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Original Research Paper

Pathology

TERATOMAS OF OVARY AND THE COMPANY THEY KEEP - CASE SERIES

Dr. Hana Kareem*	Assistant Professor, M.D. Pathology Department of pathology, Karuna Medical College, Chittur, Palakkad, Kerala – 678103 *Corresponding Athor
Dr. Niranjana Suresh	Junior resident,Department of Obstetrics and Gynaecology, Karuna medical college, Chittur, Palakkad, Kerala – 678103
Dr. Karpagam Janardhan	Assistant Professor, M.D. Pathology, Department of pathology, Karuna Medical College, Chittur, Palakkad, Kerala – 678103.

ABSTRACT Teratoma of ovary is a special type of mixed tumor that contains recognizable mature and immature cells or tissues derived from one or more of the three primordial germ cell layers. The word teratoma is derived from the Greek word "teras", meaning monster or deformed and "oma" meaning tumor, Virchow coined the term "teratoma" in his book on tumors published in 1863. Teratomas originate from totipotential germ cells such as those normally present in the ovary and testis and sometimes abnormally present in sequestered midline embryonic rests. They are the most common ovarian tumors and though more common in children, can occur in all ages. Teratomas display wide range of differentiation from most primitive immature elements on one end to highly organized axial and metameric structures such as fetus - in - fetu at the other end. In this study we would like to present seven cases of teratomas with distinct tumor combinations, thereby emphasizing the importance of careful examination of the specimens and extensive sectioning from the representative areas so as to not to miss mixed tumors. One of our case presented here - Mature cystic teratoma with Primary Krukenberg's is not reported previously and up to our knowledge is the first case to be reported.

KEYWORDS : Teratomas, Immature, Krukenberg's and Struma Ovarii, MCT (Mature Cystic Teratomas)

INTRODUCTION:

Teratomas are the most common germ cell tumors comprising 20% of all ovarian neoplasms and are composed of 3 germ cell derivatives with most common one being dermoid cyst derived from the ectoderm. They are classified based on site as intragonadal and extragonadal and based on histology as mature, immature, monodermal and teratomas with malignant change. Gonzalez and Crussi have graded them into Grade 0 (No immature tissue), Grade 1 (<10% of immature tissue), Grade 2 (10 - 50% of immature tissue) & Grade 3 (> 50% of immature tissue).

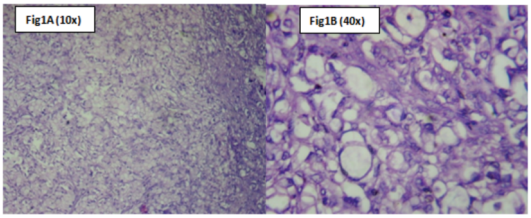
There are three theories postulated for the origin of teratomas. (a) Gastrulation theory - arising from primitive streak. (b) Missed target theory - arising from totipotent germ cells along the origin of allantosis with migration to the gonadal ridges during embryogenesis. (c) Incomplete twinning - Fetus in Fetu. A teratoma can be pure and not malignant, yet highly aggressive, which is exemplified by growing teratoma syndrome (1b) in which chemotherapy eliminates malignant elements of a mixed tumor leaving pure teratomas to proliferate rapidly. A recently discovered condition where ovarian teratomas cause encephalitis associated with antibodies against N - methyl D aspartate receptor referred to as anti NMDA receptor encephalitis (2) is a serious complication. Rarely they undergo malignant transformation and here we analyze rare and malignant transformed teratomas with collision tumors.

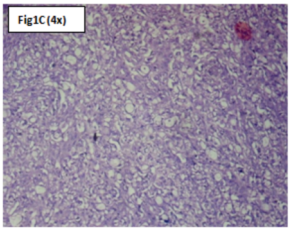
METHODS:

This study is a retrospective study of rare and malignant transformed teratomas over a period of 2 years from March 2018 to March 2020. As this is a case series, we chose to describe cases received during this period at Karuna Medical College, Palakkad and Histolab, Coimbatore. We received a total of 160 ovarian lesions during this period of which teratomas and their accomplices numbering upto 28 cases.

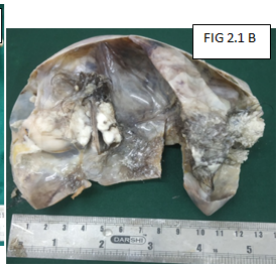
Case Reports:

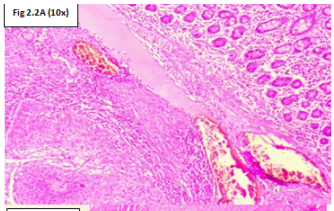
(1) 48 years female presented with abnormal uterine bleeding and lower abdominal pain. USG showed multiple fibroids in the anterior and posterior aspect of uterus with left ovary appearing enlarged and predominantly solid. Laparoscopic hysterectomy with bilateral salpingo oopherectomy done and sent for histopathological examination. Left ovary showed cystic and solid areas grossly with histopathological examination showing dermoid cyst with signet ring carcinoma. IHC showed CK 20 negativity and as PET scan didn't reveal any primary elsewhere, a diagnosis of Dermoid Cyst with Primary Krukenbergs tumor was made. Fig 1 a b c

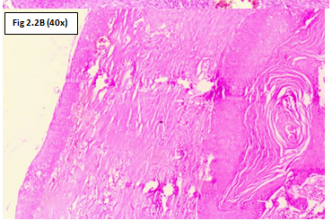


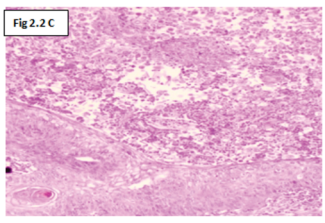


(2) 37 years old female presented with intestinal obstruction and USG showed right ovarian tumor - cystic and solid infiltrating the adjacent small intestine. Emergency laparotomy was done and hysterectomy with bilateral salpingo oopherectomy - including cystectomy and resection specimen of obstructed small intestine were sent for histopathology examination. Grossly right ovary showed a mass measuring 12x9cm with uniloculated cystic cavity filled with hair and pultaceous material with one focus of solid area with solid area adherent to the small intestine that shows greyish areas extending into the wall. Histopathological examination showed Mature Cystic Teratoma with Squamous Cell Carcinoma, infiltrating the intestine fig 2.1 A and B and fig 2.2 A,B and C.

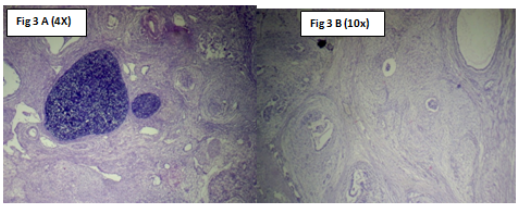


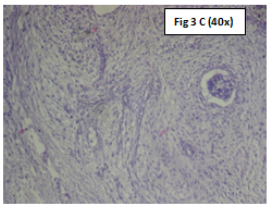




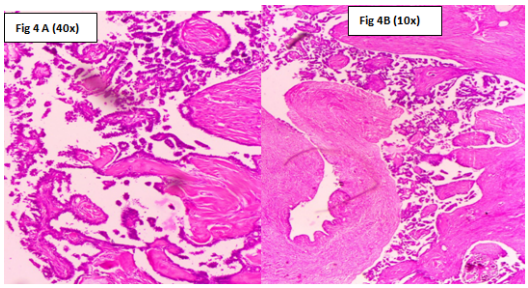


(3) 13 years old girl presented with pain abdomen and USG reveled a retroperitoneal mass which on excision showed an Immature Teratoma.FIG 3 A B C

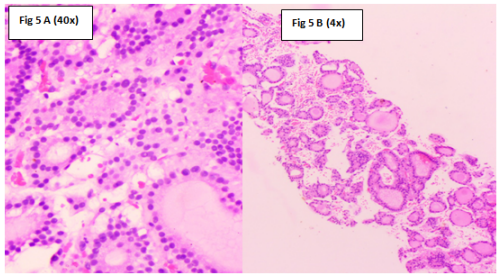




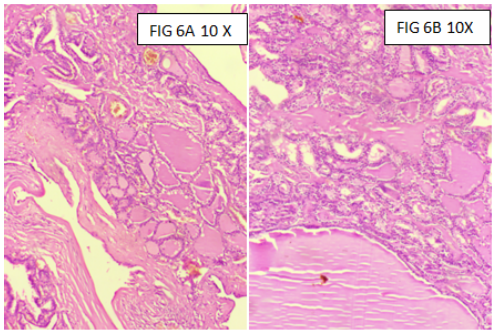
(4) 28 years female during LSCS was found to have a small left ovarian cyst, which showed Mature Cystic Teratoma with predominant choroid plexus epithelium histologically. FIG 4 A B



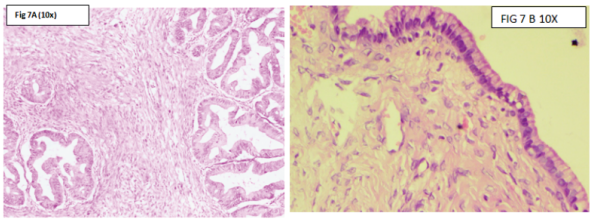
(5) 32 years female presented with menorrhagia and USG showed multiple fibroids and adenomyosis with left ovarian cyst. Laparoscopic hysterectomy with left salpingo oopherectomy done and sent for histopathological examination. Left ovary showed cystic areas with predominantly thyroid follicles of varying size - confirming struma ovarii. FIG 5



(6) 48 years female presented with abdominal pain and abnormal uterine bleeding and hysteroscopy showed thickened endometrium with polyp. Left ovary showed solid area on the surface and hysterectomy specimen with bilateral salpingo oopherectomy showed simple hyperplasia of the endometrium with left ovarian surface mass showing features of struma ovarii. FIG 6 A B



(7) 52 years female presented with abdominal pain with vomiting and USG showed a right ovarian mass with ? torsion. Right salpingo oopherectomy done and sent for histopathological examination that showed Mature Cystic Teratoma and mucinous cyst adenoma. FIG 7 A B



DISCUSSION:

WHO classifies germ cell tumorsincluding teratomas into:

- Immature
- Mature
- Solid
- Cystic (dermoid cyst)
- Monodermal (e.g., struma ovarii, carcinoid)
- Dysgerminoma
- Yolk sac tumor (endodermal sinus tumor)
- Mixed germ cell tumors

(1) Mature cystic teratoma with primary Krukenberg's tumor:

Krukenbergs tumors are unusual metastatic tumor of the ovaries first described by Friedrich Krukenberg in 1896 (3). In 1902, (4) Schlagenhauferemphasised that these tumors do not originate in the ovary but are metastasis from elsewhere, mostly from GIT. However the WHO states that the diagnostic criteria for Krukenberg's (5) (6) is (1) stromal involvement, (2) mucin producing signet ring cells and (3) ovarian stromal

sarcomatoid proliferation. Primary Krukenbergs can be considered only if we make sure that there is no primary elsewhere.

The major features favouring metastatic Krukenbergs (7) are (a) bilaterality, (b) size of the mass around 10cms, (c) surface involvement, (d) extensive intraabdominal spread and (e) wide spread infiltration pattern. On the contrary, features favouring a primary Krukenbergs are (a) unilaterality, (b) size greater than 12cms, (c) smooth external surface and (d) often associated with other ovarian pathologies. Our case is associated with mature cystic teratoma. IHC (8) is very valuable and essential to diagnose Primary Krukenbergs as differential diagnosis includes:- (I) Primary mucinous carcinoma, (II) mucinous carcinoid tumor& (III) signet ring stromal tumor. CK 7 positivity and CK 20 negativity favours primary ovarian cancer. IHC on this tissue showed CK 20 negativity. (9)

In review of literature, case report of primary Krukenbergs by Vijaya V. Joshi et al (3), out of 38 cases reported, 17 were accepted as primary krukenbergs and origin from germinal epithelium having Mullerian potentialities is favoured.

TakakoOkumato et al (10), used DPEP 1 (dipeptidase 1) to differentiate primary and secondary mucinous tumors, where DPEP 1 is positive in secondary tumor, especially of GI origin.

Upto our knowledge, our case is the first case of Primary Krukenberg with mature cystic teratoma to be reported.

(2) MCT with malignant transformation to squamous cell carcinoma:

Malignant transformation of a teratoma to non-germ cell malignant tumor is very rare and sometimes associated with i 12 p mutations in malignant components which is absent in mature teratomas area. Prolonged exposure to various carcinogens in the pelvic cavity, hormonal factors, HPV infection (11) and chemotherapy and radiotherapy induced are few causes for malignant transformation of teratomas. Asarantiet al in Indian Journal of pathology in year 2013, has reported a case of carcinosarcoma arising from dermoid cyst.

As squamous cell carcinoma arising in MCT is quite rare, one must exclude metastasis particularly from the cervix. Stromal invasion by malignant appearing epithelium should be used as definite criteria for categorizing MCT with malignant transformation. Mode of infiltration of tumor cell in the stroma was first described by kikkawa et al, in the year 1997 (12) and are classified into three patterns. In alpha mode, the tumor cells invade the stroma expansively with a well-defined border between the tumor and the stroma, while in gamma mode, the tumor cells diffusely invade the stroma without a clear border. Beta mode shows intermediate features between alpha and gamma mode. However, staging, vascular involvement and mode of infiltration are good predicators of recurrence and prognosis of the disease.

Pre-operative diagnosis is difficult. MRI may be helpful and serum markers (13) may give a clue. Takagi et al have found CEA to be more useful than CA 125 and CA 19.9 in malignant transformation of MCT. Elevated serum SCC antigen is the most useful marker to detect squamous cell carcinoma changes in benign teratomas (14). Also post menopausal status and size > 10cm should raise a suspicion of malignant change. ROMA (Risk of ovarian malignancy algorithm) using 2 markers CA 125 and HE4R may be useful with premenopausal women with ROMA value of 1.14 or greater and post menopausal ROMA value of 2.99 or greater indicating a high risk of finding an ovarian epithelial cancer. Recent next generation sequence analysis indicated that TP53 mutation was detected in 80% of squamous cell carcinoma transformation.

(3) Immature teratomas:

WHO defines Immature Teratomas as teratomas containing variable amount of immature embryonal type, usually neuroectodermal tissue with median age of presentation 10 - 20 years with few patients presenting with para neoplastic syndrome. Presence of immature mesenchymal elements, which is present in most of the cases is not sufficient to diagnose immature teratomas and presence of them should prompt a careful search for immature neuroepithelium (15). Rarely immature teratomas can present with no neuroectodermal components. Few cases with high AFP and only endodermal liver and intestinal structures have been reported. Presence of Yolk Sac component is the best predictor of recurrence with most important prognostic marker being stage of the disease and grade of the tumor.

Immature teratomas are graded based on neuroepithelial elements. According to Norris et al.

Grade	Percentage of immature tissue
Grade 0	No immature tissue
Grade I	<10% immature tissue
Grade II	10%-50% immature tissue
Grade III	>50% immature tissue

Six cases of immature teratomas of ovary were karyotyped and analyzed for chromosomal heteromorphisms, enzyme polymorphism and HLA specifities(16) to determine their mechanism of origin. 3 cases were chromosomally abnormal with karyotype of 48, xx, +14, +21, 47, xx, +20, 47 xxx. First 2 originate from premeiotic cells or failure of meiosis and had a poor prognosis. Third and other three with normal karyotype originated from failure of meiosis II or duplication of mature haploid ovum. This shows that immature teratomas are like mature teratomas in having 3 mechanisms of origin. However, they have high proportion of chromosomal abnormalities leading to malignant transformation.

(4) Monodermal Teratomas:

Monodermal teratomas are composed predominantly or solely of one tissue type and are of 3 types (17) – struma ovarii, ovarian carcinoids and tumors with neural differentiation.

We have presented here 2 cases of struma ovarii and one with neural differentiation in this article.

(5) Mature cystic teratoma with choroid plexus epithelium:

Though neurogenic tissue was predominant in our case, it cannot be regarded as purely Monodermal due to presence of skin and appendages. Benign cystic monodermal teratoma with pure neurogenic origin is extremely rare and only one case is reported and association with choroid plexus epithelium is very rare. The report of Marcial and Rojas and Medina (18) contained 22 – 47% peripheral nerves, 25 – 41% brain tissue, 19 – 25% ependymal cells, 19 – 22% ganglion cells and 6% of choroid plexus cells. Our case had only choroid plexus epithelium.

(6) Struma ovarii:

Although as many as 20% of dermoid cysts contain thyroid tissue, struma ovarii is reserved for lesions with more than 50% of thyroid tissue with peak frequency being 5th decade and was first described as Boettlin (19) in 1889. USG showed a solid and cystic pattern with no fat and Doppler shows struma pearl appearance, which is well defined solid tissue with smooth vascularized margin. These solid areas may result in extensive staging laparotomy for suspected ovarian malignancy&ROMA may be used to assess the lesion clinically.

Malignancy in struma ovarii is extremely rare and can be biologically or histologically malignant (20). Features that predict biological malignancy with adverse outcome are adhesions (graded 2 – 4%), peritoneal fluid (> 1 L), ovarian serosal breach and strumal component of more than 12cms. Histological features of malignancy are (a) Follicular

Adenoma, (b) Papillary Carcinoma and (c) Unequivocal vascular or capsular invasion. Another important finding is birefringent calcium oxalate monohydrate crystals which features aggressive behavior.

The second case of struma ovarii in our case series had capsular breach and follicular adenoma like pattern and hence considered aggressive and may be malignant.

Shaco – Ley et al reported that histopathological factors of poor prognosis are tumor size ≥ 10cms, > 80% of stromal tissue affected by carcinoma, presence of necrosis, ≥5 mitosis / 10 HPF and marked cell atypia. BRAF is a predicator of aggressive behavior. Tumor with VEGF and P53 mutation has the risk of malignant transformation. HDFCO (Highly Differentiated Follicular Carcinoma of Ovarian Origin) is a new entity described by Roth (21) and Karseladze, characterized by extra ovarian dissemination of thyroid elements that resemble thyroid tissue. While surgery is treatment, adjuvant therapy includes radiation, chemotherapy, thyroidectomy, radioactive iodine and thyroid suppression. Post operative iodine scans are useful to assess residual disease.

(7) Teratomas with mucinous cyst adenoma:

Collision tumor is coexistence of 2 different tumors in the same organ without any intermixing and though it is described in many organs, ovarian site is very rare with teratomas with mucinous cyst adenomas being the most common collision combination in the ovary. Whenever, multilocation of cysts (22) with fat is seen on USG, the lesions should be extensively examined radiologically and histopathologically, not to miss any component, that can bear the prognosis of the patient. Serum markers, especially 19.9 (23) is very useful in detecting mucinous cyst adenomas, especially higher in bilateral ovarian lesions. Claudin – 18, another marker is over expressed in intestinal types of mucinous tumors and used to differentiate from endocervical type of mucinous tumor. IHC markers like CK 7 and CK 20 are useful to confirm the diagnosis and to rule out metastasis from GIT. (24) (25)

Various hypothesis have been suggested for these collision tumors (26) (1) First is that the coexistence of 2 primary tumors is due to chance accidental meeting, (2) Second is that the presence of first tumor creates changes in the micro environment, engendering the development of second primary tumor and (3) The third theory proposes that each primary tumor has its origin in a common stem cell – germ cell origin. Although not all mucinous tumors are of germ cell origin, mucinous elements is dermoid cysts may be teratomatous origin as they are more likely intestinal rather than Mullerian. In a study by Fuji et al, homozygous genetic patterns like those of the teratomatous components were shown in mucinous tumors, thus supporting origin of mucinous tumors from preexisting teratomas, which can be confirmed with evidence of clonal relationship with molecular analysis.

CONCLUSION:

Teratomas, the most common germ cell tumor of the ovary is not always a simple dermoid cyst. As there are many associated lesions or malignant changes seen with these tumors, extensive and meticulous sampling with correlation with serum markers or IHC and molecular analysis is essential not to miss any lesion that warrants extensive debulking and further therapy. Of the 7 cases reported here, teratoma with primary Krukenbergs tumor is very rare and upto our knowledge, this is the first case to be reported. Finally teratomas can be mature, immature, pure, non malignant – Yet aggressive like Growing Teratoma Syndrome or associated with malignant changes. But prognosis and treatment depends on the anatomical site of the lesion, age of the patient, clinical staging and histological grading of immature tissue.

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