Original Research Paper

Volume-9 | Issue-2 | February-2019 | PRINT ISSN - 2249-555X

Pathology

STUDY OF HISTOPATHOLOGICAL DIAGNOSIS, CLINICORADIOLOGICAL FINDINGS AND IMPORTANCE OF IMMUNOHISTOCHEMISTRY IN SURFACE EPITHELIAL OVARIAN TUMORS: A STUDY OF 100 CASES

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ABSTRACT Ovarian Cancer is one of the leading cancers in Indian women. In India, ovarian cancer is the third leading site of cancer among women, trailing behind cervix and breast cancer. A detailed clinical history, abdomen and pelvic examinations, determination of CA-125 levels and ultrasonography are necessary steps in making diagnosis.

Use of immunohistochemistry (IHC) has significant role in diagnostic ovarian pathology in recent years. In the Surface Epithelial Tumors the most common problem is its discernment from metastasis. The use of different cytokeratins, primarily CK7 and CK20, as well as Cdx-2, beta-catenin, and P504S is helpful in differentiating between metastatic adenocarcinoma, particularly of colorectal origin.

The present study aimed to compare the Clinicoradiological findings and its correlation with Histopathological diagnosis in Surface Epithelial Ovarian Tumors & utility of Immunohistochemistry in diagnosis of Surface Epithelial Ovarian Tumors.

A total of 100 cases histopathologically diagnosed as surface epithelial ovarian tumors on paraffin section were included in the present study and it concluded that Pre-operative Serum CA 125 levels and Radiological Findings have Limited Role in Categorizing Ovarian Tumors. Thorough Sampling & Careful Histopathological Examination is Most Helpful in typing & subtyping of Tumor.

Immunohistochemistry plays an important role in Differentiating Primary Ovarian Epithelial Tumors from Metastatic Tumors and in Histologic Subtyping of the Tumors in Poorly Differentiated Cases. It should be interpreted in view of Clinical History, Radiological Findings and Histomorphological Findings.

KEYWORDS : Immunohistochemistry, Surface epithelial Tumors, Ovarian Tumors

INTRODUCTION

Ovarian Cancer is one of the leading cancers in Indian women.[1] 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.[2] The overall 5-year survival is approximately 45%, primarily due to the late stage at diagnosis of the disease.[3]

Ovarian tumors ordinarily produces no distinctive symptoms, as a result most tumors metastasize, or spread to other abdominal organs before they are diagnosed.[4] A detailed clinical history, abdomen and pelvic examinations, determination of CA-125 levels and ultrasonography are necessary steps in making diagnosis.

Recent years have witnessed significant development in the use of immunohistochemistry (IHC) in diagnostic ovarian pathology. In the surface epithelial tumors the most common problem is its discernment from metastasis. The use of different cytokeratins, primarily CK7 and CK20, as well as Cdx-2, beta-catenin, and P504S is helpful in differentiating between metastatic adenocarcinoma, particularly of colorectal origin.[5]

The present study aimed

- To study the Clinicoradiological findings and its correlation with Histopathological diagnosis in Surface Epithelial Ovarian Tumors.
- To study the role of Immunohistochemistry in diagnosis of Surface Epithelial Ovarian Tumors.

MATERIALS & METHOD

The study was conducted in the department of pathology over a period of 2 years.

A total of 100 cases histopathologically diagnosed as surface epithelial ovarian tumors on paraffin section were included in the study.

Ovarian tumors other than Surface Epithelial Tumors like Germ Cell tumors, Sex Cord Stromal Tumors and Metastatic Ovarian Tumors were excluded.

CLINICAL WORK UP

- Clinical findings of the patients were recorded: Name, age and presenting symptoms and signs, pelvic and abdominal examination.
- Radiological investigations including USG abdomen & CT scan
- Tumor markers in blood were recorded whenever done.

HISTOPATHOLOGY

- All specimens were fixed in 10% buffered formalin. Complete gross examination was done with special emphasis on Weight of the specimen, Ovarian size, Capsule status in details, Tumor size; External appearance - solid/cystic, smooth/papillary; Content of cystic masses- mucinous, serous and Presence of haemorrhage/necrosis/calcification.
- Representative sections are taken, processed in a tissue processor and then embedded in paraffin wax. Multiple 4-5 micron sections were cut using rotary microtome and are mounted on the glass slide for hematoxylin and eosin stain. The slides are mounted with DPX and then examined under microscope.
- Immunohistochemistry was done wherever required to reach the diagnosis. It was performed on paraffin sections by "VENTANA BENCHMARK XT" & Auto stainer on tissue blocks using DAB detection kit.

The distribution of cases was done according to Age, Radiology findings, Size of the tumor, Morphology on paraffin section, Preoperative CA125 levels and Positive Ascitic fluid cytology.

OBSERVATION & RESULTS

This study was conducted in the department of pathology for the period of two years. A total of 204 consecutive patients of adnexal mass underwent laparotomy and intra-op frozen section evaluation was requested. Out of 204 cases, 104 cases were excluded from the study, of which 15 were metastatic ovarian tumors, 40 were non-neoplastic masses, 24 were sex cord stromal tumour and 25 cases were germ cell tumours. Thus 100 cases were included in the study and statistical analysis of the data was done as below:

The mean age of the patient with malignant histology (50 years) was older than the patients with borderline (38.6 years) or benign tumours (46 years). (Table 1)

Serum CA125 levels were available in 84 of 100 cases. The mean serum levels of CA-125 were statistically raised in the patients with

malignant tumours (352.1 U/ml) as compared to benign (38.62U/ml) and borderline histology (151.9 U/ml). (Table 2)

The mean tumour size of the patients with benign histology was 20 cms (6.5-40cms) as compared to 13.4 cms (4.3-25cms) in patients with borderline and 16 cms (3-32cms) in patients with malignant histology.

In our study radiological investigations were available in all the 100 cases. On USG, malignant tumours were identified as solid or complex solid cystic masses. All the benign epithelial tumours were cystic with internal septations except one case of Brenner tumour which had solid appearance on USG. Most of the borderline tumours showed varying appearance on USG. Similarly, on gross inspection, of the 34 adnexal mass with benign histology, 29 (85.3%) tumours were cystic, 4(11.8%) tumours were solid-cystic and 1 tumour had solid consistency. 7(70%) and 3(30%) tumours with borderline histology had cystic and solid-cystic consistency respectively. No tumour with borderline histology had solid consistency. Of 56 tumours with malignant histology maximum number of 26 (46.4%) tumours had solid-cystic consistency followed by 20 (35.7%) tumours with solid and 10 (17.9%) tumours with cystic consistency.

Ascitic fluid was sent for cytological examination in 92 out of 100 cases, out of which 8 cases with malignant histology on paraffin section showed metastasis from the primary surface epithelial tumor.

Of the 100 patients with surface epithelial ovarian tumors in the study, 34% had benign, 10% had borderline and 56% had malignant histology at the paraffin section. Maximum tumors with serous histology on paraffin section were malignant (60.5%) however most of the tumours with mucinous histology were benign (69%). The tumours were further subtyped histopathologically on paraffin section. (Table 3)

Table-1 Distribution According to age of patients

Age (Years)	Final histopathology (no. of cases)			Total
	Benign	Borderline	Malignant	
<20	0	1	0	1
21-30	7	3	4	14
31-40	6	2	12	20
41-50	9	5	13	27
51-60	5	0	17	22
>60	6	0	10	16
Total	34	10	56	100
Mean (Years)	46	38	50	-

Table 2 : Preoperative CA 125 levels

CA-125 (U/ml)	Benign	Borderline	Malignant
Normal (0-35)	19	2	8
< 100	5	2	12
100-200	3	1	12
200-400	0	3	5
400-1000	0	0	8
>1000	0	0	4
Total	27	8	49
Mean (U/ml)	38.62	151.9	352.1

Table 3: Subtype of Tumors on paraffin section

Subtype of Tumor	Benign	Borderline	Malignant	Total
Serous	6	7	29	42
Mucinous	26	3	14	43
Endometrioid	-	-	8	8
Brenner	1	-	-	1
Seromucinous	-	-	4	4
Adenocarcinoma, Unspecified	1	-	-	1
Adenocarcinoma, Non mucinous	-	-	1	1
Total	34	10	56	100

DISSCUSION

CA-125 has an established role in monitoring treatment and detecting recurrence of ovarian cancer and has been advocated as a prognostic marker for advanced ovarian cancer. Serum levels of CA-125 are believed to correlate with the volume of disease and elevated serum CA125 levels can be found in 50% of patients with disease confined to the ovaries. Only one study claims that CA-125 has prognostic significance for stage I ovarian cancer.[6] In the present study majority of the patient (56%) operated for the adnexal mass were diagnosed as malignant tumours on paraffin section.

The mean age (50 years) and the mean CA-125 (352.1 U/ml) levels were significantly higher in the patients diagnosed of having malignant tumours on paraffin section. This co-relates with most of the available literature regarding the adnexal mass. In a pre-operative series studying the prediction of ovarian malignancy by serum CA-125 levels by Bejapibal et.al, 35 U/ml was taken as a cut off value and sensitivity, specificity and accuracy of CA-125 levels were 83.1%, 39.3% and 60.8%.[7] However in our study on univariate analysis CA-125 levels did not significantly affect the rate of discordance on frozen section.(p=0.655)

The mean tumour size (20 cm) was higher in patients with benign adnexal masses.

Pre-operative ascitic fluid cytology is an integral part of staging surgery in ovarian cancer (Sneige et al.).[8] Ascitic fluid cytology showed definitive metastasis in eight (8/56,14.3%) patients with malignant histology in our study. However most of the patients with malignant histology (n=48, 85.7%) had negative ascitic fluid cytology. None of the patients with benign or borderline epithelial tumours showed positive cytological analysis. Thus ascites can be considered as a good predictor of malignancy in our study similar to a retrospective study by Gunther et al of 125 ovarian tumours.[9]

The distributions of histological pattern in benign, malignant and borderline tumours were comparable with the present available literature. Most of the tumours of mucinous pattern were benign in nature however most of the tumours of the serous type were malignant in nature. Similarly, most of the tumours of clear cell and endometrioid patterns were malignant in nature. (Figure 1,2,3) There was a single case of mixed pattern (serous + mucinous) of tumour histology which was malignant in nature. (Figure 4)

Recent years have witnessed significant development in the use of immunohistochemistry (IHC) in diagnostic ovarian pathology. In the surface epithelial tumors the most common problem is its discernment from metastasis.

CK7 and CA125 are positive in primary ovarian surface epithelial tumours with WT1 usually positive in serous carcinomas. CEA is usually positive in metastatic gastrointestinal tumors. About 40 % of primary ovarian tumors show expression for ER and PR. So ER and PR alone cannot differentiate between primary ovarian tumours from metastatic breast carcinomas. In this situation, GCDFP-15 play an important role to rule out metastasis from breast.

Panel which is used to differentiate primary endometrioid adenocarcinoma from metastatic colonic carcinoma is: CK7, CK20, ER, PR, CA125 and Cdx2. Primary endometrioid ovarian carcinomas are positive for CA125, CK7, ER, PR but usually negative for CK 20 and Cdx2.

A panel of CK7, CA125, CK20 and Cdx2 is used to differentiate between primary mucinous and metastatic colon carcinoma. Metastatic large intestinal adenocarcinomas are positive for CK20 and cdx2 and negative for CK7 and CA125. Primary mucinous carcinomas of ovary are positive for CA125 and more diffusely positive for CK7 than CK20. Metastatic carcinomas from upper GIT and pancreaticobiliary origin are usually positive for CK7 and Cdx2 and negative for CK20 and Ca125.

However, these results are not absolute. There is lot of overlapping. Overlapping IHC results sometimes makes it difficult to differentiate between primary mucinous carcinomas of ovary and metastasis for GIT. Then, the combination of clinical history, light microscopy, Immunohistochemical and radiological parameters play an important role. [10-12]

CONCLUSION

- Pre-operative Serum CA 125 levels and Radiological Findings have Limited Role in Categorizing Ovarian Tumors as Benign, Borderline or Malignant.
- Thorough Sampling & Careful Histopathological Examination is Most Helpful in Categorizing Ovarian Tumors as Benign, Borderline and Malignant with Subtyping of Tumor.

Immunohistochemistry plays an important role in Differentiating Primary Ovarian Epithelial Tumors from Metastatic Tumors and in Histologic Subtyping of the Tumors in Poorly Differentiated Cases. It should be interpreted in view of Clinical History, Radiological Findings and Histomorphological Findings.

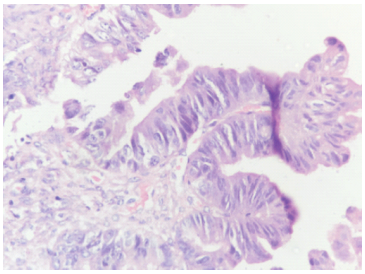

Fig 1- Borderline Mucinous Tumor: Paraffin Section- On High Power, The Lining Epithelium Shows Nuclear Crowding And Overlapping With Moderate Atypia. (H&E, 40x)

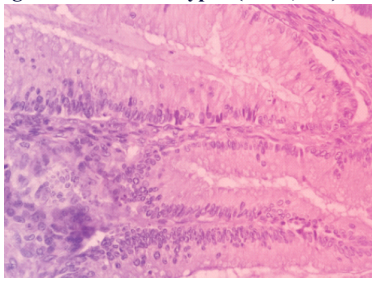

Fig 2- Mucinous Cystadenocarcinoma: Paraffin Section- On Further Magnification, Tumor Cells Have Basally Located Nucleus Showing Mild To Moderate Atypia And Abundant Amount Of Cytoplasm And Apical Mucin. (H&E, 40x)

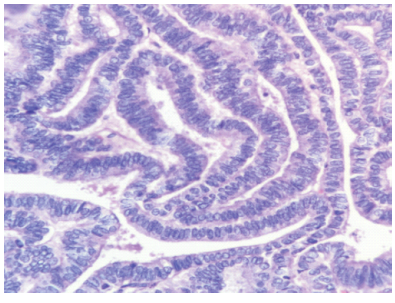

Fig 3- Endometrioid Adenocarcinoma: Paraffin Section Shows Tumor Cells With Elongated Nuclei, Moderate Atypia And Crowding. (H&E, 40x)

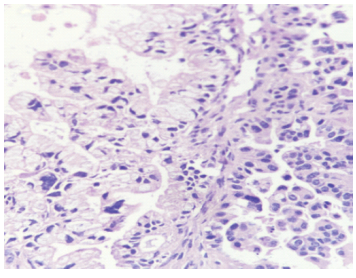

Fig 4: Paraffin Section Shows Mixed Epithelial Tumor With Area Of Both Serous Papillary Adenocarcinoma(on Right) And Mucinous Adenocarcinoma (on Left). (H&E, 40x)

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