were higher in carcinomas rather than benign and borderline serous tumors. However, this difference was not statistically significant regarding KIM-1 expression. In the Kaplan-Meier survival analyses, both KIM-1 ($p = 0.832$) and NGAL ($p = 0.473$) positivities were not associated with the survival rates.

TABLE 1. Features of the patients according to NGAL and KIM-1 expression of inflammatory cells and tumors.

Parameters	NGAL Status (NGAL-expression of inflammatory cells)		*p* value	KIM-1 Status (KIM-1 expression of tumor cells)		*p* value
	NGAL negative n = 102	NGAL positive n = 26		KIM-1 positive n = 41	KIM-1 negative n = 87	
Age (yr)	47.8 ± 13.1	39.9 ± 16.6	0.019	48.08 ± 14.2	45.3 ± 14.1	0.445
NGAL-positive inflammatory cell/HPF	7.3 ± 7.1/HPF	0/HPF	-	7.8 ± 7.1	4.8 ± 3.9	0.827
Event free survival (mon)	57.1 ± 51.3	44.09 ± 39.8	0.948	55.9 ± 51.0	51.4 ± 48.0	0.991
Overall survival (mon)	63.0 ± 62.4	46.2 ± 38.1	0.440	59.4 ± 50.1	61.6 ± 59.1	0.696
Prognosis	N/%	N/%		N/%	N/%	
Survived	77/75.5%	22/84.6%		6/14.6%	9/10.3%	
Exited	12/11.8%	3/11.5%	0.676	30/73.2%	69/79.4%	0.676
Lost	13/12.7%	1/3.8%		5/12.2%	9/10.3%	
Tumor type	N/%	N/%		N/%	N/%	
Benign serous tumor	20/19.6%	14/53.8%		10/24.4%	24/27.6%	
Borderline serous tumor	7/6.9%	3/11.5%		1/2.4%	9/10.3%	
Serous carcinoma	24/23.5%	5/19.2%	0.001	11/26.8%	18/20.7%	0.508
Endometrioid carcinoma	35/34.3%	3/11.5%		14/34.2%	24/27.6%	
Mucinous carcinoma	16/15.7%	1/3.8%		5/12.2%	12/13.8%	
Diagnosis	N/%	N/%		N/%	N/%	
Benign or borderline tumors	27/26.5%	17/65.4%	<0.001	10/24.4%	24/27.6%	0.217
Carcinomas	75/73.5%	9/34.6%		31/75.6%	63/72.4%	
KIM-1 or NGAL	KIM1 (+) N/%	KIM1 (+) N/%		NGAL (+) N/%	NGAL (+) N/%	
Positive	33/32.4%	8/30.8%	0.877	33/80.5%	69/79.3%	0.877
Negative	69/67.6%	18/69.2%		8/19.5%	18/20.7%	
Stage I (A, B, C)	69/67.6%	20/76.9%		27/65.9%	62/71.3%	
Stage II	1/0.9%	1/3.8%	0.573	2/4.9%	0/0.0%	0.270
Stage III (A, B, C)	31/30.6%	5/19.2%		11/26.8%	25/28.7%	
Stage IV	1/0.9%	0/0.0%		1/2.4%	0/0.0%	

KIM-1: kidney injury molecule-1; NGAL: neutrophil gelatinase-associated lipocalin; HPF: high-power field.

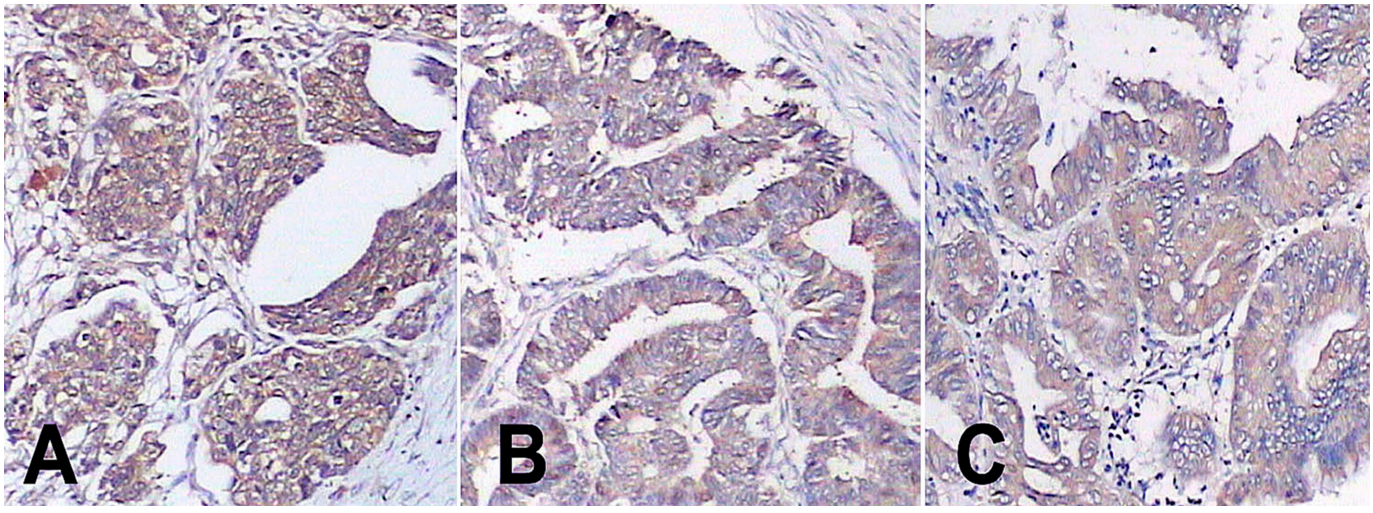

FIGURE 1. Strong cytoplasmic expression of KIM-1 in tumor cells. (A) Serous Carcinoma (B) Endometrioid Carcinoma (C) Mucinous Carcinoma (DAB ×200). DAB: Diaminobenzidine.

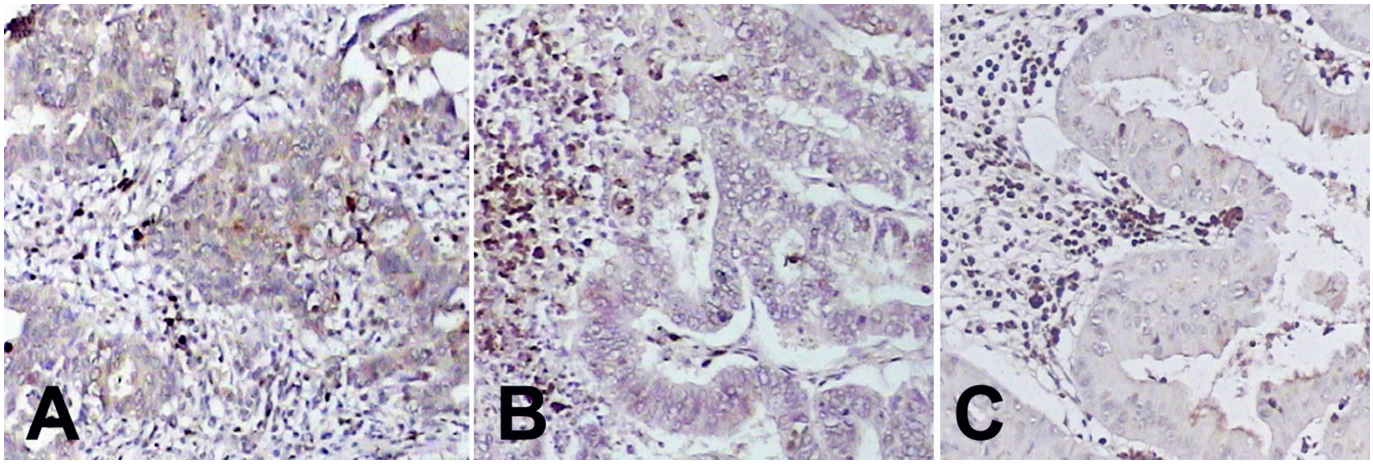

FIGURE 2. Note the weak cytoplasmic NGAL-expressions in the tumor cells relative to the inflammatory cells. (A) Serous Carcinoma (B) Endometrioid Carcinoma and (C) Mucinous Carcinoma (DAB ×200). DAB: Diaminobenzidine.

4. Discussion

KIM-1 expression in ovarian tumors has been evaluated in scarce number of studies cited in the literature [1–6]. Previous research studies examined the connection between ovarian cancers and NGAL expression. However, KIM-1 expression has typically been measured to identify kidney damage brought on by anti-tumoral medications or malignancies [7]. In our study, we identified KIM-1 expressions in more than one-third of our cases with ovarian carcinomas, while lower rates of KIM-1 expression were detected in cases of benign tumors. Therefore, we suppose that this biomarker can be used both to select the eligible patients with ovarian malignancies for anti-TIM-1 therapy, and to discriminate between malign and borderline tumors.

NGAL is normally expressed by the granulocyte precursors in the bone marrow and granulocytes in the peripheral blood [16, 17]. Earlier, NGAL was only accepted as an inflammatory marker of different kidney damages [7]. Therefore, increased NGAL expressions in blood and/or urine due to the inflammatory cells have been used as indicators for detection and confirmation of kidney injury [7–10]. The significant predictive value of NGAL expressions in malignancies generally has been ignored until recently. Nowadays, several studies have demonstrated potential carcinogenic and anti-tumoral effects of NGAL [11–20]. The critical roles played by NGAL and NGAL receptor (NGALR), which has been identified as a cell surface receptor detected in some tumors, have been revealed in the literature. For instance, it has been proposed that NGAL is a prognostic marker independent of tumor stage, and overexpression of NGAL is significantly correlated with poor prognosis in cases with lung adenocarcinomas [19]. Elevated NGAL mRNA expression was determined in some cancers, such as pancreas, lung, kidney, breast, colorectal and uterine cervix carcinomas [18, 19, 21–24]. It was previously reported that especially in the hematological malignancies, NGAL mRNA expression was higher than tissue NGAL protein expression [17–19]. But until today, the correlation between the NGAL gene and protein expression has not been confirmed yet. As an important limitation of this study, NGAL protein expression was investigated only by immunohistochemical analyses, without knowledge of the NGAL gene status.

Today, a variety of prognostic biomarkers are being employed to assess the advancement of various malignancies [25–28]. For instance, it has been noted that elevated NGAL levels increase the invasive potential of chronic myelogenous leukemia, breast, bladder, stomach, thyroid, lung, esophagus, colon and gynecological malignancies. On the other hand, invasiveness of oral and pancreatic tumors is negatively correlated with rising NGAL levels [3, 17–20]. It is yet unknown, therefore, how NGAL is expressed and how it relates biologically to the way ovarian cancers behave [21, 29]. Lim *et al.* [30] have evaluated the NGAL levels by different techniques and found that the grade of ovarian cancers was changed according to the blood level of NGAL. They reported that the NGAL expression was higher in low grade tumors than high grade ones. This finding supported the fact that NGAL expression may be associated with carcinogenesis in ovarian cancers. Interestingly, NGAL expression was detected in only inflammatory cells in our study. We also detected that expression pattern of NGAL confined in leucocytes was similar to that indicated in another study about Wilms tumor [2]. When all these studies are evaluated, it can be noticed that different techniques have been used to evaluate NGAL expressions. In addition, various primary antibodies have been utilised in immunohistochemical analyses [17–29]. Therefore, different NGAL expression levels may be expected. We even thought that this difference might be due to nonspecific cross-reactions between host antigens and NGAL. In the present study, numerous NGAL-positive inflammatory cells were identified in cases of carcinomas, especially in mucinous carcinomas contrary to benign serous tumors. So, we concluded that the presence of NGAL-positive leucocytes was correlated directly with the invasiveness of ovarian tumors. If a similar finding will be demonstrated in larger series, ovarian cancers may be evaluated by measuring the levels of NGAL in urine or blood samples [31–33].

5. Conclusions

In conclusion, additional research is needed to assess the functions of KIM-1 and NGAL in the development of ovarian can-

cer as well as the possibility of focusing on them for diagnosis and therapy. This study has demonstrated relatively higher expression levels of NGAL and KIM-1 in carcinomas when compared to benign and borderline serous tumors. However, this difference for KIM-1 was not statistically significant. The reason why we could not find statistically significant results may be related to the small number of patients included in our study. Considering the development of anti-KIM1 therapies, the presence of KIM-1 expression may gain ever-increasing importance in clinical practice in terms of opening up new treatment alternatives in ovarian cancers. But these findings should be confirmed in larger series. Evaluation of KIM-1 expression in the tumor may also shed light on the indication for the use of recently developed immunotherapeutic agents targeting the TIM-1 antigen to be used in the treatment of aggressive and resistant ovarian cancers. Therefore, we recommend immunohistochemical evaluations of tissue KIM-1 and NGAL expressions during the routine histopathological analyses of ovarian cancer specimens.

AVAILABILITY OF DATA AND MATERIALS

The data and materials used in this study are available upon reasonable request from the corresponding author (Sayhan S).

AUTHOR CONTRIBUTIONS

SS—project development; material preparation; data collection and analysis; manuscript writing; management. GD—protocol and project development; data analysis and collection. DSK—data collection and manuscript writing. DA—protocol and data collection. SK—protocol and project development; data collection and management. PA—project development and management. IC—protocol and project development; data collection. IG—protocol and project development; data collection. All authors contributedto the study conception and design of the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research protocol received approval from the Ethics Committee of Izmir Tepecik Education and Research Hospital under the reference number 2-21, 19 March 2015. Informed consent forms were signed by all patients before surgery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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