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ORIGINAL ARTICLE

Osteopontin as a Prognostic Indicator in Grading of Ovarian Epithelial Tumors

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ABSTRACT

Aim: To determine if osteopontin expression by immunohistochemistry (IHC) can correlate with histological type and grade of epithelial ovarian cancer.

Materials and methods: The present work has been carried out at department of pathology, of a reputed medical college in Belgaum district of Karnataka state. The study is carried out for a period of 18 months for data collection, evaluation of the marker and data analysis. All consecutive specimens of ovarian tumors are included in the study. The study included 55 epithelial ovarian tumors and these are analyzed histopathologically. In all the cases, osteopontin expression has been studied with IHC on paraffin slides.

Results: This study included 41 (74.5%) benign tumors and 14 (25.5%) malignant tumors. High grade (grade III) was common in serous carcinomas than in other histological types. Fisher's exact test p-value < 0.001 was significant for expression of osteopontin and all the malignant ovarian epithelial tumors expressed osteopontin by IHC procedure on paraffin tissue sections. All high-grade epithelial ovarian tumors showed increased expression of osteopontin of +++ and low-grade tumors expressed +/++osteopontin.

Conclusion: The osteopontin expression was seen in all the malignant epithelial ovarian cancers and the osteopontin expression was significantly higher in high-grade epithelial ovarian cancers than low-grade epithelial ovarian cancers.

Keywords: Grading, Osteopontin expression, Ovarian epithelial tumors, Prognostic indicators.

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INTRODUCTION

As per statistical review of cancer by Miller et al (1993), from National Cancer Institute, Bethesda, epithelial ovarian carcinomas (EOC) are the fifth most common cancer following breast, lung, colorectum and endometrium and fourth leading cause of death among women.[1]

According to Cannistra SA (2004), the incidence of ovarian cancer is 1.4%.[2] The benign epithelial ovarian tumors are common in the reproductive age group. Whereas, the malignant epithelial ovarian tumors are common after the age of 40.

Osteopontin is a marker which is expressed in various human cancers and associated with tumor progression, invasion and metastasis in many ways. Osteopontin, a phosphorylated glycoprotein secreted in the extracellular matrix, was discovered by Senger et al in an epithelial cell line undergoing malignant transformation in 1979. Osteopontin mediates the molecular mechanisms that determine metastatic spread, such as prevention of apoptosis, extracellular matrix proteolysis and remodeling, cell migration and neovascularization.[3]

There are many studies with immunolocalization of osteopontin with varying reports in malignant and borderline ovarian tumors.[4,5]

Hence, the present study is undertaken to know if osteopontin expression by immunohistochemistry (IHC) can correlate with histological type and grade and further ovarian cancer and aggressiveness of the malignant ovarian tumor can be predicted.

MATERIALS AND METHODS

The present work has been carried out at department of pathology, of a reputed medical college in Belgaum district of Karnataka state. Before starting the work, the permission from the institutional ethic committee is obtained. The study is carried out for a period of 18 months for data collection, evaluation of the marker and data analysis. The study design is a hospital based cross-sectional study and has been carried out on specimens of ovarian tumors. All consecutive specimens of ovarian tumors are included in the study.

In inclusion and exclusion criteria, all the patients suspected of epithelial ovarian tumor and those who underwent ovariotomy are included in the study. All the ovarian tumors apart from above group (germ cell tumors and sex cord-stromal tumors) are excluded from the study.

The sections from tumor representative areas are routinely processed for paraffin sectioning and cut into several 3 to 4 μm thick sections and stained for conventional H&E staining for histopathological study. In all these cases the type of ovarian tumor, grade of tumor and possible stage is studied. The slides are studied for type of ovarian tumor. They are categorized as benign, borderline and malignant tumors.[6] Histological grading of malignant tumors is assessed according to the universal grading system proposed by Silverberg.[7]

In all the cases, osteopontin expression has been studied with IHC on paraffin slides. The tissues are fixed in 10% formalin for 24 hours at room temperature. Four micron sections on silane coated glass slides are taken. Osteopontin antibody from NeoMarkers, Fremont, CA (RB-9097, Ready-to-use) has been used. The antibody is stored at 2 to 6°C. Positive and negative controls are used while doing the procedure.

The expression of osteopontin has been examined by a pathologist who is blinded regarding the type and grade of tumor and clinical findings of the patient. The osteopontin immunoreactivity has been evaluated in five different areas of each slide to classify into three groups by osteopontin expression intensity: negative, trace positive +, moderate or focal strong positive for ++ and strong positive for +++.

RESULTS

The present study included 55 epithelial ovarian tumors. This study included 41 (74.5%) benign tumors and 14 (25.5%) malignant tumors.

Table 1: Histological types of primary epithelial ovarian tumor

Type	*Incidence*	*Percentage*
Benign		
Serous cyst adenoma	28	50.90
Mucinous cyst adenoma	12	21.82
Adenofibroma		
Brenner tumor		
Mixed seromucinous adenoma	1	1.82
Borderline malignant		
Serous and mucinous cyst adenomas	2	3.64
Malignant		
Papillary serous cyst adenocarcinoma	5	9.09
Mucinous cystadenocarcinoma	5	9.09
Transitional cell carcinoma	2	3.64

The commonest benign ovarian tumor was serous cyst adenoma followed by mucinous cyst adenoma. In malignant tumors, serous and mucinous malignant tumors were five each. There were two borderline tumors (one serous and one mucinous) (Table 1).

High grade (grade III) was common in serous carcinomas than in other histological types (Table 2). Fisher's exact test p-value <0.001 was significant for expression of osteopontin in the above groups and all the malignant ovarian epithelial tumors expressed osteopontin by IHC procedure on paraffin tissue sections (Table 3).

All high-grade epithelial ovarian tumors showed increased expression of osteopontin of +++ and low-grade tumors expressed +/++ osteopontin (Figs 1 to 3).

DISCUSSION

Ovarian cancer is the most common cancer and is the leading cause of cancer deaths among women worldwide.[8]

In most of the population-based cancer registries in India, ovarian cancer is the third leading site of cancer among women, trailing behind cervix and breast cancer. The age-adjusted incidence rates of ovarian cancer vary between 5.4 and 8.0 per 100,000 population in different parts of the country.[9] Ovarian cancer has the worst prognosis among all gynecological malignancies. The overall 5-year survival is approximately 45%, primarily due to the late stage at diagnosis of the disease.[10]

Epithelial ovarian tumors have significant mortality. A sensitive marker is required to correlate grade, stage and as a prognostic indicator. Prognosis depends upon

Table 2: Histological type and grade of epithelial ovarian cancers

Type	*Grade*		*Percentage*
Papillary serous cystadenocarcinoma	Grade I	1	20
	Grade II		
	Grade III	4	80
Mucinous cystadenocarcinoma	Grade I	3	60
	Grade II	2	40
	Grade III		
Transitional cell carcinoma	Grade I		
	Grade II	2	100
	Grade III		

Table 3: Osteopontin expression and histological grade

		Histological grade		
		High grade	*Low grade*	*Total*
Osteopontin expression	Expressed	+++ in 4 cases	+/++ in 10 cases	14
	Normal	0	0	0
	Total	4	10	14

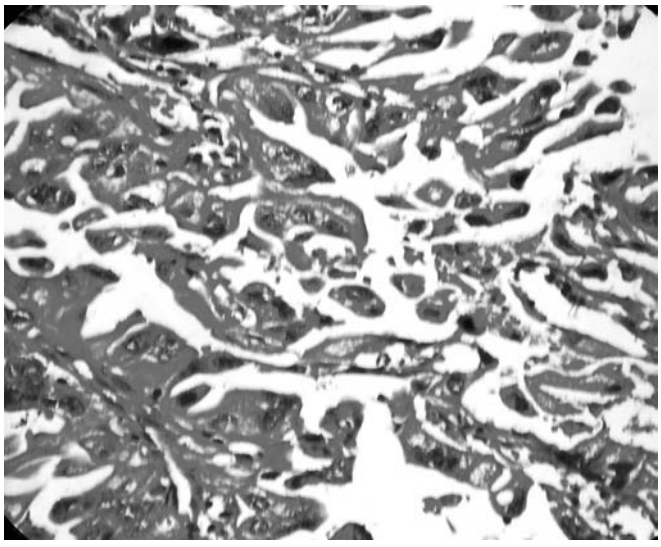

Fig. 1: Malignant serous tumor with papillae showing anaplastic features (H&E—200×)

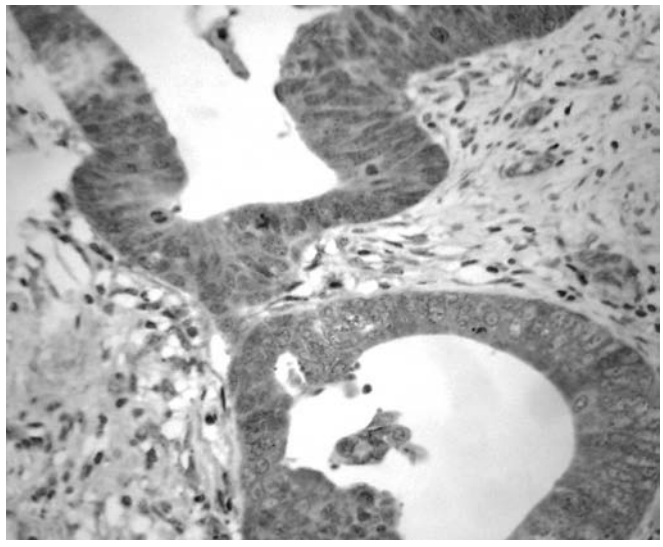

Fig. 2: Focal positivity (++) for osteopontin in malignant mucinous ovarian tumor (IHC—200×)

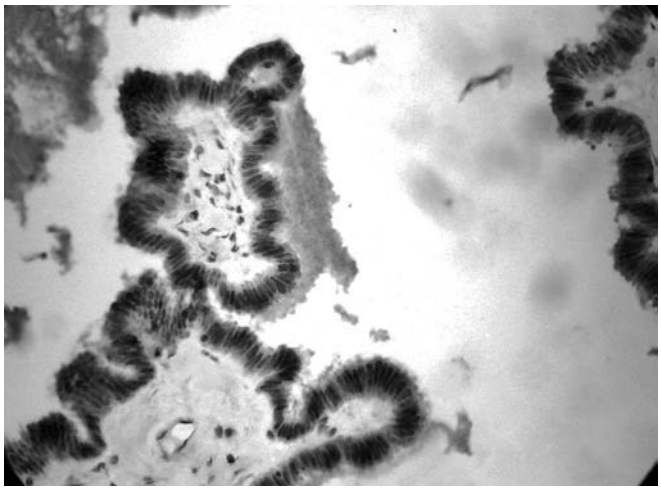

Fig. 3: Strong positivity (+++) for osteopontin in malignant serous ovarian tumor (IHC—200×)

type of ovarian tumor, grade of histological type and stage of the tumor.

In the present study, the osteopontin marker expression is studied in relation, nature of tumor (benign, borderline, malignant), histological type and grade of the tumor. Out of 55 epithelial ovarian tumors, osteopontin was expressed in all 14 malignant ovarian epithelial tumors including borderline tumors. In four papillary serous carcinomas of high-grade nature osteopontin expression was +++, rest other malignant tumors including mucinous carcinomas, TCC, borderline tumors osteopontin expression was +/++ expression. Benign tumors did not express osteopontin positivity. Similar findings with higher expression is reported by Kim JH et al and Hong Bao et al.[4,11]

Osteopontin was associated with increased grade and thus this is prognostic marker to assess the outcome of the patient.

SUMMARY

The osteopontin expression was seen in all the malignant epithelial ovarian cancers.

The osteopontin expression was significantly higher in high-grade epithelial ovarian cancers than low-grade epithelial ovarian cancers.

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