■ *Original Article*

Histopathological patterns of ovarian tumors at BPKIHS

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Abstract

Introduction: Ovarian tumors account for fifth most common cause of cancer related death in females involving a variety of histological diagnosis. It accounts for 6% of all cancers. Though it is one of the treatable cancers due to its sensitivity to anticancer therapies, it frequently does not result in symptoms until the cancer has spread extensively. **Objectives:** To study the incidence, histopathological spectrum and clinical correlates of ovarian tumours at B.P. Koirala Institute of Health Sciences (BPKIHS). **Methods:** A cross-sectional study was undertaken during a period of one year (1st Jan – 31st Dec 2006). The tumors were classified according to WHO classification after thorough examination of H&E slides under light microscope. Data on clinical presentation and physical findings were also recorded in each case. **Results:** There were a total of 83 cases. Surface epithelial tumors emerged as the commonest variety accounting for 47%, followed by Germ cell tumors (45.8%). Sex – cord stromal tumors and metastatic tumors accounted 3.6% each. The age range was 10 – 86 years. Metastatic tumors involved younger age groups. Abdominal mass was the commonest clinical presentation followed by pain abdomen. **Conclusion:** At BPKIHS, ovarian tumors were found to occur in wide range of age (10-86years) with abdominal mass and pain abdomen being the commonest mode of clinical presentation .Histology revealed that surface epithelial tumors and germ cell tumors together constitute the large majority of the case (92.8%). An accurate histological diagnosis and staging is therapeutically and prognostically important.

Keywords: ovarian tumors, surface epithelial tumors, germ cell tumors, sex-cord stromal cell tumors, teratoma, cystadenoma, borderline tumor, metastatic, histopathological.

Introduction

Ovarian tumors include a complex wide spectrum of neoplasm involving a variety of histological diagnosis ranging from epithelial tissues, connective tissues, connective tissue, specialized hormone secreting to germinal and embroyonal cells.[1]

It is one of the most treatable tumors because majorities are sensitive to anticancer therapies[2]. It accounts for 6% of total cancers in female and is the 5th most common form of cancer related death in females, ranked behind neoplasm of the lung, breast, intestine and uterus in United States and almost half of the deaths from gynecological cancers. Among cancers of female genital tract, the incidence of ovarian cancer ranks below only carcinomas of the cervix and the endometrium[3]. The disease has the highest fatality-to-case ratio to all the gynecologic cancers.[2]

It is estimated that about 1 in every 70 women have a life time risk of developing ovarian cancer. The American Cancer Society estimated that each year approximately 25,000 new cases of ovarian cancer are diagnosed, about 14,000 of these women die from the disease. Unfortunately, the survival rate is less than 50% because a widely screening test has not yet been developed and the disease is not very symptomatic[4].

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The risk of developing ovarian cancer is highest around the age of 55. The benign tumors mostly occur in young women between the ages of 20 and 45 whereas the malignant tumors are common in older women between ages of 40 and 65. The incidence is high in postmenopausal women, unmarried women or in married women with low parity.[3] Oral contraceptives and tubal ligation decreases the risk of developing ovarian cancer. Only 10-15% is discovered in pre menopausal women.[2] The aim of this study was to study the incidence, histopathological spectrum and clinical correlates of ovarian tumors at BPKIHS.

Methods

This cross-sectional study was done within a period of one year (2006) in the Department of Pathology and Department of Obstetrics and Gynecology at BPKIHS.

Only the specimens of ovarian tumors (OT) were considered in this study. The normal ovaries and the ovaries with other non- specific findings like follicular cyst, cystic follicles, surface inclusion cysts, hemorrhagic inclusion cysts were excluded from the study.

A detailed history, clinical examination, routine relevant laboratory investigation were obtained from the patients.

Procedure

The excised specimens of ovaries were fixed in 10% formalin. From cysts, up to 3 sections of 3mm were taken, especially from areas with papillary appearance. From solid tumors, one section for each centimeter was taken. Also one section of non - neoplastic ovary was taken where it was identifiable. After sectioning tissues were processed in an automated tissue processor. An overnight schedule of 16 - 18 hours was used. After processing, paraffin blocks were made. The tissue sections of 5mm were cut and stained by Hematoxylin and Eosin. The stains were cleared by xylene and mounted on a glass slide. These slides were then examined under a light microscope for a histopathological diagnosis. The histopathologic diagnosis was based on morphologic features and the tumors were classified according to WHO classification.

Results

A total of 83 cases were studied out of which 66 cases (79.5%) were benign, 2 cases (2.4%) borderline and 15 cases (18%) malignant.

These tumors were categorized into 4 main groups. Surface epithelial tumors (SET) constituted majority of the ovarian neoplasm with 39 cases (46.9%), followed by Germ cell tumor (GCT) which constituted 38 cases (45.7%). Sex cord stromal tumors (SCST) and Metastatic tumors (MT) constituted 3 cases (3.6%) each**.**

Among the total benign tumors 66 (79.5%), GCT comprised the commonest 33 (50%) followed by SET 31 (47%) and SCST 2 (3%).

Borderline tumors 2 (2.4%) comprised of one case each (50%) in the surface epithelial tumors.

Among the total malignant tumors 15 (18.1%), 12 (80%) were primary malignant tumors and 3 (20%) were secondary tumors. The commonest malignant tumor was from the SET 6 (40%) followed by GCT 5 (33%), metastatic tumors 3 (20%) and SCST 1 (7%).

The age group of the patients ranged from the youngest being 10 years, the oldest being 86 years with the mean age of 39.1 years. The youngest patient was of dysgerminoma and the oldest patient was of Benign Serous Cystadenoma. The younger age range was seen in GCT followed by SET.

Younger age involvement was an interesting observation made in relation to metastatic tumors in this study. On the contrary, ovarian neoplasm involving older age group was observed in SET followed by GCT.

Comparing the clinical presentation of all the tumors with the histopathological diagnosis we found out that the most common clinical presentation was of distension of abdomen and mass in the lower abdomen (67), followed by pain abdomen (65). Irregular bleeding per vagina was seen in 12 cases. Postmenopausal bleeding was not a common presentation (6). Pregnancy was associated with 5 cases among which 2 were of serous cystadenoma,

2 of mature cystic teratoma and 1 of immature teratoma. Primary amenorrhea was seen in 4 cases. Ascites and urinary symptoms were seen in 3 malignant cases. Loss of weight was a common presentation of malignant tumors comprising of 8 out of 15 malignant cases. Symptoms related to torsion were seen in 3 cases and there was one incidental finding of ovarian tumor in patient who had presented with strangulated bowel obstruction.

Gross pathology

Gross examination of the specimens revealed that majority of the tumors were cystic (C) (44.5%) followed by solid(S) (13.2%) and mixed (M) (42%). In the benign group majority of the cases (42.1%) were cystic, (4.8%) solid and (32.5%) mixed. The two cases in borderline group were cystic grossly. In malignant group both solid (Fig. 9) and mixed tumors were almost equal with mixed being 8 (9.6%) and solid 7 (8.4%).

Unilateral (UL) tumors were observed in 65 (78.3%) cases. Involvement of left (LT) ovary (65%) was more common than the right (RT) (35%). Bilaterality (BL) was seen in 18 cases (22%). The bilateral tumors were serous tumors (9), mature cystic teratoma (4), metastatic tumors (3), mucinous cystadenoma (1) and mixed seromucinous (1). Bilaterality was seen in 11 (16.6%) benign cases, 1 (50%) borderline and 5 (33.3%) malignant cases.

Histopathology

Surface epithelial tumors

These tumors comprised the largest group of the total ovarian tumors (OT) (46.9%) with 31 benign, 2 borderline and 6 malignant cases (Table 1).

Table 1: Age range, gross and histology of SET

Histopathology	Nature of lesion	Types	Age range	Size (cm)	Side			Gross		
					UL		BL	Cystic	Solid	Mixed
					RT	LT				
1.Serous	i.Benign	a.Cystadenoma (12)	18-86	6-22	3	3	6	13		
		b.Cystadenofibroma (1)	38	10		1		1		
	ii.Borderline (1)		48	10		1		1		
	iii.Malignant (4)		30-50	4-8		1	3		2	2
2.Mucinous	i.Benign (12)		17-68	8-6	3	8	1	12		
	ii.Borderline (1)		60	8		1		1		
	iii.Malignant (2)		60(both)	10-16	1	1				2
3.Brenner (2)			41-53	3	1	1			2	
4.Mixed		i.Mucinous & MCT (2)	26-45	7-6		1		1		
		ii.Mucinous & Serous (1)	30	11	1					1
		iii.Mucinous & Brenner (1)	41	14		2				2
Total (39)					9(23%)	19(49%)	11(28%)	28(72%)	4(10%)	7(18%)

Of the SET, serous tumors were the commonest comprising of 21.6% of all OT and 46.15% of all surface epithelial tumors. Amongst the serous tumors, serous cystadenoma showing cysts lined by single layers of ciliated columnar epithelial cells (Fig. 1) comprised of 30.76 % of all SET. There was one case of borderline serous tumors. Serous cystadenocarcinoma (10.25%) was the commonest malignant epithelial tumors. These tumors showed predominantly papillary structures with fibrovascular cores, complex glands, solid sheets and nests of tumor cells with diffuse invasion of the stroma. Variable amount of hemorrhage and necrosis along with numerous psammoma bodies were observed (Fig. 2).

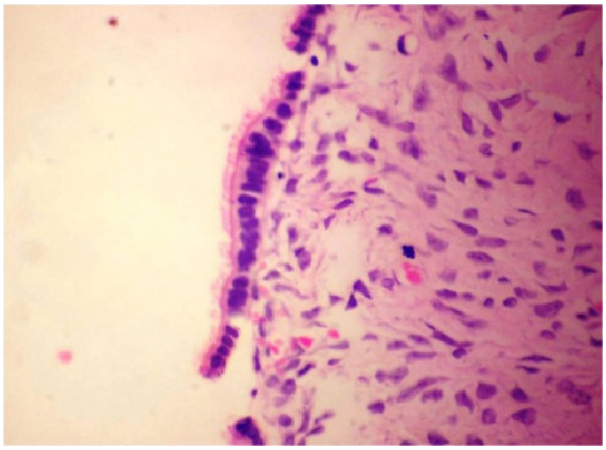

Fig.1. Serous cystadenoma lined by single layer of ciliated columnar epithelial cells.(H & E; 20X)

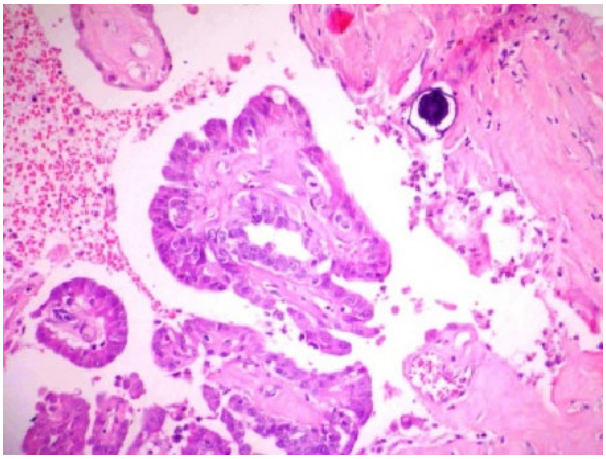

Fig. 2. Papillary Serous cystadenocarcinoma showing cytological atypia and psammoma body (H & E; 20X)

Mucinous tumors were the second commonest among SET (38.4%) and constituted 38.4% of total OT. Mucinous cytadenoma composed of multiloculated cysts lined epithelial cells with apical mucin (Fig. 3) was the commonest in this group followed by one case of borderline and two cases of malignant mucinous tumor.

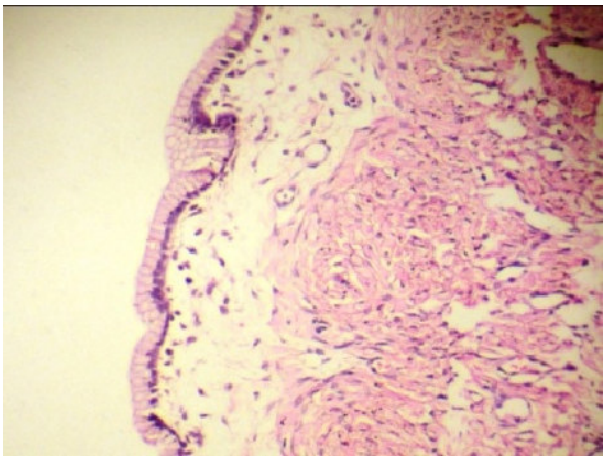

Fig. 3. Mucinous cystadenoma. Cyst lined by columnar cells with apical mucin. (H & E; 20X)

Benign Brenner tumor was observed in 2 cases with 5% of total SET and 2.4% of total OT.

There were 4 cases of mixed surface epithelial tumors, comprising of 10.2% of all SET and 4.8% of total OT. All the 4 cases had components of mucinous tumor with 2 cases mixed with mature cystic teratoma, one with serous and one with brenner tumor.

Germ cell tumors

This group of tumors comprised the second commonest tumor 38 (45.7%) of all OT. It showed 33 (86.8%) benign and 5 (13.1%) malignant cases of GCT and 50%and 3.3% of total OT respectively. Teratoma constituted 92% of all GCT, among which mature cystic teratoma (Fig. 5) (92.1%) was the commonest amongst the GCT. There were two cases of immature teratoma. There was one case of Struma ovarii, constituting 29% of total teratoma. Only 2 cases of dysgerminoma and one case of yolk sac tumor were observed in this study.

Sex cord stromal tumor

This group of tumor comprised 3.6% of all OT. Among the benign OT it constituted 33.3% and of all malignant ovarian tumors it constituted 66.7%. One case each of Fibroma and fibroma – thecoma were observed. A single case of Sertoli - Leydig cell tumor was noted in this group.

Metastatic tumors

Metastatic tumors, like sex cord stromal tumors, constituted the least number (3) in this series and all of them were Krukenberg tumor, comprising 3.6% of all malignant OT.

FIGO staging of primary ovarian tumors

Amongst the total 15 (18%) malignant tumors in this study, 12 (80%) cases were primary ovarian tumors and 3 (20%) were metastatic. The FIGO staging was applied only to the primary tumors.
Most of the patients had presented in FIGO IA 7 (58.3%) and 2 (16.7%) cases were seen in FIGO IIIA.

FIGO IB, IC and IIA had one (8.3%) case each from malignant surface epithelial tumors.

Among the borderline tumors, borderline serous tumors presented in FIGO stage I B and borderline mucinous tumor in stage I A.

Discussion

Ovarian neoplasm has become increasingly important not only because of its large variety of histomorphological patterns but more because they have gradually increased the mortality rate in female genital cancers. The incidence, clinical appearance

and the behavior of the different types of ovarian tumors is extremely variable. Though certain investigations like peritoneal fluid cytology, estimation of serum lactic dehydrogenase, fibrin degradation products and immunological tests have been reported to be of some help in predicting the nature of the pathology, it is generally impossible to diagnose the nature of the ovarian tumor preoperatively just by clinical examination and exploration. Hence, one has to depend on the microscopic appearance of the tumor for further management of the ovarian tumors[10].

Incidence

A total of 83 cases of ovarian tumors were documented in this study period, out of which benign tumors comprised of (79.5%), borderline (2.4%) and malignant (18%). Almost similar results were seen in studies conducted by Pilli et al[21] and Nowak et al[25] where the incidence of benign, borderline and malignant ovarian tumors comprised of 75.2%, 2.8%, 21.9% and 79.5%, 2.1% and 18.4% respectively.

Reverse result was shown by Tyagi et al[17] where the malignant tumors outnumbered the benign tumors. A higher incidence 40.81% of malignant tumors was shown by Ahmad et al[20] in comparison to other studies.

Study of Thanikasalam et al[16] showed similar frequency of borderline tumor (2%) as seen in our study.

Nature of the tumors

Among the different histopathological patterns, SET constituted majority of the ovarian neoplasm with (47%), followed by GCT of (45.8%), SCST of 3 (3.6%) and metastatic tumors of 3 (3.6%) cases, similar to the results of many studies. [10, 12,14,21,22, 21, 25] Results with GCT comprising the commonest of all ovarian neoplasm were seen in studies conducted by Lucus et al[11] and Lancaster et al.[18]

Among the benign lesions, GCT was the commonest (50%), followed by SET (47%) and SCST (2.4%) which is similar to many studies. Mature Cystic Teratoma comprised the commonest of all benign tumors in our study (48.4%) – similar to the study conducted by Ahmed et al[20] (35.17%), whereas Di Bonito L et al[13] reported epithelial tumors to be the commonest. This was followed by serous cystadenoma (66.6%) as reported by Maheshwari.[31] The commonest malignant tumor in this series were of surface epithelial tumors (40%), followed by germ cell tumors (33%), metastatic tumors (20%) and sex-cord stromal tumors (7%). This finding is similar to the findings of Shy et al[24] and Di et al.[13]

In this study serous cystadenocarcinoma constituted the most common malignant tumor (26.6%) as shown by various other studies.[19, 20, 26]

Age

Age range of 10 – 86 years was seen in this study with the mean age of 39.1. Similar results were reported by Ahmed et al[22] and Chow et al.[12] Sarkar[19] in his study has shown a case of benign cystic teratoma in 7months child. Similarly Pilli et al[21] reported the youngest patient of 8months.

Interestingly, our study shows opposite relationship between age and the nature of the tumor. The youngest patient in our study was 10 years old who had presented with dysgerminoma and the eldest patient was of 86 years old who had presented with serous cystadenoma.

Site of involvement

Unilateral (78%) involvement was more common than bilateral (22%) coinciding with the findings of other studie.s[9, 24] Involvement of left ovary (65%) was more common than the right (35%). Reverse was seen in the study conducted by Tyagi et al[17] and Fusey et al.[29]

Gross

Majority of the OT were grossly cystic 44.5% followed by solid and mixed tumors. Majority of the tumors in benign groups were cystic 42.1%. In the malignant group solid and mixed tumors were common. This goes in agreement with the findings of Fusey et al[29] who reported that most of the cystic swellings were either benign or non neoplastic while almost all the solid and mixed tumors were malignant. Chhanda et al[15] in a 10 years study of ovarian tumors revealed that in the benign group majority of the cases were cystic 86.7%. While in the malignant group majority cases 69.2% were solid. Sarkar[19] in a 14

years study of ovarian tumors revealed that majority of the cystic tumors 91.4% were in benign groups.

Clinical presentation

The most common clinical presentation in our study was of mass per abdomen along with distension and pain abdomen. This is in agreement with majority of studies.[10, 17, 28, 29] Irregular bleeding per vagina constituted the third common clinical finding as seen in the study of analysis of ovarian tumors in teenage by Fusey et al.[29] Pregnancy was associated in 6% of cases – an exact incidence of 6% reported by Bhattacharya et al.[10] Symptoms related to torsion were seen in 3.6% of cases, a similar incidence of 4.8% shown by Bhattacharya.[10]

In malignant cases, loss of weight 9.6% was a common finding followed by ascites and urinary symptoms with 3.6% each. In a study of Bhattacharya et al[10], ascites constituted half of the malignant ovarian tumors.

FIGO staging

Among the 12 primary malignant tumors, majority of the patients presented in IA 58.3% followed by IIIA 16.7% and 8.3% each of IB, IC and IIA. In a study of primary ovarian cancer by Chow et al[12] about 21% of the patients were in stage I, 18% in stage II, 50% in stage II and 11% in stage IV.

Among the 2 cases borderline tumors, one (50%) borderline serous tumor presented in IB and one (50%) borderline mucinous tumors in IA. Bostwick et al[35]**,** in a study of 109 cases of ovarian epithelial tumors of borderline malignancy showed that majority of the borderline tumors presented in stage IA.

Histopathology

Surface epithelial tumors

In this study SET (46.9%) constituted the most common of all OT – very similar findings to various studies conducted by different authors at different times.[10,12,14,15,17,19,21,36]

Serous tumors (46%) constituted the commonest tumor among SET as shown by many studies.[15, 19, 21, 32] Serous cystadenoma (66.6%) was the most common among the serous tumors in this study – an observation identical to Maheshwari V et al[31]. It is stated by Czernobilsky et al[33], in their clinicopathologic study of 34 cases of cystadenofibroma and their comparison with serous cystadenoma that it is more common than generally believed and that is of an entirely benign nature. Serous cystadenocarcinoma (26.6%) comprised the most common. It is in agreement with the findings reported by Ahmad et al[20] Ahmed et al[22] and Shy et al.[24]

Mucinous tumors (38.4%) constituted the second common SET in this study – as stated by Chauhan AS et al[34] in their study. Maheshwari et al[31] reported that mucinous cystadenoma comprised the second commonest 30.8% of all SET. Among the mucinous tumors, 12 (80%) were benign, 1 (6.7%) borderline and 2 (13.3%) malignant.

Borderline tumors are those that have some but not all of the morphological features of malignancy (i.e. they are not invasive) – as stated by Harlow et al.[37] We had one case each of borderline serous and mucinous tumor. In a study of 109 ovarian epithelial tumors of borderline malignancy by Bostwick et al[35]**,** 67% were of serous, 27.5% mucinous and 5.5% seromucinous.

Brenner tumor is best considered as a tumor of urinary tract (urothelium) type epithelium.[42] It is composed of nests of transitional epithelial cells in an ovarian stroma (Fig. 4). This tumor constituted 5% of all SET and 2.4% of all OT in this study. Literatures suggest it's incidence as 2% of all ovarian tumors.[5] Maheshwari et al[31] found its incidence to be 1.18% of all SET. In our study, out of two cases, one was an incidental finding. Silverberg [41] also reported that 5 of 54 Brenner tumors were an incidental finding in his study. Similarly 53 out of 57 patients were an incidental finding in a clinicopathological study of 57 Brenner tumors conducted by Ehrlich et al.[42]

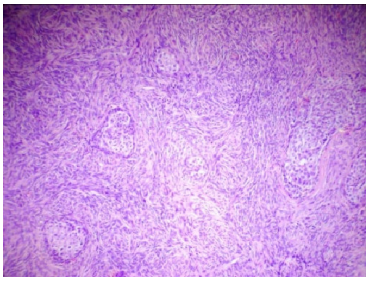

Fig. 4. Brenners tumor showing presence of nests of transitional epithelium in an ovarian stroma (H&E; 20X).

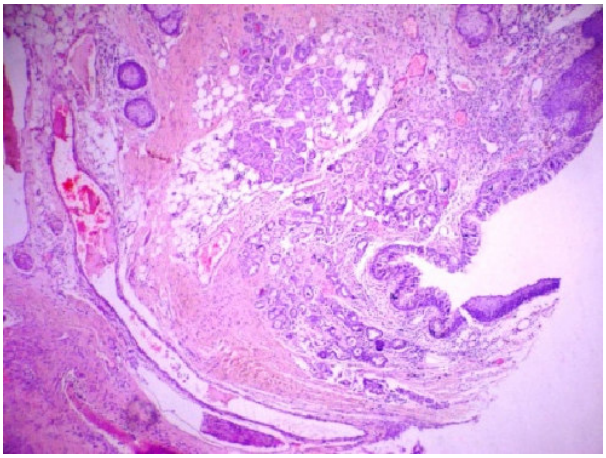

Fig. 5 Various tissue components of Mature Cystic Teratoma - stratified squamous epithelium, skin adnexa, respiratory epithelium, seromucinous glands, mature adipose tissue, muscle and blood vessels. (H & E; 10X)

Of all SET in this study, 10.2% showed mixed nature. Histologically all the cases contained mucinous cystadenoma mixed with mature cystic teratoma in 2 (50%) cases, with serous and Brenner in one (25%) case each.

Waxman M[43] in his clinicopathologic and histogenetic observations of pure and mixed brenner tumors of the ovary reported 58.3% out of 12 Brenner tumors mixed with mucinous cystadenoma. Shappel HW et al[40] evaluated clinicopathologic features of 54 endocervical – type and mixed cell type mucinous tumors in which he found that serous - type differentiation was present in all cases and all the tumors were composed of a heterogenous population of cells consisting mainly of serous (ciliated) and endocervical – type.

In this study germ cell tumors accounted the second most common tumor (45.7%) of all OT similar to the findings of many other studies.[10, 13,14,15,17,19,21,22] Literature suggests its frequency as approximately 20% among the OT[7]. Among benign tumors, this group was the commonest. It constituted the second commonest (33.3%) among the total malignant tumors like in many studies.[14, 23, 24]

Teratoma was the commonest (92%) of all GCT. In a clinicopathological study of 121 GCT in BPKIHS Nepal conducted by Sah SP et al [44] it constituted (98%) of all GCT. Immature teratoma constituted 60% of all GCT. Struma ovarii constituted 3% of all OT; agreeing with the literature with its incidence as 1 – 3% of all benign ovarian tumors.[5] It is characterized by the presence of thyroid tissue in an ovarian stroma (Fig. 6).

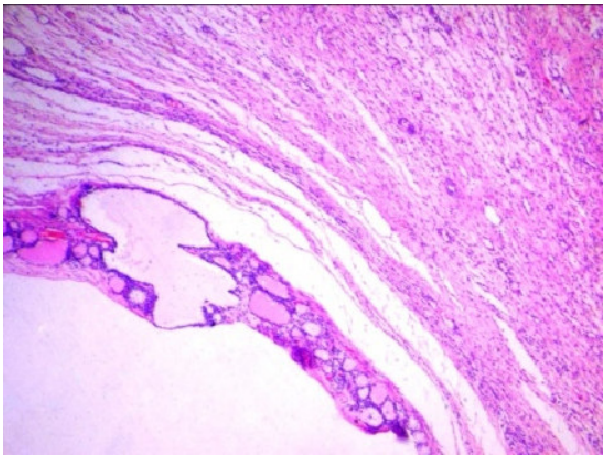

Fig. 6. Struma ovarii. Presence of thyroid tissue in ovarian stoma which is sharply delimited from it. (H & E; 10X)

Dysgerminoma had the youngest group of patients comprising 5.2% of GCT and 2.4% of all OT.[44, 46, 51, 52] The tumors presented in solid nests and sheets separated by variable amount of fibrous strands infiltrated by lymphocytes (Fig. 7).

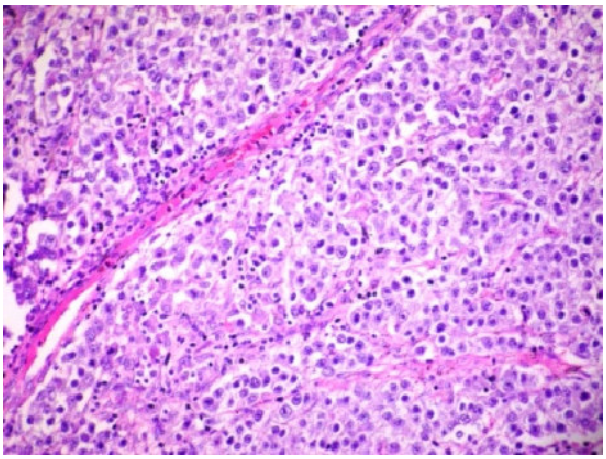

Fig. 7. Dysgerminoma. The tumor cells are separated by fibrous septa containing lymphocytes. (H & E; 20X)

Yolk sac tumor (Fig. 8) comprised 3 % of total GCT, findings similar to many studies.[15, 44, 46]

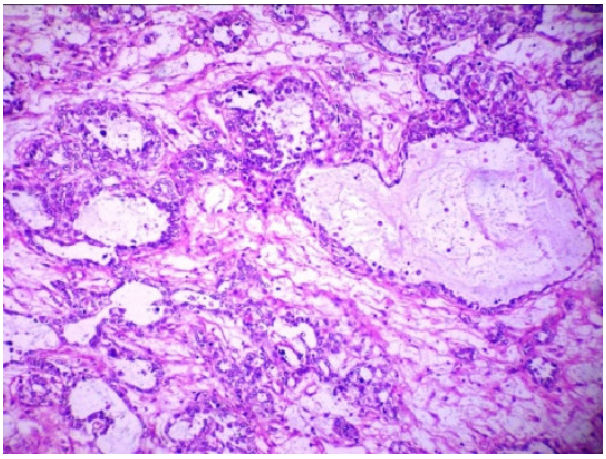

Fig. 8. Yolk sac tumor showing tumors cells arranged in microcytic and macrocystic patterns (H&E; 20X).

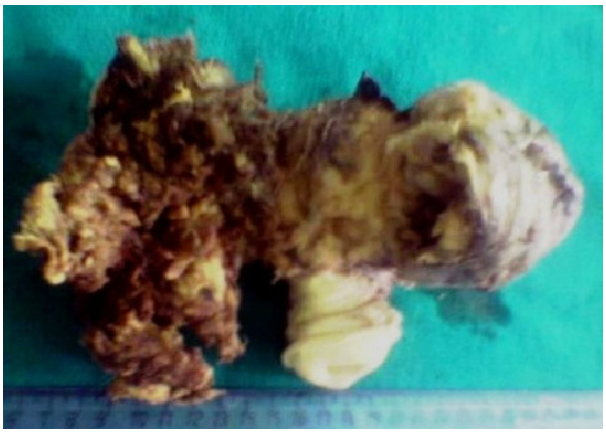

Fig. 9. Gross picture of Papillary Serous Cystadenocarcinoma, bilateral ovaries. Cut surface reveals solid growth with papillary excrescences and capsular breach.

Sex Cord Stromal tumors comprises of 5-8% of all OT but our study showed a lower incidence (3.6%)-incidence very close to the finding of Salvi V[31] (3.3%). Among SCST, there was each case of Fibroma, Fibroma-Thecoma and Sertoli-Leydig cell tumor. Androgenic effect of the tumor was not seen in this study while it was seen in 100% of the 34 cases reported by Roth et al.[55]

Metastatic tumors involve the ovaries, more than any other site in the female genital tract comprising 5 – 10% of all malignant OT. In this study an incidence of 3.6% of all OT were observed, similar to many studies.[10, 15, 17] Pilli et al[21] have shown a smaller incidence rate of 0.7% only. All the metastatic tumors were diagnosed as Krukenberg tumor. Microscopically all the three tumors predominantly comprised of signet ring cells staining positive for PAS and alcian blue. Tumor emboli were present in 33.3% of all MT. The usual primary sources of Krukenberg tumor are stomach, large bowel, appendix and breast.[7] Primary site could not be ruled out in this study due to loss of follow up of the patients. Woodruff and Novak suggested that the term "Krukenberg tumor" should apply only to those ovarian tumors, primary or secondary, with features consistent with Krukenberg's original criteria: a) the presence of the tumor in the ovary; b) evidence of intracellular mucin secretion by the formation of signet cells; and c) diffuse infiltration of the stoma, giving a "sarcoma – like" picture.[56]

Webb et al [56], in his study of 357 cases of cancer metastatic to the ovary reported that the primary site of cancer metastasis to the ovary were gastrointestinal (47%) comprising the commonest followed by breast 31%, genital 18% and other 15% while Petru et al [57], in the study of 82 nongenital cancers metastatic to the ovary reported primary carcinomas of the breast 34.1% to be the commonest.

Conclusion

Ovarian cancer presents a tremendous clinical challenge to gynecologists, medical oncologists and radiotherapists. It is a silent menace and is not associated with significant symptoms. It is not easily detected by physical or laboratory examination; hence one has to depend in the microscopic appearance of the tumor for further management of the ovarian tumors. The classification of OT is primarily morphologic but is intended to reflect current concepts of embryogenesis and histogenesis of this complex organ. Ovarian malignancies occur at all ages. This study has shown the occurrence of younger age groups in the primary malignant ovarian tumors and the metastatic tumors. Hence this study emphasizes that in a young female with ovarian mass the possibility of malignancy and metastatic tumors should not be neglected.

Acknowledgement

We would like to thank and acknowledge for the invaluable suggestions and advice from my teachers Dr. Sagar Raj Pandey and Dr. Bipin Kumar. We are also thankful to my seniors Dr. Smriti Karki and Dr.

Paricha Upadhyaya for their constant advice, help and encouragement. Dr. Pragya, Dr. Rojan, Dr. Punam, Dr. Meenu and Dr. Mrinalini helped and supported me during the study and we are very grateful to them.We would also like to thank all the technical staffs for their support.

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