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Original Research

Expression of heat shock protein Hsp 27 in ovarian carcinoma

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Summary

Objective: The aim of the present study was to determine the expression of heat shock protein 27 (Hsp 27) in patients with ovarian carcinoma and its relationship with clinical and histopathological characteristics. *Materials and Methods:* Cross-sectional study in patients diagnosed with ovarian carcinoma. From paraffin blocks with tumor material, archived in the pathology services of the San Jose and Infantil Unversitario de San Jose hospitals since 2013 to 2016 the expression of Hsp 27 was analyzed using a semi-quantitative measurement method. Patients´ clinical records were reviewed to analyze clinical and histopathological characteristics. *Results:* Immunohistochemistry was performed on 31 patients. Hsp 27 immunostaining was positive in more than 50% of tumor cells in 17 (54.8%) cases. The intensity of Hsp 27 expression was strong in 13 (41.9%) cases. The most frequent location was membranous and cytoplasmatic in 25 (80.6%). The characterization of patients with intensity of 3+ occurred mainly in high-grade serous papillary stage IIIC carcinomas. *Conclusion:* A stronger Hsp 27 expression occurred mainly in patients with high-grade serous, histology, advanced FIGO stage and in whom optimal or complete cytoreduction could not be performed.

Key words: Ovarian cancer; Heat shock protein 27; Neoplasia.

Introduction

Ovarian cancer is the eighth most common cancer in women. According to GLOBOCAN 295.414 new cases were estimated in 2018, and on average 184.799 women die annually from the disease [1]. There are multiple histological types with the epithelial being the most common variant and therefore attributed the highest morbidity and mortality [2]. Epithelial tumors constitute approximately 90% of all malignancies of the ovary and occur in 75% of cases in advanced stages [3].

In the constant search for tools to improve the survival prognosis of these patients as tumor markers of early expression and better specificity, heat shock proteins emerge as molecules that could behave as independent prognostic markers of survival in patients with ovarian cancer [4, 5]. These proteins are evolutionarily conserved. They have ubiquitous function in addition to other functions in cellular homeostasis that include the regulation of gene expression, DNA replication, translation signals, differentiation, apoptosis and senescence and cellular immortalization [6, 7]. They are also involved in cell protection against hypoxia, ischemia or heat shock damage [8].

Hsp 27 is overexpressed in several types of cancer and is related to poor prognosis and resistance to chemotherapy [8]. Recently, it has been shown that the translocation of intracellular proteins across cytoplasmic membranes plays an important role in terms of tumor aggressiveness, invasiveness and metastases which suggests that the location of the protein is associated with an abnormal reprogramming of the cell toward a tumor phenotype [8].

An increase in the expression of Hsp 27 has been found in ovarian cancer, but results are controversial, since its overexpression has been associated with a favorable and unfavorable prognosis in different studies [4, 9-11]. Considering the importance of the expression of this protein, the objective of the present study is to determine the expression of Hsp 27 through immunohistochemistry and its correlation with the clinical and histopathological characteristics of patients with ovarian cancer.

Materials and Methods

A cross-sectional study of patients diagnosed with ovarian carcinoma whose surgical specimens were stored at the pathology services of the San Jose and Infantil Unversitario de San Jose hospitals in Bogotá, Colombia. All participant patients were asked to sign an informed consent form for the use and analysis of the samples stored in the pathology department.

All clinical records of patients with a pathological diagnosis of ovarian cancer between 2013 and 2016 were reviewed. Exclusion criteria were: women with a history of

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Table 1. — *Patient demographics and clinical characteristics*

Characteristics	N = 31 (%)
Mean age (SD)	53.03 (12.51)
Mean Ca-125 levels (IQR)	616 (85-1328)
Personal history of breast cancer	0
Family history of cancer	10 (32.3)
Tobacco use	1 (3.2)
Mean age at menarche (SD)	12.3 (1.42)
Menopausal status N, (%)	14 (45.2)
Multiparous * N, (%)	22 (71)
Hormonal contraceptive use	3 (9.7)
Duration of use, < than 5 years	3 (9.7)
Breastfeeding †	20 (64.5)
Mean maternal age at first delivery (SD)	14.4 (11.5)
Use of hormone replacement therapy	0
Use of treatment for infertility	0
Complete cytoreduction (achieved in)	15 (48.4)
Optimal cytoreduction (achieved in)	18 (58.6)
FIGO Staging	
IA	5 (16.1)
IB	1 (3.2)
IC	4 (12.9)
IIB	2 (6.4)
IIIC	18 (58.1)
IVA	1 (3.23)

*More than one child; † More than 6 months

Table 2. — *Distribution of ovarian carcinoma by histopathologic characteristics*

Characteristics	N = 31 (%)
Histologic types	
Serous	15 (48.4)
Mucinous	3 (9.7)
Endometrioid	6 (19.4)
Clear-cell	3 (9.7)
Carcinosarcoma	0
Seromucinous	0
Undifferentiated carcinoma	0
Mixed carcionoma	1 (3.2)
Non-classifiable adenocarcinoma	3 (9.7)
Histologic Grade	
Well differentiated	3 (9.7)
Moderately differentiated	7 (22.6)
Poorly differentiated	1 (3.2)
Undifferentiated	0
Low –Grade	0
High- Grade	20 (64.5)
Lymph node clearance/dissection	18 (58.1)
Peritoneal implants	16 (51.6)
Capsule compromise	16 (51.6)
Unknown	
Widespread to other organs	14 (45.1)
Vascular space invasion	16 (51.6)
Lymphatic space invasion	14 (45.1)

antineoplastic therapy prior to surgery and metastatic tumors to the ovary. Clinical variables such as, age, smoking, age at menarche, multiparity, age of menopause, use of oral contraceptives and time of use, age of first birth, breastfeeding of 6 months or more, use of fertility therapies, use of hormone replacement therapy, personal history of breast cancer, family history of cancer, previous gynecological surgery, complete or optimal cytoreductions, FIGO stage and Ca-125 levels were reviewed. The histopathological variables analyzed were the type and histological stage, laterality of the tumor, capsule integrity and involvement, tumor extensions, compromise of adjacent tissues, vascular or lymphatic invasion, Hsp 27 expression in tumor cells and signal intensity. Missing data were not analyzed in this study.

Tissue samples from patients with ovarian carcinoma were obtained through surgical staging performed by the gynecological oncology group of the two hospitals. Paraffin blocks were taken from the processed specimens of the patients with the diagnosis in the database of the pathology services of both hospitals. Hematoxylin-Eosin slides were reviewed by two expert pathologists in order to choose the material with the highest percentage of tumor cells. The tissue blocks were then sliced and processed by immunohistochemistry. Tissue sections measuring 3 μM of each tumor were kept at 60°C for 2 hours, dewaxed by incubation with xylol for 10 minutes and rehydrated with ethanol in different grades. Heat-mediated antigen recovery was performed with EDTA 10X (Lab Vision™) at a 1/10 dilution in a "vaporizer" for 50 minutes. Next, the paraffin blocks were immersed in a 1/10 hydrogen peroxide solution (Hydrogen Peroxide Block UltraVision) for 10 minutes at room temperature. They were incubated with primary Anti- Hsp 27 (antibody [G3.1] (abcam2790®) at a 1/500 dilution for 2 hours at room temperature in a wet chamber. After washing twice with TBS 1/10 (Dako Tris-Buffered Saline, pH 7.6), the slides were incubated with biotinylated secondary antibody (Primary Antibody Amplifier) for 10 minutes at room temperature. The sample was then buffered with DBA for color development and the slides were counterstained with hematoxylin for two minutes. Negative controls were performed by omission of the primary antibody. Positive control slides included sections of melanoma specimens.

The reading was done with the use of a light microscope. All observations were made with the 40x objective by two independent observers and the staining pattern was classified semi-quantitatively as follows: (-) negative staining; (+) less than 10 % staining; (++) 10-50 % staining; (+++) > 50% tissue with staining. Grade of staining intensity was classified as weak (+), moderate (++) and strong (+++) [12] (Figure 1). Excel 2010 software was used to record data. Qualitative variables were analyzed by calculating ab-

Table 3. — *Hsp 27 expression in the study population*

	N = 31 (%)
Expression	
Negative	0
(+)	5 (16.1)
(++)	9 (29.03)
(+++)	17 (54.8)
Intensity	
Negative	0
(+)	5 (16.13)
(++)	13 (41.9)
(+++)	13 (41.9)
Location	
Membrane	0
Cytoplasmic membrane	25 (80.6)
Cytoplasm	6 (19.3)

solute and relative frequencies; quantitative variables were expressed in central and dispersion tendency measures in STATA 13. The study was approved by the Research and Ethics Committee of the San Jose Hospital.

Results

Hsp 27 expression was assessed by immunohistochemistry in 31 patients. Demographic characteristics of our study population are summarized in Table 1. The average age was 53 years, Ca-125 level was greater than 600. More than 70% of the patients were multiparous with a history of breastfeeding in more than 60%. Forty-five percent (14/31) were menopausal patients at the time of diagnosis. Complete cytoreductions were achieved in 48.4% (15/31) and optimal cytoreductions in 58.6% (18/31) of cases. The most frequently diagnosed FIGO stage was IIIC (58,1%).

The histological type most frequently diagnosed in our population was ovarian serous carcinomas 48.1% (15/31), followed by endometrioid carcinomas 19.3% (6/31) and clear cell 9.7% (3/31) and mucinous carcinomas 9.7% (3/31). A lymph node clearance was performed in 58.1% (18/31) of the cases. Tumor implants, capsule involvement and vascular invasion were identified in 51.6% (16/31), and in 45.1% (14/31) other organ involvement and lymphatic invasion were observed (Table 2).

The expression of Hsp 27 was positive (+++, ++ or +) in 31 cases showing different grades of intensity. The intensity of Hsp 27 staining varied between different tumors and was cytoplasmic and membranous staining in 80.6% and cytoplasmic only in 19.3%. Five cases showed weak staining and 13 cases moderate and strong staining (Figure 1). Fifty-four percent (17/31) of the cases presented more that 50 % of positivity of Hsp 27 protein in the tumor cells, 29 % (9/31) presented positivity in 10 to 50% of the tumor cells and 16% of the cases (5/31) presented positivity in less than 10% of the tumor cells (Table 3).

The expression of Hsp 27 with greater intensity was identified in 54% (17/31) of the 31 cases evaluated, predominantly in women over 50 years old, and advanced FIGO stages between III/IV. The histological type that most frequently marked positivity for Hsp 27 was the serous type showing strong intensity in 80% (12/15) of cases. The prevailing histological grade represented was the high-grade in 20 patients, 65% (13/20) with strong intensity. In patients with high Ca-125 level the intensity of expression of Hsp 27 was also high. Of the 15 patients who underwent a complete cytoreduction procedure, 46 % (7/15) presented strong Hsp 27 expression, and of the 18 patients who underwent optimal cytoreduction 44% (8 cases) presented Hsp 27 expression with strong intensity.

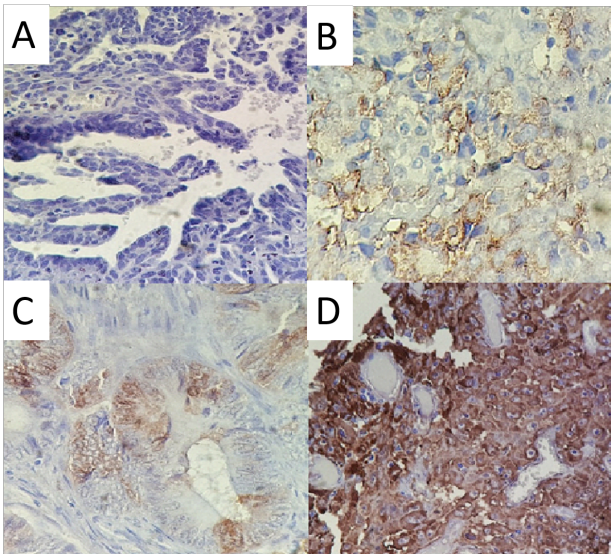

Figure 1. - Hsp 27 staining patterns. Hsp 27 protein expression levels by immunohistochemistry assay. A. Negative. B. Weakly positive (1+), mild staining (less than 10% of tumor cells), C. Moderately positive (2+) moderate staining (from 10 to 50% of tumor cells, and D. Strongly positive (3+) staining of more than 50% of tumor cells. These photos were taken using the 40 × objective lens of a light microscope.

Discussion

Heat shock proteins play a role in multiple cell functions; the main one being protein synthesis [13]. In addition, they participate in important processes such as protein folding, secretion, intracellular trafficking of proteins and coping with protein degradation and regulation of transcription factors for which their expression and activity has been related with cell survival [14].

The association between expression and adverse or favorable outcomes in different types of cancer has been widely reported in the literature [8, 9, 15]. Those with favorable results have been associated with expression and lower tumor grade, less aggressive histological subtypes and early stages of the disease [4], while those which show

Table 4. — *Hsp 27 expression according to prognosis variables*

Characteristics	Number of patients	Hsp 27 (+)	Hsp 27 (++)	Hsp 27 (+++)
Total cases	31	5	9	17
AGE				
< or equal to 50 years	12	3	4	5
> or equal to 50 years	19	2	5	11
FIGO Staging				
I/II	12	3	4	5
III/IV	19	2	5	12
Cytoreduction				
Complete				
Yes	15	3	5	7
No	16	2	4	10
Optimal				
Yes	18	4	6	8
No	13	1	3	9
Histologic Type				
Serous	15	0	3	12
Mucinous	3	1	1	1
Endometrioid	6	2	2	2
Clear-cell	3	1	2	0
Carcinosarcoma	0	0	0	0
Seromucinous	0	0	0	0
Undifferentiated carcinoma	0	0	0	0
Mixed Carcinoma	1	1	0	0
Non-classifiable adenocarcinoma	3	0	1	2
Histologic Grade				
Well differentiated	3	1	1	1
Moderately differentiated	7	3	2	2
Poorly differentiated	1	0	0	1
High-Grade	20	1	6	13
Low-Grade	0	0	0	0
Contraceptive use				
Yes	3	1	0	3
No	28	4	9	15
Menopausal status				
Yes	14	2	4	8
No	17	3	7	9
Lactancy				
Yes	20	3	6	11
No	11	2	3	6
Family history of cancer				
Yes	10	2	4	4
No	21	3	5	13
Specimen integrity				
Yes	26	4	8	14
No	5	1	1	3
Median Ca-125 level (IQR)		226 (38-923)	217 (85-489)	1090 (423-1367)

a negative association do so predominantly with the role of chemoresistance [16]. Hsps have been evaluated in patients with colon cancer [16, 17] where Choi *et al*. [17] studied a 20 patient population, finding 16 patients showing Hsp 27 expression associated with a 10 times increased resistance to Irinotecan compared with cases showing no expression and was postulated as a predictor of poor prognosis. In contrast, Suzuki *et al*. [18] in an evaluation of samples from 37 patients with oral squamous cell carcinoma found that over-expression was associated with a good prognosis, as they presented a higher tumor grade and less lymph node involvement regardless of the tumor stage at a follow-up of 60 months.

Hsp 27 protein has also been detected in endometrium and dysplastic cervical tissue [19, 20]. Dobo *et al*. [20], found 100% Hsp 27 expression in CIN I, 98.11% in CIN II and 98.1% in CIN III, in a population of 204 patients. In patients with endometrial cancer, Hsp 27 expression has been related with well-differentiated endometrioid tumors with less myometrial invasion, lympho-vascular involvement and FIGO stage [10].

In ovarian cancer, as in other neoplasms, the results remain controversial. There are studies that relate Hsp 27 to a good prognosis and others to a poor one. Arts *et al*. [9] evaluated the prognostic value of Hsp 27 expression in 77 patients by immunohistochemistry assay, finding that a low expression correlated with a lower FIGO stage, early age at onset, less than 1 liter ascites and better response to first line chemotherapy, as well as, greater progression-free survival at 60 months. Likewise, Song *et al*. [21] demonstrated an association with a higher FIGO stage in 73 patients. Other authors relate low expression with shorter survival [4 11]. For example, Geisler *et al*. considered Hsp 27 expression as an independent prognostic marker in a population of 99 patients [4], they found an average age of 62 years, the most frequent histology pattern was serous papillary carcinoma and tumor grade 3, in 77 of the 93 patients, and FIGO stage III in 57 patients. Optimal cytoreduction was achieved in 70 of the 93 patients. These results show that the most important prognostic factors were the cytoreduction level, FIGO stage and the weak expression of Hsp 27 achieving statistical significance in the three cases with an overall survival of 2 years. In our study population the most frequent histological subtype was high-grade serous papillary carcinoma and FIGO III C stage, with optimal cytoreduction in a lower percentage. On the other hand, peritoneal tumor implants were present in more than half of the study population and this is directly associated with advanced stages of the disease with worse prognosis [22]. Zhao *et al*. [23], found a correlation of Hsp 27 overexpression with risk factors and peritoneal metastases.

In this study, when classifying the patients with stronger Hsp 27 expression and other ovarian cancer prognostic variables, the authors found a greater percentage of expression in patients with a more advanced FIGO stage, as well as, in those patients in whom an optimal or complete cytoreduction could not be achieved. Another important feature of our results is a greater Hsp 27 expression in recognized adverse histopathology serotypes, as well as elevated levels of Ca-125.

Membrane expression has been associated with increased resistance to lysis. We observed this feature in 80.6% [25] of our population. Langdon *et al*. associated intense expression of Hsp 27 with chemoresistance and disease progression during treatment [24]. Song *et al*, not only found an increase in chemoresistance, but also demonstrated that silencing Hsp 27 expression improves chemosensitivity [21]. Lu *et al* evidenced that Hsp 27 exert its chemoresistance role by inhibiting p21 transferring from the nucleus to the plasma through the activation of a phosphorylated-Akt pathway [26].

The follow-up of our patients is necessary to determine Hsp 27 as a prognostic marker in our study population, based on their response to treatment, tumor progression and disease-free period. We did not find significant differences in the distribution of characteristics such as menopausal status, use of oral contraceptives and breastfeeding.

There are contradictory results regarding the presence of anti-Hsp 27 antibodies in the sera of women with ovarian cancer. Olejek *et al*. determined the concentrations of anti-Hsp 27 antibodies in 158 patients and found they were significantly higher with respect to the control group without cancer [27]. These findings indicate that a pre-surgical measurement of this protein may help the clinician to make decisions regarding the surgical management and stratification of patients.

This study is limited by its sample size therefore additional studies with larger sample sizes and prospective studies are needed to be able to establish an association between Hsp 27 expression with overall survival, progression-free survival, relapse, and chemoresistance in our population.

Conclusions

Ovarian cancer is a poorly understood pathology and investigating on the biological behavior will allow a better understanding for the development of therapeutic targets based on the molecular profile in order to provide better therapeutic options and improve survival in our patients.

The tendency evidenced in our sample was the presence of a stronger Hsp 27 expression in patients with advanced FIGO stage, histological variables with more aggressive behavior, and in those patients in whom optimal or complete cytoreduction could not be achieved.

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Conflict of Interests

The authors declare that there is no conflict of interests related to the topic and results of this study.

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