



Original Article

Ovarian Germ Cell Tumor – Histopathological and statistical analysis

Ghosh A¹, Gharti Magar D¹, Sathian B², Narasimhan R¹, Talwar Op¹

¹Department of Pathology, Manipal College of Medical Sciences, Pokhara, Nepal

²Department of Community Medicine, Manipal College of Medical Sciences, Pokhara, Nepal

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ABSTRACT

Background: Ovarian cancers are common among females. The ovarian tumors are classified according to its histogenesis. In the present study, we analyzed the germ cell ovarian tumors reported in our institute.

Materials and Methods: This study was a hospital based retrospective study. All ovarian germ cell tumor reported from Jan 2001 to Feb 2013 were retrieved and analyzed. The specimens were routinely processed and the slides were stained with H&E and special stains wherever required.

Results: A total of 340 cases of ovarian tumors were reported and 150 cases (44%) were of germ cell origin. We had 137 cases of benign and 13 cases of malignant germ cell tumors. Most common subtype was mature cystic teratoma comprising 125 cases. Among the malignant cases, the most common was immature teratoma (5 cases). Age range in our series was from 8 to 82 years (mean 28 years). The most common age group affected was 21-30 years. Most of the malignant cases (76.9%) were in less than 30 years. Among the malignant cases majority (84.6%) were more than 10 cm in size. None of the malignant germ cell tumors were bilateral.

Conclusion: Among germ cell tumors of ovary, mature cystic teratoma is the most common tumor and malignant subtypes are uncommon. Malignant tumors tend to occur in younger age group.

INTRODUCTION

Ovarian cancers are common among females comprising 30% of cancers of female genital tracts and 6% of all cancers in females.^{1,2} It is the most common cause of death due to cancer of female genital tract and the fifth leading cause of cancer related deaths in females.³ It is least in the developing countries of South East Asia and Africa and highest in the industrialized developed countries of Europe and North America.^{1,4} In the present study, we analyze the germ cell ovarian tumors reported in our institute.

MATERIALS AND METHODS

Design

This study was a hospital based retrospective study carried out in the department of pathology, Manipal Teaching Hospital. All the ovarian tumors of germ cell origin reported in the department over a time period from January 2001 to February 2013 were retrieved and the data were analyzed. The tissues were routinely fixed with 10% formalin and the slides were stained with Hematoxylin and Eosin (HE) stains and also with special stains wherever required.

Outcome Variable

Main outcome variable was germ cell tumor. Others were

Correspondence:

Dr Arnab Ghosh, MD Associate Professor,

Department of Pathology Manipal Teaching Hospital, Manipal College of Medical Sciences, Pokhara, Nepal

Email: drghosharnab@yahoo.com

all the subtypes including benign and malignant tumors.

Explanatory Variable

Age (<10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, >70) , Side (uni-, bilateral), Size (upto 5cm, >5-10, >10-20, >20-30) , and were the explanatory variables at individual level.

Sample size calculation

For 95% confidence interval and, significance level $\alpha = 5\%$, $P = 50\%$, $Q = 50\%$, allowable error = 11%, required sample size was 317. $P =$ percentage of germ cell tumor. In the pilot study done prior to the original study with 10 patients.⁵

Ethical committee approval

Prior the study, ethical committee approval was taken from the institutional ethical committee, Manipal Teaching hospital, Pokhara, Nepal. The Research was conducted in accordance to latest version of the Declaration of Helsinki.

Data management and statistical analysis

The data collected was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and EPI Info 3.5.1 Windows Version. The Z test was used to observe the difference between different variables. $p < 0.05$ was considered as statistically significant.⁶

RESULTS

A total of 340 cases of ovarian tumors have been reported

in the same period and among them, 150 cases (44%) were of germ cell origin. The number and percentage of different types as well as 95% confidence interval of all benign and malignant germ cell tumors have been tabulated in Table 1. Benign germ cell tumors were 137 (40.3%) of all ovarian tumors and 91.3% of germ cell tumors. Malignant germ cell tumors constituted 3.8% (n=13) of all ovarian tumors and 8.6% of germ cell tumors. Most common subtype in our series was mature cystic teratoma (n=125). Among the malignant cases, the most common type was immature teratoma (n=5). The age distribution and bilaterality of different types of benign and malignant germ cell tumors have been tabulated in Table 2. Age range in our series was from 8 to 82 years with a mean of 28 years. The commonest age group affected was 21-30 years followed by 31-40 years and 41-50 years. Most of the malignant cases (10/13, 76.9%) were in women of less than 30 years. Out of all 150 cases 11 were bilateral. None of the malignant germ cell tumor was bilateral. Size of all different types of germ cell tumors including bilateral cases are shown in Table 3. The tumor size ranged from 3 cm to 27 cm with 95 cases (63%) in the category 5-10 cm followed by 10-20 cm (n= 51, 34%). Among the malignant cases majority (11/13, 84.6%) were more than 10 cm in size. Statistical analysis of age and size distribution of all the subtypes were carried out and are tabulated in Tables 4 and 5 respectively.

DISCUSSION

Germ cell tumors are a heterogeneous group, majority originating at different stages of development from germ cells.⁷ Some are composed of undifferentiated cells (dysgerminoma, embryonic carcinoma) while in others there is differentiation towards embryonic (teratoma)

Table 1: Frequency and percentage of different types of germ cell tumor

GERM CELL TUMOR		Percentage and 95% CI among Germ cell tumors (n =150)	Percentage and 95% CI among all ovarian tumor (n = 340)
BENIGN	137	91.3 (86.83,95.84)	40.3(35.08,45.51)
Mature cystic Teratoma	125	83 (77.37,89.30)	36.8(31.64,41.89)
Struma ovarii	2	1.3 (0,3.17)	0.6(0,1.40)
Mature teratoma with Serous cystadenoma	5	3.3 (0.46,6.21)	1.4(0.19,2.75)
Mature teratoma with Mucinous cystadenoma	3	2 (0,4.24)	0.9(0,1.88)
Mature teratoma with benign Brenner tumor	2	1.3 (0,3.17)	0.6(0,1.40)
MALIGNANT	13	8.6 (4.16,13.17)	3.8(1.79,5.86)
Mature teratoma with Mucinous borderline	1	0.6 (0,1.97)	0.3(0,0.87)
Mature teratoma with Sq Cell CA	1	0.6 (0,1.97)	0.3(0,0.87)
Mature teratoma with Sq Cell CA and Mucinus borderline	1	0.6 (0,1.97)	0.3(0,0.87)
Mature teratoma with undiff CA	1	0.6 (0,1.97)	0.3(0,0.87)
Immature teratoma	5	3.3 (0.46,6.21)	1.4(0.19,2.75)
Dysgerminoma	2	1.3 (0,3.17)	0.9(0,1.40)
Choriocarcinoma	1	0.6 (0,1.97)	0.3(0,0.87)
Yolk Sac Tumor	1	0.6 (0,1.97)	0.3(0,0.87)
TOTAL	150	100%	44.1%

or extraembryonic (choriocarcinoma, yolk sac tumor) structures.⁸ They account for nearly 30% of all ovarian tumors.^{7,9} In the current data, they constituted 44% of all ovarian tumors.

Benign germ cell tumors

Mature cystic teratoma is the most common ovarian neoplasm comprising 25% or more.⁹ In studies by Mondal SK et al and Jha R et al mature cystic teratoma comprised 68.9% and 95.6% of all germ cell tumors.^{13,14} In Western literature 95% of ovarian germ cell tumors are mature cystic teratoma.^{15,16} In our study, 125/150 cases were mature cystic teratoma, comprising 83.3% of all germ cell tumors and 36.8% of all ovarian tumors.

Grossly it is mostly unilocular cyst filled with grumous sebaceous material and hair. Microscopy reveals mature adult type tissue derived from two or three embryonic layers, most commonly being ectoderm. Struma ovarii is the most common type of monodermal teratoma.⁷ However, only 2 cases out of 150 cases were reported as struma ovarii. There were 10 cases of composite tumors where mature teratoma was associated with serous cystadenoma (n=5), with mucinous cystadenoma (n=3) and with benign Brenner tumor (n=2).

Majority of mature cystic teratoma are known to occur in less than 50 years with the peak being between 20 and 29 years.^{7,8} Similarly, in the present series majority (n=110; 88%) were below 50 years and it was statistically significant with p value 0.001. The peak for mature cystic teratoma was

in the age group 21-30 comprising 54 cases (43.2%). Benign teratomas are known to be bilateral in 10-15% cases.⁸ In our series, 8% (n=13) benign teratomas were bilateral. Benign teratomas range in size from a few centimeter to large tumor with average being 7-8 cm.⁸ We reported cases with a range from 2 cm to 27 cm. Majority were less than 10 cm with significant p value and most common group being 5-10 cm. However though the average size of Struma ovarii is 5-10 cm, the 2 cases we reported were of 8 cm and 15 cm in size.

Malignant germ cell tumors

Immature teratoma is one of the most common malignant germ cell tumors representing 20-30% of these tumors at major cancer centers.^{17,18} Only 3% of ovarian teratomas are immature.^{15,16} They occur in young age group and are typically unilateral with average size of 18 cm.⁸ In our study, 5 cases (3.4%) were immature teratoma. Age and size distribution were statistically significant in the present study, as all were below 30 years of age and majority were more than 10 cm. One case had size of less than 10 cm while rest 4 cases were between 10 and 20 cm. A mixture of mature and immature tissue; mostly in the form of neuroectodermal rosettes and tubules were seen. Histologically, they can be graded into grade 1, 2 and 3 according to extent of neuroectodermal component.^{7,8} We had 2 cases of grade 1 and 3 cases of grade 2 tumor.

Approximately 1-3% of benign mature teratoma may undergo malignant transformation.⁸ In a study of 87 ovarian teratomas, Papadias et al reported 5% cases with malignant changes.¹⁹ Secondary malignancies are typically

Table 2: Age distribution and bilaterality of different types of germ cell tumor

GERM CELL	AGE									SIDE	
	<10	11-20	21-30	31-40	41-50	51-60	61-70	>70	Uni	Bilatearal	
BENIGN											
Mature cystic Teratoma	125	1	5	54	29	21	10	4	1	114	11
Struma ovarii	2				1	1				2	
Mature teratoma with Serous cystadenoma	5			3	1	1				4	1
Mature teratoma with Mucinous cystadenoma	3			2	1					3	
Mature teratoma with benign Brenner tumor	2					1	1				1
MALIGNANT											
Mature teratoma with Mucinous borderline	1				1					1	
Mature teratoma with Sq Cell CA	1					1				1	
Mature teratoma with Sq Cell CA and Mucinus borderline	1						1			1	
Mature teratoma with undiff CA	1					1				1	
Immature teratoma	5	2	3							5	
Dysgerminoma	2		1				1			2	
Choriocarcinoma	1	1								1	
Yolk Sac Tumor	1	1								1	
TOTAL	150	2	8	63	33	26	13	4	1	134	13

Table 3: Size distribution of different types of germ cell tumor

GERM CELL TUMORS (including bilateral cases)	SIZE in cm			
	Upto 5	>5-10	>10-20	>20-30
BENIGN				
Mature cystic Teratoma	10	88	36	2
Mature teratoma				
with Serous cystadenoma	2	3	1	
with Mucinous cystadenoma			3	
with benign Brenner tumor	2	1		
Struma ovarii		1	1	
MALIGNANT				
Mature teratoma				
with Mucinous Borderline				1
with SCC*			1	
with SCC and Mucinus borderline			1	
with undifferentiated Ca**			1	
Immature teratoma		1	4	
Dysgerminoma			2	
Choriocarcinoma		1		
Yolk Sac Tumor			1	
TOTAL	14	95	51	3

† Statistical significance (p<0.05), * - Squamous Cell Carcinoma, ** - Carcinoma

seen in postmenopausal women and 85% are squamous cell carcinoma.⁷ We had only 4 cases of teratomas with secondary malignancy; 2 with squamous cell carcinoma and 1 with undifferentiated carcinoma and 1 with mucinous

borderline areas.

Dysgerminoma is a common malignant germ cell tumor of the ovary. 10-12 Eighty percent of tumors develop in women younger than 30 yrs of age with mean age 21 years. They are extremely rare above 50 years.⁹ Out of 2 cases in our study, 1 case was of 55 years. Microscopically predominantly diffuse pattern of primitive monotonous germ cells with PAS positive cytoplasm are seen (fig.1). The stroma is usually thin with varying number of lymphocytes.

Pure primary ovarian choriocarcinoma of germ cell origin is extremely rare and comprise less than 1% of all ovarian germ cell neoplasms.^{7,8} We reported only one case in the current study. Diligent search for other germ cell component should be carried out as choriocarcinoma is seen mostly as a component of a mixed germ cell tumor. Grossly they are typically hemorrhagic and microscopy is similar to its endometrial counterpart.

Yolk sac tumors are morphologically heterogenous and may show many epithelial patterns. The only case we had was of 16 years of age and showed classical reticular pattern and Schiller Duval bodies (fig 2.).

Mixed germ cell tumors are composed of at least two different germ cell component, the most common combination being dysgerminoma and yolk sac tumor.³ All the components with their approximate proportion should be noted in the diagnosis.⁷ Therapeutic regimen is based on the most malignant element.²⁰ We did not encounter any case under this category.

Table 4: Statistical analysis and significance of age distribution of different types of germ cell tumor

BENIGN	Age						
	<50 n (%)	<50 n(%)	Total	95% CI for Difference		Z-value	P-value
Mature cystic Teratoma	110(88)	15(12)	125	67.9435	84.0565	18.49	0.0001†
Struma ovarii	2(100)	0	2	-	-	-	-
Mature teratoma with Serous cystadenoma	5(100)	0	5	-	-	-	-
Mature teratoma with Mucinous cystadenoma	3(100)	0	3	-	-	-	-
Mature teratoma with benign Brenner tumor	1(50)	1(50)	2	-	-	-	-
MALIGNANT							
With Mucinous Borderlie	1(100)	0	1	-	-	-	-
Mature teratoma with Sq Cell CA	1(100)	0	1	-	-	-	-
Mature teratoma with Sq Cell CA and Mucinus borderline	0	1(100)	1	-	-	-	-
Mature teratoma with undiff CA	1(100)	0	1	-	-	-	-
Immature teratoma	5(100)	0	5	-	-	-	-
Dysgerminoma	1(50)	1(50)	2	-	-	-	-
Choriocarcinoma	1(100)	0	1	-	-	-	-
Yolk Sac Tumor	1(100)	0	1	-	-	-	-
Total	132 (88)	18(12)					

† Statistical significance (p<0.05)

Table 5: Statistical analysis and significance of age distribution of different types of germ cell tumor

			Total	Age		Z-value	P-value
	<50 n (%)	>50 n(%)		<50	>50		
BENIGN							
Mature cystic Teratoma	98(72.05)	38(27.94)	136	33.45	54.78	8.11	0.0001†
Struma ovarii	1(50)	1(50)	2	-	-	0	1
Mature teratoma with Serous cystadenoma	5(83.33)	1(16.67)	6	24.49	100	3.10	0.001946†
Mature teratoma with Mucinous cystadenoma	0	3(100)	3	-	-	-	-
Mature teratoma with benign Brenner tumor	3(100)	0	3	-	-	-	-
MALIGNANT							
With Mucinous Borderlie	0	1(100)	1				
Mature teratoma with Sq Cell CA	0	1(100)	1				
Mature teratoma with Sq Cell CA and Mucinus borderline	0	1(100)	1				
Mature teratoma with undiff CA	0	1(100)	1				
Immature teratoma	1(20)	4(80)	5	-	-	2.37	0.017706†
Dysgerminoma	0	2(100)	2				
Choriocarcinoma	1(100)	0	1				
Yolk Sac Tumor	0	1(100)	1				
Total	109	54					

† Statistical significance ($p < 0.05$)

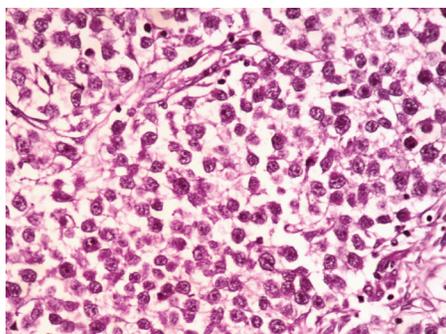


Figure 1: Dysgerminoma showing tumor cells in diffuse sheets separated by thin fibrous septae lymphocytes and capillaries (HE stain, X400)

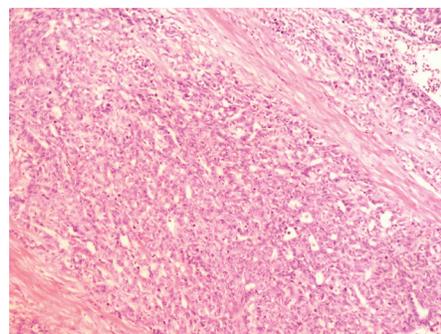


Figure 2: Yolk sac tumor showing reticular pattern and Schiller-Duval bodies (HE stain, X100)

CONCLUSION

Among germ cell tumors of ovary, mature cystic teratoma is the most common tumor and malignant subtypes are uncommon. Malignant tumors tend to occur in younger age group.

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