Study of Histomorphological Spectrum of Mucinous Tumours of Ovary in a Tertiary Care Center in Thrissur, Kerala, India

Bharathi Udhayakumar[1], Lovely Jose[2], Freena Rose[3]

[1]Department of Pathology, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry, India.
[2, 3] Department of Pathology, Government Medical College, Thrissur, Kerala, India.

ABSTRACT

BACKGROUND

Mucinous ovarian tumours have various histomorphological patterns. Histopathological examination plays an important role in classifying ovarian tumours for prognosis and better treatment. Mucinous ovarian tumours are classified into benign cystadenomas, borderline mucinous tumours and malignant mucinous cystadenocarcinomas. This study was done to evaluate the distribution of ovarian tumours with respect to various parameters like age, laterality, size, loculation, stratification of cells, nuclear atypia, to study the gross morphological patterns of the various histopathological tumour types and evaluate the association between various parameters of ovarian tumours and risk of malignancy.

METHODS

A cross sectional study was conducted in the Department of Pathology, in a tertiary health care centre over a period of 5 years. The study includes cases of mucinous cystadenomas, borderline mucinous tumours and cystadenocarcinomas. Formalin fixed and paraffin embedded sections were reviewed. Data was collected & entered in Microsoft Office Excel 2007 sheet.

RESULTS

Among 32 cases of mucinous tumours studied 15 are mucinous cystadenomas, 10 are borderline tumours and 7 are cystadenocarcinomas. The mean age is 45 years. 1 case of mucinous cystadenocarcinoma showed bilateralism. 68.8 % of the tumours were more than 15 cms in size. 72 % of the tumours were multiloculated and 28 % were uniloculated. 78.1 % of the tumours have stratification of less than 4 cell-thickness. 46.9 % of tumours had no nuclear atypia, 31.2 % had mild atypia and 21.9 had severe nuclear atypia.

CONCLUSIONS

Benign cystadenomas were more common than malignant and borderline tumours. The mean age of presentation was 45 years.

KEYWORDS

Benign Cystadenomas, Mucinous Borderline Tumours, Mucinous Cystadenocarcinomas

Corresponding Author:
Dr. Lovely Jose,
Assistant Professor,
Government Medical College,
Thrissur, Kerala, India.
E-mail: bharathi25nov@gmail.com

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BACKGROUND

Ovarian neoplasms have been classically categorised depending on cell type (2). Tumours of ovary arise from one of the three ovarian components:

1. Surface epithelium derived from the coelomic epithelium.
2. The germ cells, which migrate to the ovary from the yolk sac and are pluripotent.
3. The stroma of the ovary, including the sex cord cells, which are forerunners of the endocrine apparatus of the postnatal ovary.

The surface epithelial tumours of ovary constitutes about 90 % of ovarian cancers.[1] The epithelial tumours of the ovary can be further divided into five major types depending on the cell type. These include serous, endometroid, mucinous, transitional and clear cell types. The first three represents the cell lining the mullerian duct (the endometrium, fallopian tube and cervical lining respectively).

Mucinous tumours are less common than serous tumours. They account for about 30 % of all ovarian neoplasm. They occur in middle adult life and are rare before puberty and menopause. Primary mucinous ovarian carcinomas are relatively rare and account for less than 5 % of the ovarian neoplasms.[2] Combination of different growth pattern with changing biologic potential of tumour cells produces a number of structural variants that are defined as benign, borderline and malignant

Benign Mucinous Tumours

Mucinous cystadenomas constitute about 13 % of benign ovarian epithelial neoplasm and consist of cystadenoma, cystadenofibroma and adenofibroma. The mean patient age is about 50 years. Mucinous cystadenomas are unilocular or multilocular tumours ranging from a few centimeters to over 30 cm. 95 % are unilateral. The capsule is thick, white with a smooth outer surface. The cysts contain thick gelatinous material. The vast majority are composed of glands and cysts lined by simple non-stratified mucinous epithelium resembling gastric foveolar-type epithelium or intestinal epithelium containing goblet cells.[3] The peripheral aspects of the cysts can form crypt-like structures where nuclei may appear reactive and exhibit mitotic activity, but the epithelium of the cysts lacks atypia. If epithelial proliferation is present, resembling atypical proliferative mucinous tumours (APMT) it must be limited to less than 10 %. Tumours composed predominantly of cystadenoma with less than 10 % of APMT are diagnosed as mucinous cystadenomas with focal proliferation.[4] Majority of tumours contain calcification which is speculated rather than psammomatous. Muciphages, pseudoxanthoma cells, and luteinized stromal cells are present in 40 - 50 % each.[3] Rarely, benign mucinous neoplasms are solid and adeno fibromatous; these are referred to as mucinous adenofibroma. Mucinous adenofibroma is composed of fibromatous stroma which may be, formed by latter component only.

Borderline Mucinous Tumours

Ovarian borderline (low malignant potential) tumours are a confusing group of neoplasms that do not fall either into benign or malignant category. Lack of proper understanding about the pathogenesis of these tumours makes it more controversial and confusing to gynaecologist and pathologist.[5] In 1901 Carl Abel described proliferating papillary cystadenomas on the borderline between benign and malignant growths.[6] The World Health Organization (WHO) applied the designation 'tumour of borderline malignancy' and added the synonym 'carcinoma of low malignant potential' (LMP) in their 1973 classification of ovarian tumours.[7] Over the past few years 'atypical proliferating tumour' has been used as an alternative designation for borderline tumours. According to the WHO definition, a borderline epithelial tumour lacks obvious invasion of the stroma and has mitotic activity and nuclear abnormalities intermediate between clearly benign and malignant tumours of a similar cell. Borderline mucinous tumours outnumber mucinous cystadenomas. They occur over a very wide age range (9 – 70 years). The mean age is 35 years.[8] 90 % of the tumours are unilateral. The surface of the ovary and the cysts are smooth in borderline mucinous tumours. However, some cysts have grossly visible papillae and thickened velvety surface. Solid areas and firm nodules may be seen. Such areas should be carefully sampled to rule out invasive carcinoma. Histologically borderline mucinous tumours are composed of varying sized glands and cysts. A filigree pattern of intraluminal short papillary in folding is common. Glands and cysts are lined by endocervical, goblet and gastric type epithelium. Neuroendocrine cells may also be seen. They have mild to moderate nuclear atypia. The cells lining the glands and cysts are stratified into less than 3 cells thick. William R Hart[9] in his review attempts to distinguish microinvasion of borderline epithelium from microinvasive carcinoma. In the former, the microinvasive tumour cells in the stroma and the epithelium lining the adjacent glands are of borderline-type epithelium with low-grade nuclear atypia. Individual microinvasive foci in mucinous tumours are less than 1 or 2 mm in most cases.[10,11]

Borderline mucinous tumours are stage I and have an excellent prognosis following surgical treatment with metastatic rates of 0 – 3 %. Survival rates for pure borderline tumours were 98 % at 5 years and 96 % at 10 years[8] Almost half of these tumours are treated by salpingo-oophorectomy.

Mucinous Cystadenocarcinomas

Mucinous cystadenocarcinomas are rare and comprise 2 - 3 % of ovarian neoplasms.[12] Mucinous tumours are often heterogeneous in composition and thorough pathologic examination with extensive sampling is required. They usually present as unilateral, multicystic mucus-containing tumours with smooth white capsules and have mean and median sizes of 18 - 22 cm. They may contain solid areas and foci of necrosis and haemorrhage. Microscopically destructive stromal infiltration by malignant mucinous epithelium is the key feature to establish a diagnosis of

invasive carcinoma. Recent studies have drawn interest in second pattern of invasion of mucinous tumours are confluent glandular or expansile pattern. In this pattern the glandular epithelium is markedly crowded, with little intervening stroma. They are interconnected in a confluent or labyrinthine pattern.[13] Mural nodules of "sarcoma-like" connective tissue, anaplastic carcinoma or sarcoma occasionally occur in mucinous tumours, usually borderline tumours or carcinomas of intestinal type.[14] Nuclear grade has been identified as an adverse prognostic feature.

METHODS

This is a prospective and retrospective study including all mucinous carcinomas and borderline mucinous tumours received during the period of study. Since about 15 times more number of mucinous cystadenomas were expected during the study period a sample of every 10th case of these tumours will be included so that the number will not be disproportionate to other types of mucinous tumours.

Inclusion Criteria

Primary mucinous tumours received in the pathology department of Govt. Medical College, Thrissur, were included in the study. Mucinous tumours diagnosed as borderline cystadenomas and mucinous cystadenocarcinomas will be studied from the material available in the department from the year 2010. Mucinous cystadenomas were included, sampling every 10th case as they form a large number.

Exclusion Criteria

Ovarian tumours e.g. other tumours considered to be of epithelial origin like serous, endometrioid, clear cell and Brenner tumour were excluded from the study.

The study included cases of primary mucinous ovarian tumours diagnosed in the pathology department of Govt. Medical College, Thrissur, from the year 2010 to 2015. The prospective study included all ovarian specimens that were received in the Department of Pathology, Government Medical College, Thrissur. For the retrospective study, the cases reported during Jan 2010 - Feb 2014 were taken from the records of the department and blocks were retrieved and relevant clinical history was noted from the requisition form. Specimens sent in 10 % formalin were routinely processed with paraffin embedding after adequate fixation. Paraffin sections, slides from fresh blocks and retrieved blocks were stained with haematoxylin and eosin (H & E). The slides were then reviewed microscopically in detail and tumours were classified according to the World Health Organization (WHO) classification of ovarian tumours.

Statistical Analysis

Data was collected & entered in Microsoft Office Excel 2007 sheet. This was then analysed using software SPSS version 19.0 The findings were presented in appropriate charts & tables.

RESULTS

The most common age group encountered in this study was between 41- 50 years. All malignant tumours were above 40 yrs. 46.8 % of the tumours were benign, 31.25 % were borderline and 21.95 % were malignant.

Age Group	Frequency	Percentage
11 - 20	3	9.4
21 - 30	5	15.6
31 - 40	4	12.5
41 - 50	8	25
51 - 60	6	18.8
> 60	6	18.8
Total	**32**	**100**

Table 1. Age Wise Distribution of Patients with Benign, Borderline and Malignant Ovarian Neoplasms

Grade	Frequency	Percentage
Benign	15	46.8
Borderline	10	31.25
Malignant	7	21.95
Total	**32**	**100**

Table 2. Grading of Mucinous Tumours of Ovary

Stratification	Frequency	Percentage
< 4 cell thickness	25	78.1
> 4 cell thickness	7	21.9

Table 3. Stratification of Cells

Nuclear Atypia	Frequency	Percentage
No atypia	15	46.9
Mild to moderate	10	31.2
Severe	7	21.9

Table 4. Nuclear Atypia

Figure 1a. Cut Section of Benign Mucinous Tumour Showing Loculations

Figure 1b. Cut Section of Borderline Mucinous Tumours Showing Solid and Cystic Areas with Smooth Inner Surface and Velvety Appearance

Figure 1c. Cut Section of Malignant Mucinous Tumours Showing Solid and Cystic Areas with Foci of Haemorrhage and Necrosis with Capsular Rupture

Figure 1. Gross Picture of Benign Cystadenomas, Borderline Mucinous Tumours and Malignant Cystadenocarcinomas

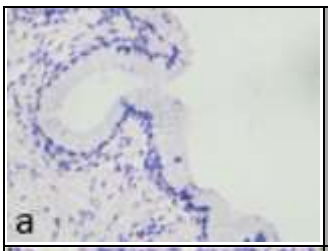

Figure 2a. Benign Mucinous Tumour Lined by a Single Layer of Endocervical Type H & E (40X)

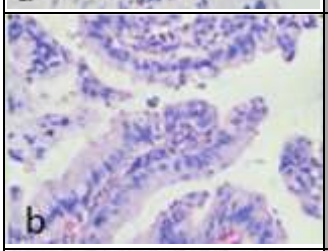

Figure 2b. Borderline Mucinous Tumour Showing Stratification (< Then 3 Cells Thick) and Mild Atypia of Lining Epithelium H & E (40X)

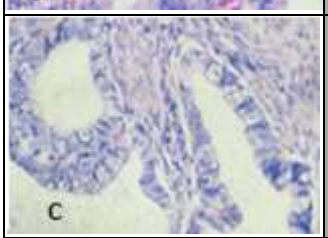

Figure 2c. Malignant Cystadenocarcinoma Showing Severe Nuclear Atypia, and Nuclear Stratification of > 4 Cells Thick (40X)

Figure 2. Microscopy of Benign Cystadenomas, Borderline Mucinous Tumours and Malignant Cystadenocarcinomas

Stratification of < 4 cell thickness was seen in 78.1 % which comprises benign and borderline category. 46.9 % of the tumours exhibited no atypia. 31.2 % of tumours showed mild to moderate atypia. 21.9 % of the tumours which exhibited severe atypia were all malignant tumours.

DISCUSSION

Ovarian tumours are one of the major health problems and their diagnosis can be difficult due to variety of pathologic conditions affecting the ovaries. Thus, knowledge of morphology and age-specific characteristics can help refine the diagnosis. The mean age of patients in the present study was 45. The most common age group was between 41 - 50 years. Benign tumours showed a wide age group ranging from 13 to 55 yrs. Borderline tumours also showed a wide variety of age group ranging from 20 - 40 yrs. The age of all malignant tumours are > 40 years. This is similar to that described in literature.

In the current study a total of 32 cases were included; among which 15 were benign cystadenomas, 10 cases were borderline tumours and 7 cases were mucinous cystadenocarcinomas. In the present study 97 % of cases were unilateral and one case was bilateral which is mucinous cystadenocarcinoma. Size of the tumour ranged from 4.5 cm to 27 cm. 68.8 % of cases had tumour size more than 15 cm. Yelmelyanova et al.[15] describes the cut off value of 13 cm in an algorithm to distinguish primary and secondary ovarian tumours and Alfred Kurtz et al.[16] found no relationship between size and malignancy by radiological study. In the present study 15 benign and 1 borderline tumour was less than 15 cm and all the malignant tumours were more than 15 cm. In the present study 28.1 % of tumours were uniloculated and 71.9 % were multiloculated. 11 benign, 8 borderline and 5 malignant tumours were multiloculated. 78.1 % of tumours were < 4 cell thickness and all belonged to benign and borderline category. William R Hart in his study stated that borderline mucinous tumours have stratification of not more than 3 cell thickness. In the present study 21.9 % of tumours showed nuclear stratification of > 4 cell thickness and all of which were exclusively seen in malignant tumours. William Watkin et al. in his study classified mucinous carcinomas based on the stratification. In his study tumours with more than 3 cell thickness were classified as malignant.[17]

Atypia of cell nucleus if present, was subjectively graded as no atypia, mild to moderate and severe. 46.9 % tumours had no atypia, 31.2 % had mild to moderate atypia and 21.9 % had severe atypia. Benign tumours showed no nuclear atypia. All borderline tumours showed mild to moderate nuclear atypia. This is similar to the study conducted by Hart R Novis et al. In the present study all the malignant tumours showed severe nuclear atypia which is similar to a study conducted by William Watkin et al. Nuclear grade has been identified as an adverse prognostic feature in a study conducted by M.L. Harrison.[18] For stage I mucinous tumours, one study found tumour grade to be an independent predictive factor for relapse, although this has not been found consistently.

CONCLUSIONS

The histopathological examination of mucinous ovarian tumours is the gold standard method to differentiate between benign, borderline and malignant tumours and also in predicting the prognosis. Incidence of benign tumours is higher compared to borderline and malignant tumours. The mean age of presentation was 45 and all the malignant tumours were above the age of 40 years. Emergence of borderline category of tumours with prognostic difference between benign and malignant tumours has opened a new field of research in ovarian tumours. Diagnosis of ovarian tumours can be made in all cases by correlating the clinical presentation, radiographic appearance and histomorphological features. Even then, in the modern era by the application of specialised methods like special stains, immunohistochemistry (IHC) markers, ultrastructural studies and cytogenetics, there is a vast scope for accurate diagnosis of difficult dilemmatic cases of ovarian tumours, by which the prognostic and therapeutic implications could be modified.

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